Hindawi Publishing Corporation
New Journal of Science
Volume 2014, Article ID 231418, 36 pages
http://dx.doi.org/10.1155/2014/231418

Review Article

Protein Kinase C (PKC) Isozymes and Cancer

Jeong-Hun Kang

Division of Biopharmaceutics and Pharmacokinetics, Department of Biomedical Engineering, National Cerebral and Cardiovascular Center Research Institute, 5-7-1 Fujishirodai, Suita, Osaka 565-8565, Japan

Correspondence should be addressed to Jeong-Hun Kang; jrjhkang@ncvc.go.jp

Received 16 January 2014; Accepted 24 March 2014; Published 4 May 2014

Academic Editor: Eric Hajduch

Protein kinase C (PKC) is a family of phospholipid-dependent serine/threonine kinases, which can be further classified into three PKC isozymes subfamilies: conventional or classic, novel or nonclassic, and atypical. PKC isozymes are known to be involved in cell proliferation, survival, invasion, migration, apoptosis, angiogenesis, and drug resistance. Because of their key roles in cell signaling, PKC isozymes also have the potential to be promising therapeutic targets for several diseases, such as cardiovascular diseases, immune and inflammatory diseases, neurological diseases, metabolic disorders, and multiple types of cancer. This review primarily focuses on the activation, mechanism, and function of PKC isozymes during cancer development and progression.

1. Introduction

Protein kinase C (PKC) is a family of phospholipid-dependent serine/threonine kinases that function in numerous different cell types. Based on their structural and activation characteristics, this protein family can be further classified into three subfamilies: conventional or classic PKC isozymes (cPKCs; α, βI, βII, and γ), novel or nonclassic PKC isozymes (nPKCs; δ, ε, η, and θ), and atypical PKC isozymes (aPKCs; ζ, ι, and λ). The activation of cPKCs requires diacylglycerol (DAG) as the primary activator along with phosphatidylserine (PS) and calcium (Ca^{2+}) as cofactors of activation. The nPKCs are also regulated by DAG and PS but do not require Ca^{2+} for activation. In the case of aPKCs, their activity is stimulated only by PS and not by DAG and Ca^{2+} [1, 2].

PKC isozymes are involved in multiple signal transduction systems that respond to a variety of external stimulators, including hormones, growth factors, and other membrane receptor ligands. For this reason, PKC isozymes can act as therapeutic targets for several diseases, such as cardiovascular diseases (e.g., atherosclerosis, myocardial fibrosis, cardiac hypertrophy, and hypertension) (for reviews, see [3, 4]), immune and inflammatory diseases (e.g., asthma, arthritis, and hepatitis) [5, 6], neurological diseases (e.g., Alzheimer's disease and bipolar disorder) [7, 8], and metabolic disorders (e.g., obesity, insulin resistance, hyperglycemia, and hypercholesterolemia) [9–11]. Further, significant work has also explored the activation, mechanism, and function of PKC isozymes in the development and progression of multiple types of cancer, which will be the primary focus of this review.

2. PKC Isozymes and Their Target Proteins

There are five consensus phosphorylation site motifs recognized by PKC isozymes, each of which has an essential basic amino acid (arginine (R) and/or lysine (K)) at the −2 and/or −3 amino-terminal position relative to that of the serine (S) or threonine (T) phosphorylation site. The five motifs are as follows: (R/K)X(S/T), (R/K)(R/K)X(S/T), (R/K)XX(S/T), (R/K)X(S/T)XR/K, and (R/K)XX(S/T)XR/K [12]. A list of target protein substrates for PKC isozymes and their phosphorylation sites are presented in Table S1 (see supplementary materials available online at http://dx.doi.org/10.1155/2014/231418) which has been modified and upgraded from a previous paper [12].

Through target protein phosphorylation, PKC isozymes can directly or indirectly participate in diverse biological phenomena, such as cell cycle regulation (e.g., MARCKS, p53, and p21 (also known as $p21^{Cip1}$ or $p21^{Waf1/Cip1}$)), cell adhesion (e.g., adducins and integrins), DNA synthesis and transcription (e.g., transcription factor C/EBP and glycogen

synthetase kinase 3β (GSK3β)), cell motility (e.g., RhoA and integrins), apoptosis (e.g., Bad and Bcl-2), drug resistance (e.g., P-glycoprotein (P-gp; also known as MDR1 or ABCB1)), and cell growth and differentiation (e.g., basic fibroblast growth factor (bFGF), epidermal growth factor receptor (EGFR), v-raf-1 murine leukemia viral oncogene homolog 1 (Raf1), and H-Ras) (Table S1).

Further, it is also possible for each PKC isozyme to phosphorylate unique "isozyme-specific" proteins, which can also alter cell function. These types of PKC isozyme-specific substrates or inhibitors may be useful for characterizing intracellular signaling pathways for each PKC isozyme. Although the function of PKC isozyme inhibitors and their clinical applications have been reported by several groups, PKC isozyme-specific inhibitors are very rare, with the majority of the inhibitor studies focusing on the use of bisindolylmaleimide (LY333531) and enzastaurin (LY317615) for PKCβ inhibition and antisense oligonucleotides (aprinocarsen (ISIS3521) and ISIS9606) for PKCα inhibition (e.g., for review, see [7, 13–16]). Furthermore, only two PKC isozyme-specific peptide substrates have been identified, peptide 422–426 (RFAVRDMRQTVAVGVIKAVDKK) of eukaryotic elongation factor-1α for PKCδ [17] and Alphatomega peptide (FKKQGSFAKKK) for PKCα [18], both of which have been utilized to characterize PKC isozyme-mediated cellular functions [19–21] and for developing cancer diagnostic [22, 23] or therapeutic tools [24–26].

3. PKC Isozymes and Cancer

In cancer cells, PKC isozymes are involved in cell proliferation, survival, invasion, migration, apoptosis, angiogenesis, and anticancer drug resistance through their increased or decreased participation in various cellular signaling pathways. During cancer cell proliferation and survival; for example, PKC isozymes stimulate survival or proliferation-associated signaling pathways, such as Ras/Raf/MEK/ERK or PI3K/Akt (also known as PKB)/mTOR pathways, but suppress the expression of cancer suppressor-associated or apoptotic signals such as caspase cascade or Bax subfamily (Figure 1). However, the activation statue of PKC isozymes and the downstream signaling cascades can be affected by different internal and external cellular conditions. This is particularly true during short- or long-term 12-*O*-tetradecanolyphorbol 13-acetate (TPA) treatment, whereby short-term TPA treatment increases PKC activation, but long-term treatment downregulates PKC isozyme function [2, 27].

Furthermore, the expression patterns and functions of PKC isozymes in cancer cells largely depend on the type of cancer being investigated; however, the mechanism is not clear. For example, PKCδ acts as an antiapoptotic regulator in chronic lymphocytic leukemia (CLL) but as a proapoptotic regulator in acute myeloid leukemia (AML) (see Section 3.10. Myeloid and lymphocytic leukemia). PKCα shows proliferative functions in several types of cancer but has antiproliferative functions in colon cancer cells (see Section 3.3. Colon cancer). Importantly, PKC isozymes that are specifically overexpressed in certain types of cancer can be used as diagnostic or therapeutic targets. Thus, understanding the role and expression of individual PKC isozymes in each type of cancer may help to elucidate important cues for discovering novel drugs and for developing diagnostic or therapeutic tools. This section further discusses PKC isozymes and their roles in multiple types of cancer cells as summarized in Table 1.

3.1. Bladder Cancer. PKCα, βI, βII, δ, ε, η, and ζ have all been detected in bladder cancer cells and tissues. PKCβI, βII, δ, and η are found primarily in low-grade and low-stage cancers and decrease with increasing cancer stage and grade. However, PKCα and ζ show the opposite expression pattern, increasing in levels as the cancer progresses [28–30], and are associated with more aggressive bladder cancer. Patients with a higher membrane/cytosol ratio of PKCα show a shorter recurrence-free period than patients with a lower membrane/cytosol ratio after treatment with the anticancer drug adriamycin. Further, transfection of PKCα into bladder cancer cells increases resistance against adriamycin [31]. It has also recently been shown that the phosphoinositide-specific phospholipase Cε (PLCε), an effector protein of Ras and Rap [32], induces the proliferation of human bladder cancer cell line BIU-87 through the activation of PKCα [33]. However, the PKCα-mediated proliferation of bladder cancer cells can be repressed. T24 cells treated with the PKCα/β inhibitor GO6976, for example, show $G_{0/1}$ arrest and reduced proliferation [34]. Moreover, addition of this inhibitor to bladder cancer cells 5637 and T24 results in more efficient inhibition of cell migration and invasion and greater promotion of cell-cell and cell-matrix junctions than those achieved using the PKCα inhibitor Safingol, which has similar but less pronounced effects [35].

Similarly, in T24 cells, the binding of hyaluronic acid (HA) fragments to CD44 can activate the NF-κB pathway through not only PKCζ, but also Ras and IκB kinases 1 and 2 [36]. Researchers have speculated that these signaling pathways may be related to cancer cell migration and invasion [37] or survival and antiapoptosis [38].

Activation of PKCδ and c-Jun N-terminal kinase (JNK) results in the depletion of growth factors, which reduces cell-cell adhesions, promotes reactive oxygen species (ROS) production, and increases T24 cell motility and scattering [39].

3.2. Breast Cancer. In breast cancer cells, several PKC isozymes, such as PKCα, β, δ, ε, ζ, η, and θ participate in cell proliferation, differentiation, survival, and apoptosis. Although PKCα is very important for controlling the proliferation of breast cancer cells through the activation of extracellular signal-regulated kinase (ERK) [40] and telomerase [41], many research efforts focus on its function in metastasis and drug resistance. PKCα expression contributes to the metastasis of breast cancer cells through upregulation of activity of matrix metalloproteinases (MMPs) (e.g., MMP-9) [42–44], urokinase-type plasminogen activator (uPA) [44, 45], NF-κB [42], and osteopontin receptor $\alpha v\beta 3$ [46], as

Table 1: PKC isozymes and their roles in multiple types of cancer cells.

Cancer types	PKC isozymes	Roles of PKC isozymes	References
Bladder cancer	PKCα	Cell proliferation and anticancer drug resistance	[31, 33]
	PKCδ	Cell motility	[39]
Breast cancer	PKCα	Cell proliferation and metastasis, antiapoptosis, antiestrogen resistance	[40, 42, 43, 45, 50, 53]
	PKCε	Cell metastasis and antiapoptosis	[63, 65, 67]
	PKCη	Cell growth, survival, and antiapoptosis	[68–70, 72]
	PKCζ	Cell metastasis	[74]
	PKCδ	Cell survival, migration, invasion, proliferation, antiestrogen resistance, and proapoptosis	[80, 83, 84, 86, 88, 90, 92, 94, 97]
Colon cancer	PKCα	Antiproliferation and anticancer drug resistance	[110–112, 119, 120]
	PKCβII	Cell proliferation and invasion when cells overexpressing PKCβII are used	[123, 124, 130]
	PKCι	Carcinogenesis	[134, 135]
	PKCζ	Antiproliferation, differentiation, and proapoptosis	[136–138]
	PKCδ	Cell proliferation and pro- and antiapoptosis	[142, 144, 145, 147, 152, 153]
Gastric (stomach) cancer	PKCα	Cell proliferation and antiapoptosis	[158, 160, 161]
	PKCβI	Antiapoptosis	[164, 165]
	PKCδ	Cell invasion and proapoptosis	[170–172]
Gastrointestinal stromal tumor (GIST)	PKCθ	Cell proliferation and antiapoptosis	[175]
Glioma	PKCα	Cell proliferation, survival, invasion, migration, antiapoptosis, and anticancer drug resistance	[189, 190, 192, 196, 197, 204]
	PKCε	Cell survival, invasion, migration, and antiapoptosis	[206, 207, 209]
	PKCζ	Cell proliferation, survival, invasion, and migration	[212–214, 216, 217]
	PKCι	Cell proliferation, survival, and invasion	[218, 220, 221, 223]
	PKCη	Cell proliferation and antiapoptosis	[224, 225, 227]
	PKCδ	Cell proliferation, invasion, and pro-/antiapoptosis	[228–231, 240–242]
Head and neck cancer	PKCα	Cell growth and survival	[245–247]
	PKCε	Cell proliferation and invasion	[248, 249]
	PKCζ	Cell proliferation, invasion, and migration	[250, 251, 253]
	PKCι	Cell proliferation and antiapoptosis	[256, 257]
Liver cancer (hepatocellular carcinoma)	PKCα	Cell growth, invasion, and migration	[269, 271, 272, 276, 280]
	PKCε	Cell growth and migration	[276, 285]
	PKCδ	Cell invasion and migration	[282]
Lung cancer	PKCα	Cell proliferation, metastasis, and antiapoptosis	[288, 291, 293]
	PKCε	Cell proliferation, metastasis, and antiapoptosis	[299, 301, 303–305]
	PKCι	Cell growth, survival, and invasion	[307, 308, 311, 313]
	PKCη	Cell metastasis and antiapoptosis	[321, 322]
	PKCδ	Cell survival, invasion, migration, and antiapoptosis	[323–326]
Melanoma	PKCα	Cell survival, invasion, and migration	[336, 337]
	PKCε	Antiapoptosis	[342–344]
	PKCδ	Cell metastasis	[347, 348]
Myeloid and lymphocytic leukemia			
Acute lymphocytic leukemia (ALL)	PKCα	Anticancer drug resistance	[367]
Chronic lymphocytic leukemia (CLL)	PKCβ	Cell survival	[357]
Acute myeloid leukemia (AML)	PKCβII	Cell proliferation, survival, and antiapoptosis	[351, 359, 360, 363]
	PKCδ	Cell survival	[364, 365]
Chronic myeloid leukemia (CML)	PKCα	Antiapoptosis	[370, 376, 379]
	PKCδ	Proapoptosis	[382–386]
	PKCβII	Cell proliferation and survival	[368]
	PKCδ	Proapoptosis	[374, 375]

Table 1: Continued.

Cancer types	PKC isozymes	Roles of PKC isozymes	References
Ovarian cancer	PKCα	Cell proliferation and invasion	[389, 390]
	PKCι	Cell proliferation	[392, 393]
	PKCζ	Proapoptosis	[394]
Pancreatic cancer	PKCα	Cell differentiation, migration, and antiapoptosis	[397, 398, 400, 401]
	PKCζ	Cell survival and metastasis	[405, 407, 408]
	PKCι	Angiogenesis and cell metastasis	[409, 411]
	PKCβI	Cell migration and antiapoptosis	[412]
	PKCδ	Cell growth and anticancer drug resistance	[416, 417]
Prostate cancer	PKCα	Cell growth, migration, invasion, angiogenesis, and pro-/antiapoptosis	[425, 428–432, 436]
	PKCε	Cell growth, survival, invasion, antiapoptosis, and anticancer drug resistance	[438–441, 443–445, 447]
	PKCζ	Cell proliferation	[456]
	PKCη	Antiapoptosis	[457]
	PKCβII	Cell growth and angiogenesis	[458]
	PKCδ	Cell migration, invasion, angiogenesis, and proapoptosis	[420, 459, 460, 468–470]
Renal cell carcinoma (kidney cancer)	PKCα	Cell invasion	[475]
	PKCε	Cell growth, invasion, and migration	[475, 479]
	PKCδ	Cell migration and invasion	[482–484]
Thyroid cancer	PKCα	Cell survival	[485, 486]
	PKCε	Cell survival and pro-/antiapoptosis	[492–494]
	PKCδ	Antiproliferation and cell migration	[497–499]

well as through increasing the cell surface levels of C-X-C chemokine receptor type 4 (CXCR4) (also known as CXCL12), which is also associated with lung metastasis of breast cancer cells [42]. During tyrosine kinase receptor ErbB2 (also known as HER2, CD340, or neu)-mediated breast cancer cell invasion, ErbB2 upregulates PKCα through c-Src kinase, leading to upregulation of uPA and uPA receptors that facilitate cell invasion and migration [44, 45].

Antiestrogen hormonal therapy (e.g., tamoxifen (TAM)) is effective for estrogen receptor α (ERα) positive/progesterone receptor positive breast cancers; however, resistance to this treatment is one of major issues to be overcome in breast cancer therapy. Breast cancer antiestrogen resistance is mainly due to the loss of ERα, but it can still occur when ERα is still present [47–49]. Further, research has indicated that PKCα may be a critical factor in breast cancer antiestrogen resistance. PKCα and ERα expression are inversely related [47] and PKCα is positively correlated with triple-negative breast cancers, which show no expression of ERs, progesterone receptors, or ErbB2 [50, 51]. Breast cancer cells with overexpression of PKCα also show high resistance for TAM treatment and hormone (e.g., estrogen)-independent growth [52–55], but inhibition of PKCα induces TAM sensitivity [53–55]. The underlying mechanism of breast cancer antiestrogen resistance also includes ERK2 activation by PKCα [48]. In addition, PKCα expression in breast cancer cells inhibits heregulin-induced apoptosis through the upregulation of Bcl-2 and downregulation of caspase-7 [56]. PKCα also participates in multidrug resistance (MDR) in breast cancer cells [57, 58]. Overexpression of PKCα in MCF-7 cells alters β5- and β3-integrin expression by translational and posttranslational mechanisms, respectively, leading to the increased metastatic capacity of cancer cells [59]. Thus, PKCα expression in breast cancer cells may be closely associated with poor prognosis and survival [49, 60].

In a previous study, activation of PKCβI and βII in MCF-7 cells promoted growth and enhanced expression of cyclin D1, which is a regulator of G_1 to S phase transition in mammalian cells [61]. Contrary to this, Grossoni's group has reported that overexpression of PKCβ1 in the breast cancer cell line LM3 actually reduces cell growth and expression of the metastasis-related proteases, uPA, and MMP-2 [62]. Thus, further research is required to decipher the true function of the PKCβ1 and PKCβ1I isozymes in breast cancer.

For PKCε, downregulation along with the overexpression of microRNA miR-31 appears to reduce oncogenic NF-κB activity and enhance apoptosis and chemo- and radiosensitivity of breast cancer cells. These responses are caused by impaired expression of antiapoptotic Bcl-2 protein [63]. However, when PKCε activation occurs through HA binding to its receptor CD44, it increases the Nanog-mediated miR-21 production in MCF-7 cells. This process inhibits production of the tumor suppressor protein PDCD4, while enhancing the expression of antiapoptosis genes and anticancer drug resistance in MCF-7 cells [38]. In addition, activation of

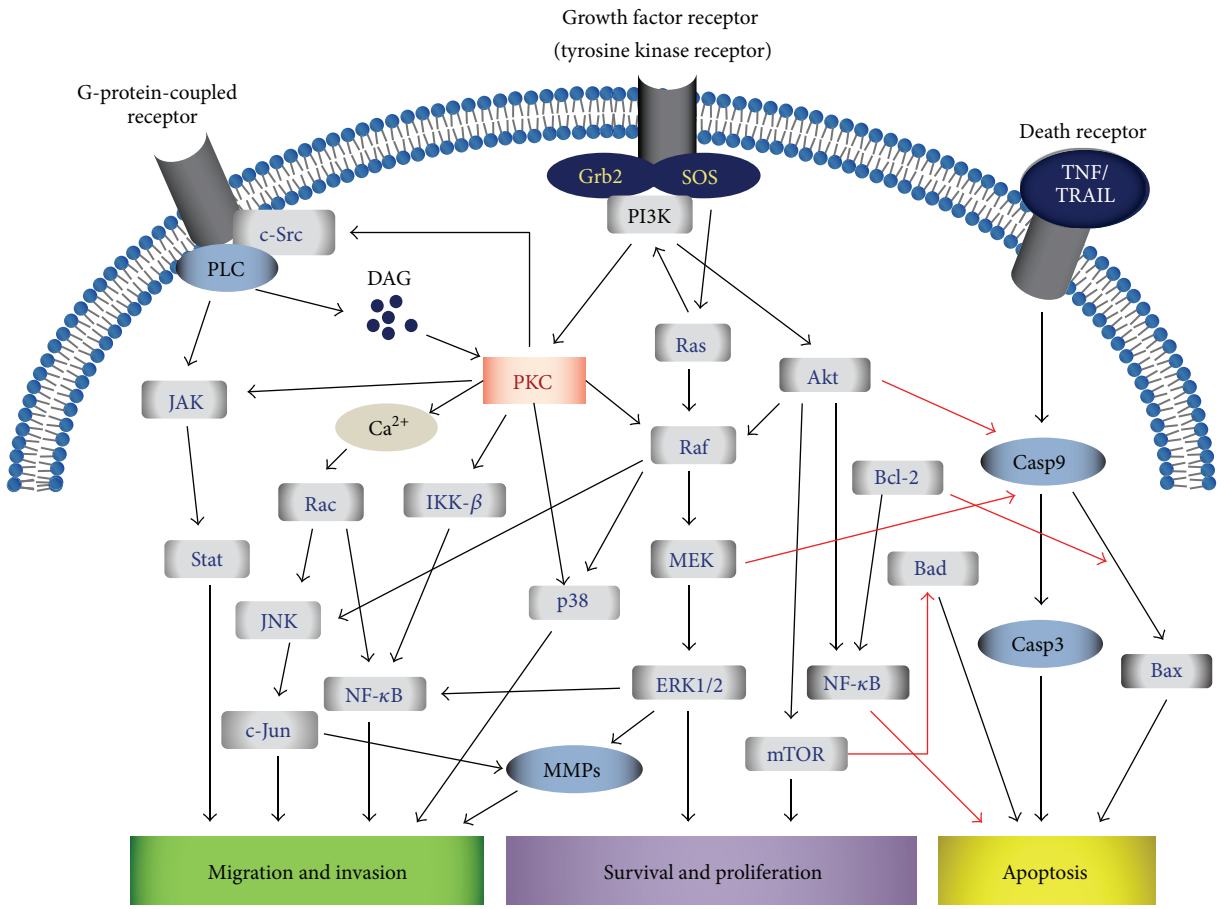

FIGURE 1: Multiple signaling pathways, involving PKC isozyme regulation and signal transduction, are affected during cancer. PKC isozymes directly or indirectly participate in diverse biological phenomena in cancer cells such as cell migration, invasion, survival, proliferation, and apoptosis. Casp, caspase; JAK, Janus kinase; Grb2, growth factor receptor-bound protein 2; SOS, son of sevenless homolog; also see abbreviations in the text. Black arrows indicate activation cascade, while red arrows are used to show the inhibition cascade.

glucocorticoid receptor (GR) by stimulating GR agonists, such as hydrocortisone and dexamethasone, can inhibit p53-dependent apoptosis of breast cancer cells through an increase in the levels of PKCε messenger RNA (mRNA) and protein [64]. PKCε can also protect breast cancer cells from major death factor tumor necrosis factor α (TNFα)-induced cell death through DNA-dependent protein kinase-mediated Akt activation [65], Akt-dependent murine double minute 2 activation, and p53 downregulation [66]. Further, PKCε-induced polymeric fibronectin assembly is required for the pulmonary metastasis of breast cancer cells [67].

Upregulation of PKCη in malignant breast cells is also associated with cancer cell growth and survival [68], likely through hormone-dependent cell growth pathways [69]. PKCη expression in the membrane of breast cancer cells after chemotherapy tends to predict a poor patient prognosis [70]. PKCη-mediated inhibition of proapoptotic JNK activity protects breast cancer cells from chemotherapy and irradiation therapy [71]. In addition, overexpression of PKCη delays TNF-induced cell death in MCF-7 cells by reducing the activation of caspase-8 and caspase-7 [72]. In spite of low levels of PKCη being found in most invasive breast cancer lesions (75%), invasive cancers containing high PKCη are associated with positive lymph node status [73].

PKCζ-mediated hepatocyte growth factor (HGF) activation increases CXCR4 expression, resulting in breast cancer cell metastasis [74]. PKCζ also stimulates estrogen-mediated breast cancer cell growth by stabilizing steroid receptor coactivator-3 (SRC-3; also known as AIB1, ACTR, pCIP, RAC3, or TRAM-1) [75]. On the other hand, overexpression of PKCζ can inhibit growth factor-mediated Akt phosphorylation and activation, namely, through feedback inhibition of the phosphatidylinositol 3-kinase (PI3K)/Akt signaling cascade [76].

Accumulation of PKCθ-activated Fra-1 in invasive, ER-negative breast cancer cells has been associated with increased cell invasion and migration [77]. In addition, PKCθ-mediated Akt activation inhibits forkhead box class-O 3a (FOXO3a), which is the transcriptional activator of ERα promoter B and its targets, ERα and $p27^{Kip1}$, and also induces c-Rel activation, which has been associated with the early development of breast cancer cells. These signaling

changes by Akt activation result in proliferation, survival, and invasion of breast cancer cells [78].

PKCδ isozyme shows both prosurvival and proapoptotic functions in breast cancer cells. PKCδ expression is significantly higher in ER-positive than ER-negative breast cancers and is associated with poor patient survival [79]. PKCδ promotes survival of breast cancer cells through the inhibition or activation of several signaling pathways, such as inhibition of TNF-related apoptosis-inducing ligand (TRAIL)-induced caspase activation [80, 81], inhibition of Notch1 intracellular domain-dependent transcriptional activity [82], reduction of anticancer drug taxol-induced monocyte chemoattractant protein-1 expression [83], and activation of Akt and NF-κB [84, 85]. PKCδ also shows increased antiestrogen resistance in estrogen- and TAM-induced MCF-7 cells through the activation of Akt and mitogen-activated protein kinases (MAPKs) [86]. In ER negative MDA-MB-231 breast cancer cells, PKCδ supports their survival by inhibiting ERK1/2 activation and increasing the levels of ERK1/2 phosphatase MKP3 and its regulator, E3 ubiquitin ligase Nedd4 [87].

On the other hand, proapoptotic effects of PKCδ in breast cancer cells have also been reported. Exposure of MCF-7 cells to ultraviolet (UV) light increases apoptosis of cells through PKCδ-dependent phosphorylation of acid sphingomyelinase [88]. Furthermore, sangivamycin, an antiproliferative agent, induces mitochondria-mediated apoptotic cell death of MCF-7/ADR cells by increasing JNK phosphorylation and cleavage of lamin A and poly (ADP-ribose) polymerase. These apoptotic responses have all been identified as being PKCδ-dependent [89]. Treating MCF-7 cells with inositol hexaphosphate (IP_6) causes an increase of PKCδ associated with a decrease of ERK1/2 and Akt activation. This IP_6-mediated PKCδ activation enhances upregulation of $p27^{Kip}$ and hyperphosphorylation of retinoblastoma protein (pRb or Rb), resulting in an increase in apoptosis (G_1 arrest) of MCF-7 cells [90]. PKCδ-dependent inhibition of ERK1/2 and upregulation of JNK also lead to G_1 arrest in SKBR3 breast cancer cells after phorbol-myristate-acetate (PMA; note that a common alternative name for PMA is TPA) treatment [91].

In addition, PKCδ acts as a proliferative signal in breast cancer cells. PKCδ elevates cell proliferation in ErbB2-positive breast cancer cells via c-Src and ERK activation [92]. The inflammatory mediator bradykinin (BK) is required for the PKCδ/ε/Akt/ERK1/2 signaling complex utilized to mediate MCF-7 cell proliferation [93]. In estrogen-dependent breast cancer cells, TPA-mediated PKCδ activation leads to activation and nuclear translocation of ERα and enhanced ER-dependent reporter gene expression thereby suggesting a role of PKCδ as a proproliferative factor [94]. Cell proliferation requiring estrogen (e.g., 17-β-estradiol) also needs ERK1/2 activation through the HRG/HER-2/PKCδ/Ras pathway [95]. Interestingly, TPA-induced PKCδ activation in ER negative cells shows a different pattern compared to ER positive breast cancer cells. The increase in PKCδ expression is significantly higher in ER positive MCF-7 cells than in ER negative MDA-MB-231 cells, leading to higher levels of cyclin dependent kinase (Cdk) inhibitor $p21^{Waf1/Cip1}$ in MCF-7 cells [96].

In addition to its proapoptotic, prosurvival, and proliferative functions, PKCδ also plays a critical role in breast cancer cell migration and invasion. In highly metastatic breast cancer cell lines (e.g., MDA-MB-231 and C3L5), expression of PKCδ efficiently increases cell migration and invasion by inhibiting the small GTPase Cdc42 [97]. TPA-induced MMP-9 activation and migration of breast cancer cells are also stimulated by the PKCδ/ERK/c-Jun/activator protein-1 signaling pathway, but quercetin and kalopanaxsaponin can be used to block these signaling pathways [98, 99]. Moreover, platelets can promote invasion of MCF-7 cells through the activation of PKCδ and upregulation of MMP-9 [100]. In contrast, Jackson's group has demonstrated that PKCδ suppresses MMP-9 secretion and breast cancer cell survival and migration [101].

3.3. Colon Cancer. PKCα, β, δ, ε, and ζ are found in both rat and human colonic mucosa, while PKCη is detected in human colonic mucosa only [102]. There is no difference in the levels of PKCα, δ, and ε mRNA between normal mucosa and human colon adenocarcinoma, but the levels PKCβ and η mRNAs are significantly lower in human colon adenocarcinoma than in normal mucosa. The reduction of PKCβ and η mRNA occurs early in the multistage process of colon carcinogenesis [103]. Western blotting analysis, on the other hand, has indicated that expression of PKCβ and ε protein is significantly decreased in colon cancer tissues, while PKCα and ζ show no significant difference in expression between normal mucosa and colon cancer tissues [104].

In a recent study, colon epithelial cells (CECs) showed high levels of PKCε with no TRAIL expression, but luminal CECs show the opposite result. This support previous results indicating that PKCε is required for TRAIL-induced differentiation of the colorectal cancer cell line HT29 [105]. Further, activated PKCε is also necessary for proteinase-activated receptor 1 (PAR1)-mediated HT29 cell migration and matrix adhesion [106].

Although the levels of PKCα are similar between normal and cancerous colon tissue, increasing evidence shows that PKCα does participate in growth arrest [107, 108] and cancer suppression in the intestine epithelium [109–113]. Suppression of cell growth in colon cancer cells by PKCα is thought to occur through the regulation of EGFR signaling [110]; ERK-mediated inhibition of the inhibitor of DNA binding 1, a proproliferative factor [112]; downregulation of β-catenin and its target genes *cyclin D1* and *c-Myc* [111, 113]; and PKCα-mediated phosphorylation of retinoic acid-related orphan nuclear receptor α, which downregulates the Wnt/β-catenin signaling [114]. In contrast to these results, a recent study has suggested that PKCα activation is involved in the activation of ERK1/2/NF-κB through the tissue factor/VIIa/PAR2 pathway and this signaling pathway leads to enhanced proliferation, migration, and survival for the colon cancer cell line SW620 [115].

Alternately, PKCα can also enhance cell adhesion and anticancer resistance through a different signal pathway than that used during antiproliferation. High migratory activity of colon cancer cells is related to high PKCα and low E-cadherin

expression [116]. PKCα also regulates transforming growth factor (TGF)-β1-induced expression of the matrix adhesion molecules, fibronectin and laminin, leading to the induction of E-cadherin [117, 118]. In addition, PKCα can induce P-gp-mediated MDR in human colon cancer cells [119–121]; thus, downregulation of PKCα may increase the sensitivity to anticancer agents [122].

The low levels of PKCβ in colon cancer cells allow transgenic mice and cells stably expressing PKCβ to be used to investigate the role of PKCβ in colon cancer cells. In transgenic PKCβII animals and PKCβII-expressing cell lines, the presence of PKCβII results in hyperproliferation of intestinal epithelial cells and enhanced cancer formation after exposure to azoxymethane, a potent carcinogen used to induce colon cancer [123–126]. These responses are achieved through the reduction of TGF-β receptor type II expression and associated growth inhibition [124, 127], activation of Wnt/adenomatous polyposis coli/β-catenin proliferative signaling [123], and reduction of cyclooxygenase type 2 (Cox-2) expression [127]. Overexpression of PKCβII also induces invasion in intestinal epithelial cells through a Ras/PKCι/Rac1/MAPK kinase (MEK)-dependent signaling pathway [128] and represses apoptosis at the luminal surface in transgenic rats [129].

PKCβI is activated in the presence of secondary bile acids (e.g., deoxycholic acid, lithocholic acid, and ursodeoxycholic acid) in colon cancer tissues [104]. Furthermore, the human colon adenocarcinoma cell line HT-29 stably expressing PKCβ1 shows high resistance to TNFα- and paclitaxel-induced apoptosis [130]. Overexpression of PKCβI and βII in differentiated colon carcinoma HD3 cells blocks their differentiation but increases their proliferation through p57 MAPK activation [131, 132]. These data suggest that PKCβ inhibitors (e.g., enzastaurin) may be efficient for the prevention of colon cancer because PKCβI and II appear to be involved in carcinogen-induced colon cancer initiation and progression [122, 124, 125, 133].

PKCι is also required for Ras- and azoxymethane-induced colon carcinogenesis [134, 135], but unlike PKCβII, PKCι functions mainly in the later stage of azoxymethane-induced colon carcinogenesis and is essential for mutant adenomatous polyposis coli (APC)-mediated carcinogenesis [135].

Like PKCα, PKCζ protein expression does not differ between normal and cancerous tissues, but PKCζ does appear to be associated with the inhibition of colon cancer cell growth and enhancement of differentiation and apoptosis [136, 137]. In a recent study, the loss of PKCζ resulted in an increase in intestinal carcinogenesis, upregulation of two metabolic enzymes, 3-phosphoglycerate dehydrogenase and phosphoserine aminotransferase-1, and inhibition of caspase-3 activation. Thus, colon cancer patients with low levels of PKCζ show a significantly poorer prognosis, compared with patients with higher levels [138]. In contrast, PKCζ stably depleted SW480 colon cancer cells by decreasing cell proliferation, expression of Wnt target gene *c-Myc*, and tumorigenic activity in grafted mice [139]. Dexniguldipine hydrochloride (B8509-035) also suppresses the growth of HT-29 cells through the inhibition of PKCζ expression [140]. Similar to PKCβ, PKCζ could likely be an efficient target for chemoprevention of colon cancer [141]. Thus, further research is needed to understand the true function of PKCζ in colon cancer.

In colon cancer cells, PKCδ can inhibit cell growth and proliferation by mediating changes in several cellular signaling pathways by enhancing phosphorylation of APC [142], p53 expression [143, 144], and $p21^{Waf1/Cip1}$ activity [144] and by reducing β-catenin stabilization [140] and cyclins (e.g., D1, D3, and E) [145, 146].

PKCδ expression may also act as a proapoptotic regulator in colon cancer cells. This regulation is required for G_0/G_1 arrest [147], inhibition of anchorage-independent growth [147], and enhanced Bax levels [146]. The apoptotic pathway utilized by PKCδ also appears to be independent of caspase-3 [148]. In contrast, PKCδ may have antiapoptotic functions as well. For example, apoptosis is prevented by the PKCδ/NF-κB/cIAP-2 pathway [149] and activation of the FLICE-like inhibitory protein [150].

Furthermore, PKCδ is involved in colon cancer cell migration and invasion through activation of the metastasis enhancing protein KITENIN [151], KIT-SCF activation, PKCδ-induced KIT recycling [152], phosphorylation of the mRNA-binding protein HuR at serine 318 [153], and stimulation of Nox1-dependent superoxide production [154].

3.4. Gastric (Stomach) Cancer

3.4.1. General Gastric Carcinoma. Overexpression of PKCα in human gastric carcinoma is significantly correlated to poor prognosis and clinicopathological parameters, such as histologic type, depth of invasion, pathologic stage, and distant metastasis [155, 156]. In the vincristine-induced MDR human gastric cancer cell line SGC7901/vincristine, higher levels of PKCα are found compared with those detected in untreated (i.e., not MDR) SGC7901 cells [157]. Thus, inhibition of PKCα may enhance antiproliferative and proapoptotic signaling in gastric cancer cells thereby increasing the therapeutic efficacy for gastric cancer [158–161]. In contrast, addition of TPA to gastric cancer cells enhances PKCα-mediated cell apoptosis [162, 163].

After addition of indomethacin, a nonsteroidal anti-inflammatory drug, into gastric cancer cells, PKCβI, but not PKCβII, acts as a mediator of cancer cell survival, and its overexpression, which is associated with overexpression of $p21^{Waf1/Cip1}$ promotes activation of antiapoptotic mechanism [164, 165]. On the other hand, addition of the PKCβ inhibitor enzastaurin into gastric cancer cells induces apoptosis through the ribosomal S6 kinase and Bad pathways [166].

Gastric adenocarcinoma exhibits loss of PKCζ [167], while overexpression of PKCλ/ι can be a prognostic factor for gastric cancer recurrence [168]. However, low PKCλ/ι expression along with high expression of kidney and brain protein (KIBRA; also known as WWC1), which is a scaffold protein containing aPKC-binding domains, has also been shown to have detrimental results, as they are correlated with invasion and poor prognosis in gastric cancer [169].

PKCδ positively controls cisplatin- and sphingosine-induced cell death in MKN28 cells. The former is correlated with overexpression of p53 and the latter with enhanced SDK and caspase-9 production [170, 171]. In addition, enhanced PKCδ expression and phosphorylation can increase cell motility and invasion by cooperating with the Smad-dependent TGF-β1 pathway and integrin (α2 or α3) expression and activation [172].

3.4.2. Gastrointestinal Stromal Tumor. Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract, being primarily found in the stomach and small intestine. The five-year survival rate of patients with KIT-negative GIST is lower than that of patients with KIT-positive GIST (KIT is also known as CD117, proto-oncogene c-kit, tyrosine-protein kinase Kit, or mast/stem cell growth factor receptor) [173]. PKCθ expression is observed in GISTs but is undetectable in other mesenchymal tumors, including non-GIST soft tissue sarcomas [174]. PKCθ knockdown in KIT-positive GISTs leads to inhibition of PI3K/Akt signaling, upregulation of the cyclin-dependent kinase inhibitors p21 and p27, and induction of antiproliferative and apoptotic factors [175]. Thus, PKCθ is recognized as a useful biomarker for the diagnosis of KIT- and/or DOG1-negative GISTs [176–178], while it shows high sensitivity toward KIT-positive GISTs [174, 179, 180]. However, it should be noted that these sensitivity and specificity of PKCθ toward KIT-negative GISTs were not observed in all studies [173].

3.5. Glioma. Among gliomas, astrocytomas are the most common and are classified in four prognostic grades: pilocytic astrocytoma (grade I), low-grade astrocytoma (grade II), anaplastic astrocytoma (grade III), and glioblastoma (grade IV). Grade III and IV are considered to be the most rapidly progressive, invasive malignant gliomas [181]. In the rat malignant glioma cell line C6, one study has reported the detection of PKCα, δ, ε, and ζ [182], but González's group did not detect PKCζ in these cells [183]. Moreover, PKCα, γ, δ (very low levels), ε, and ζ have been identified in multiple human malignant glioma cell lines (e.g., A172, A2781, U87, U138, U373, and A1235) and tissues [184–186]. For PKCβ, there are conflicting reports, some which indicate PKCβ detection [186, 187], while others show no PKCβ expression [184, 185, 188]. In TPA-treated glioma cells, PKCα is translocated from the cytosolic fraction to the membrane following short-term exposure but is downregulated following long-term exposures [182, 185].

Higher levels of PKCα in malignant gliomas compared to low-grade astrocytomas result in enhanced proliferation and decreased apoptosis for the malignant gliomas [186]. PKCα-mediated ERK1/2 activation is also required for the proliferation and survival of glioma cells [189]. Moreover, PKCα acts as a signaling intermediate between EGFR and mammalian target of rapamycin (mTOR) in glioma cells; the activation of which leads to Akt-independent proliferation of glioma cells [190]. Interestingly, PKCα protein, but not its activity, is essential for glioma cell proliferation and survival. These results mean that the use of adenosine triphosphate (ATP) competitive inhibitors to treat glioma will be less efficient [191]. In addition, increased expression of glutamate transporters, also known as excitatory amino-acid transporters, leads to prolonged survival and reduced tumor growth in glioma-bearing animals [192]. Further, PKCα is involved in the activation and redistribution of glutamate transporters [183, 193, 194]. However, there is a report that inhibition of PKCα and ε has no effect on proliferation of glioma cells thereby suggesting no therapeutic benefit of PKCα in regard to proliferation prevention [195].

Cooperation of inhibition of PKCα and suppression of glutathione S-transferase P1, which is associated with anticancer drug resistance, can efficiently increase the apoptosis of glioma cells by the anticancer drug cisplatin [196]. Combination of endostatin, an inhibitor of angiogenesis, and PKCα inhibition significantly increases the survival of malignant glioma-bearing animals [197]. Reduction of the antiapoptotic protein Bcl-XL is also involved in glioma cell death through the inhibition of PKCα [198]. However, aprinocarsen, an antisense oligonucleotide against PKCα, shows no clinical benefit in patients with recurrent high-grade astrocytomas [199].

There are many reports proving a close relationship between PKCα expression and high invasion and migration of malignant glioma cells [200–204]. As mentioned above, translocation of PKCα from the cytosolic fraction to the glioma cell membrane after TPA treatment increases ERK/NF-κB-dependent MMP-9 activation and cell migration [200]. PKCα-induced phosphorylation and downregulation of low-density lipoprotein receptor-related protein stimulate the secretion of uPA and the invasion of glioma cells into the surrounding normal brain tissue [201]. Furthermore, invasion and migration of glioma cells involve several signaling pathways such as PKCα-mediated N-cadherin cleavage [202], increased motility by PKCα-mediated NG2 phosphorylation at Thr-2256 [203], and PKCα or ε/SRF-mediated RTVP-1 expression [204].

PKCε also appears to be overexpressed in malignant glioma cell lines and tissues (grades III and IV) [184–186, 205]. Its overexpression in glioma cells inhibits proteasome inhibitor- and TRAIL-induced apoptosis and increases cell survival [206, 207]. Signal transducers and activators of transcription 3 (Stat3) activation by PKCε in glioma cells also stimulate cell invasion. These responses are found in not only glioma, but also several additional types of human cancer cells, including prostate, skin (melanoma), bladder, colon, lung, pancreatic, and breast [208]. Furthermore, galectin-1, a homodimeric adhesion molecule, is linked with the trafficking of β1-integrin, which is controlled by a PKCε/vimentin-dependent pathway. These molecular responses are important for glioma cell migration [209]. In PMA-induced adhesion and migration of glioma cells, PKCε shows different response compared to PKCα in regard to ERK activation. PKCε induces the activation of ERK at focal adhesions, while PKCα induces the activation of nuclear ERK [210]. Importantly, inhibition of PKCε has been shown to block the proliferation of glioma cells [211].

PKCζ may also be a therapeutic target for treating gliomas because of its involvement in proliferation, invasion,

and migration of glioma cells. Phosphorylated PKC$\theta/\delta/\beta$1-integrin and PKC ζ/β1-integrin complexes are stimulated following radiation exposure, resulting in enhanced radioresistance of glioma cells [212]. Further, downregulation of uPA receptor and cathepsin B using small hairpin RNA efficiently disrupts these complex formations [212]. In addition to β1-integrin activation [212, 213], PKCζ is involved in glioma cell migration and invasion by controlling its interaction with ZIP/p62 [214] and MMP-9 expression [213, 215]. Furthermore, PKCζ also plays a key role in the proliferation of glioma cells, which in C6 cells is modulated through $P2Y_{12}$ receptor signal transduction by the RhoA-dependent PKCζ/Raf1/MEK/ERK pathway [216]. Activation of PKCζ/p70S6K pathway by muscarinic acetylcholine receptor also increases carbachol-induced DNA synthesis and proliferation in 1321 N1 astrocytoma cells [217].

Although previous studies have failed to show the existence of PKCι in normal glioma cells [184–186], PKCι is abundant in all malignant gliomas, especially in highly proliferative glioma cell lines, such as T98G and U-138MG [218]. Proliferation of glioma cells is controlled through the PI3K/PKCι/Cdk7/Cdk2-mediated pathway [219, 220]. Inactivation of Bad and disruption of the Bad/Bcl-XL dimer by PKCι also enhance glioma cell survival [221]. Furthermore, PKCι participates in antiapoptosis of glioma cells through the downregulation of p38 MAPK signaling [222] and glioma cell invasion and motility through the repression of actin stress fiber formation by RhoB [223].

Although PKCη shows low detection rates in glioma cell lines [195], its potential as a therapeutic target for glioma has been demonstrated. PKCη expression enhances glioma proliferation and cell growth through MEK1/2/ERK1/2/Elk-1 [224] or Akt/mTOR pathways [225]. PKCη also plays an important role in rapamycin-insensitive cell proliferation [226]. Moreover, PKCη expression increases glioma cell resistance to UV- and γ-irradiation-induced apoptosis through the downregulation of caspase-9 activation [227].

PKCδ phosphorylation at tyrosine 311 (e.g., by c-Ab1 tyrosine kinase) and 332 (e.g., by c-Src tyrosine kinase) is an important process during caspase-3-dependent cleavage of PKCδ, a process that can enhance apoptosis of glioma cells [228, 229]. For example, PKCδ phosphorylation at tyrosine 332 by c-Src increases the sensitivity of glioma cells to TRAIL and cisplatin [228]. Moreover, different locations of PKCδ expression in glioma cells can influence its proapoptotic and antiapoptotic effects. Cytosolic PKCδ increases p38 phosphorylation and decreases Akt phosphorylation and expression of X-linked inhibitor of apoptosis protein (XIAP), while nuclear PKCδ increases JNK activation, all of which result in enhanced apoptotic effects. However, PKCδ localized in the endoplasmic reticulum leads to antiapoptosis of glioma cells [230]. Phosphorylation at tyrosine 155 and cleavage of PKCδ increase its translocation to the endoplasmic reticulum and ability to block TRAIL-induced apoptosis [231]. Phosphorylation of PKCδ at tyrosine 52, 64, and 155 is associated with the virulent strain of Sindbis virus neurovirulent and can induce glioma cell apoptosis [232]. Phosphorylation of PKCδ at 64 and 287 is also essential for the apoptotic effect observed after etoposide treatment [233–235]. Furthermore, penta-acetyl geniposide-induced apoptosis requires the interaction of activated neutral sphingomyelinase and p75, which is mediated by activated PKCδ [236, 237]. PKCδ-mediated ROS production has also been indicated to increase paraquat (1,1′-dimethyl-4,4′-bipyridinium)-induced glioma cell death [238]. In a recent study, however, activation of PKCδ in patient-derived glioma cells increased the fractionated-radiation-induced expansion of glioma-initiating cells and resistance to cancer treatment [239].

EGFR transactivation by enhanced PKCδ/c-Src signaling pathway stimulates glioma cell proliferation [240]. Activation of PKCδ also stimulates glioma cell invasion and motility by EGF-induced translocation of sphingosine kinase 1 and upregulation of plasminogen activator inhibitor-1 [241] as well as tenascin-C-induced upregulation of MMP-12 [242].

3.6. Head and Neck Cancer. Head and neck cancers occur mainly in the squamous cells of the oropharynx, oral cavity, hypopharynx, and larynx and are often referred to as head and neck squamous cell carcinomas (HNSCCs) [243, 244].

PKCα activation increases DNA synthesis and cell growth by activating ERK and cyclin E synthesis, but miR-105 acts as an inverse regulator for both DNA synthesis and cyclin E protein expression [245]. In chemokine receptor 7-positive HNSCC cells, PKCα is required for activation and nuclear translocation of NF-κB induced by chemokine (C-C motif) ligand 19, resulting in enhanced cell survival [246, 247].

PKCε, on the other hand, is involved in cell proliferation, DNA replication, and invasion in HNSCC cells [248, 249]. These cellular functions can be blocked by miR-107, which can inhibit PKCε activation [249]. PKCε-mediated HNSCC cell invasion and motility can be induced through activation of RhoA and C [248].

PKCζ activation by phosphorylation at tyrosine 417 plays an important role in EGF-mediated ERK activation, DNA synthesis, and cell proliferation in HNSCCs [250, 251], while depletion of PLC-γ1 or PI3K enhancer may abolish EGF-mediated SCC cell proliferation [252]. Furthermore, inhibition of PKCζ can reduce epithelial-mesenchymal transition (EMT), invasion, and migration of oral SCC mediated by the loss of interferon-induced protein with tetratricopeptide repeats 2 (IFIT2) and E-cadherin. Oral SCC patients with reduced IFIT2 levels show higher rates of metastasis and poorer prognoses compared with oral SCC patients with enhanced IFIT2 levels [253]. In addition, PKCα, βI, δ, and ζ are involved in the regulation of telomerase activity by direct or indirect phosphorylation of telomerase proteins, and PKCζ is also a key regulator in nasopharyngeal cancer originating in nasopharynx [254].

PKCι expression is elevated in HNSCCs [255]. Further, there is a positive relationship between PKCι expression and esophageal SCC cell size, lymph node metastasis, and clinical stage [256]. PKCι activation is also related to the expression of S-phase kinase-associated protein 2 through the PI3K/Akt pathway, leading to resistance of esophageal SCCs to anoikis [257]. However, downregulation of PKCι enhances the sensitivity of esophageal SCC KYSE30 cells to oxidative stress-induced apoptosis [258]. Thus, PKCι may

be related to poor SCC prognosis. It also seems that high nuclear PKCθ and PKCβII expression has been correlated to a high recurrence of oral SCCs and poor survival in patients [259, 260].

3.7. Liver Cancer [Hepatocellular Carcinoma (HCC)]. Five PKC isozymes α, βII, δ, ε, and ζ are present in normal rat hepatocytes, the rat HCC cell line FAO, and in the human HCC cell line HepG2 (all but PKCδ) [261]. In Hep3B cells, different patterns of PKC isozymes have been reported, such as PKCα, δ, ε, ζ, and ι [262] and PKCα, γ, δ, ε, and ζ [263]. Furthermore, PKCβII and θ are downregulated in human HCC tissues and are correlated with the grade of HCC and hepatitis B virus infection, respectively [264]. High levels of PKCι are detected in HCC tissues compared with that in adjacent normal tissues, and show a positive correlation with cyclin E expression, pathological differentiation, and cell invasion and metastasis [265, 266]. PKCη is downregulated in HCC tissues and its downregulation is correlated with poor long-term survival in patients [267].

PKCα expression is higher in poorly differentiated HCC (e.g., SK-Hep-1) than in well-differentiated HCC (e.g., HepG2 and Hep3B) [268]. A remarkable reduction of cell growth, migration, and invasion has also been identified in the poorly differentiated HCC cell type SK-Hep-1 treated with siRNA PKCα or antisense PKCα oligonucleotide. These responses are associated with the downregulation of p38, rather than JNK and ERK signaling, indicating that p38 plays a key role in PKCα-mediated HCC cell invasion [269]. Furthermore, Tsai's group has reported that lower levels of membrane-bound PKCα are detected in surgical specimens of HCC compared to adjacent normal tissue and they hypothesize that a negative correlation exists between PKCα activity and the size of HCC [270]. In HepG2 cells, TPA-induced generation of ROS is PKCα-dependent and leads to sustained activation of PKCα and ERK along with a reduction of E-cadherin. These changes in signaling stimulate HepG2 migration and cell cycle arrest [271–273]. TPA-induced growth arrest in the G_0/G_1 phase, upregulation of cancer suppressor gene miR-101, and downregulation of enhancer of zeste homolog 2 during embryonic ectoderm development in HepG2 cells are all PKCα-dependent [274]. Downregulation of PKCα by adding TPA into Hep3B cells also decreases the production of erythropoietin [263], which is a glycoprotein hormone that is stimulated under the hypoxic environment [275]. On the other hand, expression of PKCα and δ suppresses HGF-induced phosphorylation of ERK and paxillin, resulting in the reduction of HepG2 cell migration, whereas PKCε and ζ are required for phosphorylation of paxillin [276]. However, high levels of PKCα mRNA in HCC tissues are correlated with poor survival in patients [277].

The expression of factors associated with certain hepatic viruses can also affect the development and progression of liver carcinomas. Hepatitis B virus (HBV) envelop glycoproteins, for instance, which are collectively known as HBV surface antigens, are divided into three types, the large (LHBs), middle (MHBs), and small surface proteins (SHBs) [278]. The PreS2, which is a 55 hydrophilic amino acid chain located at the N-terminal of SHBs, is found in LHBs and MHBs [278] and stimulates the Raf1/MEK pathway through PKCα and β signaling pathways [279]. Further, LHBs can promote carcinogenesis and proliferation of HCC cells through the c-Src/PI3K/Akt pathway, which is trigged by PKCα/Raf1 activation. Stable LHB expression in HuH-7 cells also increases G_1/S cell cycle progression and antiapoptosis via c-Src activation [280].

PKCδ is involved in caspase-3-dependent apoptosis induced by the synthetic sphingosine immunosuppressant FTY720 [281]. Moreover, activation of the c-Abl/PKCδ signaling pathway results in claudin-1-induced MMP-2 expression as well as cell invasion and migration [282]. Further, PKCδ also increases phosphorylation of heat shock protein-27 (HSP-27) via p38 MAPK [283] and this may be correlated with cell migration and invasion [284].

In addition, PKCε may be involved in growth and migration of HCC cells [276, 285], while the PKCβ-specific inhibitor LY317615 or siRNA significantly reduces migration and invasion of HCC cells [286].

3.8. Lung Cancer

3.8.1. Small and Nonsmall Cell Lung Carcinoma. The two major types of lung cancer are nonsmall cell lung cancer (NSCLC) (85%) and small cell lung cancer (SCLC) (15%); NSCLC can be further divided into three subtypes: squamous-cell carcinoma, adenocarcinoma, and large-cell lung cancer [287]. NSCLCs show significantly higher survival and anticancer drug resistance than SCLCs; as they have been shown to have enhanced anticancer drug transport activity [288] and/or JNK activation [289]. Although expression of PKCα, β, ε, η, ι, and ζ is identified in NSCLCs and SCLCs, it seems that the important isozymes for therapeutic use are PKCα, β, ε, and ι.

PKCα is highly expressed in patients with NSCLCs, which higher levels being found for adenocarcinoma compared to squamous cell carcinoma [290]. PKCα exerts an important effect on antiapoptosis and metastasis of NSCLC cells. Metastasis of NSCLC cells can be stimulated by the activation of PKCα through a C-terminal class I PDZ-dependent interaction with its substrate, discs large homology-1 [291]. In addition, an increase in the activity of PKCα and nuclear PKCβ has been detected in lung metastatic nodules originating from other cancers such as HCC [292].

In regard to the antiapoptotic function of PKCα, PKCα-mediated phosphorylation of RLIP76 at Thr-297 increases doxorubicin (DOX)-transport activity, resulting in lower levels of apoptosis. This phenomenon is higher in NSCLC cells than in SCLC cells [288]. Moreover, miR-203 can regulate the expression of PKCα in NSCLC, where down-regulation of PKCα by the miR-203 induces apoptosis of A549 cells while also reducing PKCα-mediated cell migration and proliferation [293]. PKCα, along with survival, is also involved in inhibition of FGF2-induced apoptosis by the stimulation of FGF2-mediated surviving expression [294]. Interestingly, a recent study has demonstrated that PKCα, through the activation of a p38 MAPK/TGF-β axis, has

a suppressor function in NSCLC formation and its loss enhances K-Ras-mediated cancer initiation and progression of bronchioalveolar stem cells [295].

These data all indicate that PKCα is an important target for treatment of SCLCs and NSCLCs, but clinical trials using PKCα-specific antisense oligonucleotides show no or low efficacy in patients [296–298]. Further, clinical trials using PKCα-targeted antisense oligonucleotides aprinocarsen [296, 297] and LY900003 [298] in combination with anticancer drugs (either gemcitabine and cisplatin or gemcitabine and carboplatin) did not enhance survival and other efficacy measures in patients with advanced NSCLC.

PKCε is abnormally upregulated in human NSCLCs and is known to regulate growth and survival of NSCLC cells [299]. PKCε-depleted NSCLC cells show low growth rates *in vitro* and *in vivo*, as well as upregulation of proapoptotic genes, such as *BIRC2*, *CASP4*, *CASP1*, *CD40*, and *FAS*, and downregulation of prosurvival genes, such as *Bcl2*, *BIRC3*, and *CD27* [300]. PKCε also enhances the proliferation of NSCLCs through the reduction of $p21/^{Cip1}$, suggesting that the $p21^{Cip1}$ serves as a negative effector in the PKCε-mediated proliferation of NSCLCs [299]. The antiapoptotic functions of PKCε in lung cancer cells involve the inhibition of TRAIL-induced cell death [301] and mitochondrial caspase signaling [302], as well as the upregulation of antiapoptotic proteins (e.g., XIAP or Bcl-XL) through S6K2, but not S6K1 signaling [303].

During metastasis of NSCLC cells, PKCε acts as a positive effector by enhancing the activation of Rac1, a Rho family member of the small GTPases, and the secretion of extracellular matrix protease (e.g., MMP-9) and protease inhibitors (e.g., tissue inhibitor of metallopeptidase 1 and 2) [304]. PKCε-dependent formation of the α_5/tight junction protein zonula occludens-1 complex enhances migration and invasion of lung cancer cells [305].

PKCι is expressed in both SCLCs and NSCLCs and is associated with their carcinogenesis, survival and antiapoptosis [306–309]. The survival mechanisms of SCLCs and NSCLCs through PKCι involve upregulation of the antiapoptotic protein Bcl-XL [310] and S-phase kinase-associated protein 2-mediated anoikis resistance via the PI3K/Akt pathway [308]. PKCι also regulates transformed growth and invasion of NSCLC cells mainly through the Rac1/PAK/MEK/ERK signaling pathway [307, 311, 312]. After PKCι phosphorylation of epithelial cell transforming sequence 2 (Ect2) at Thr-328, binding of activated Ect2 to the PKCι-Par6 complex enhances Rac1 activity [312]. In this process, MMP-10 acts as a critical effector of the PKCι-Par6/Rac1 signaling axis that is required for anchorage-independent growth and invasion of NSCLC cells [313]. In PKCι-dependent adenocarcinoma transformation, PKCι induces four target genes, *COPB2*, *ELF3*, *RFC4*, and *PLS1*, whose expression has been correlated with PKCι activity [314]. Therefore, overexpression of PKCι is connected with poor survival in patients with NSCLC and can be used as a prognostic indicator [306].

Among oncogenic *Ras* genes (*H-Ras*, *K-Ras*, and *N-Ras*), activating mutations in *K-Ras* are the most frequently found in NSCLCs [315, 316] and PKCι is required for *K-Ras*-mediated bronchioalveolar stem cell expansion and lung cancer growth. This suggests that PKCι may be an attractive therapeutic target for the protection of lung cancer-initiating stem cells. In fact, aurothiomalate, which is a potent inhibitor of PKCι-Par6 interactions [317], can target lung cancer-initiating stem cell niches and efficiently inhibit *K-Ras*-mediated bronchioalveolar stem cell expansion [318]. In addition, aurothiomalate decreases the proliferation of lung cancers by inhibition of MEK/ERK signaling [311]. Interestingly, oncrasin-1, a small molecule RNA polymerase II inhibitor, requires K-Ras or PKCι for its apoptosis induction in lung cancer cells [319].

PKCη overexpression may be related to the advanced stages of NSCLC because its highest levels are identified in patients with clinical stage IV NSCLC [320]. Inhibition of PKCη enhances caspase-3 activity in NSCLC A549 cells after treatment with anticancer drugs [321]. On the other hand, EGF-mediated PKCζ activation is required in NSCLC cell chemotaxis, which plays a critical role in NSCLC cell metastasis [322].

PKCδ may be a potential therapeutic target for lung cancer because of the close relationship between its expression and antiapoptosis and cell survival. In fact, inhibition of PKCδ suppresses anchorage-independent growth, invasion, and migration in K-Ras-dependent NSCLC cells [323] and promotes chemotherapy-induced apoptosis [324]. Interaction of HSP-27 with PKCδ, especially amino acid residues 668–674 (EFQFLDI) of the V5 region, increases radioresistance and chemoresistance of NSCLC cells [325]. PS-341 (bortezomib), a proteasome inhibitor, upregulates PKCδ-dependent death receptor 5 (DR5) expression and apoptosis of NSCLC cells through the activation of ERK/RSK2 and ER stress pathways [326]. On the other hand, PKCδ also triggers the upregulation of p21 and downregulation of Rb hyperphosphorylation and cyclin A expression, resulting in PMA-induced G_1 arrest of NSCLC cell lines H441 and H358 [327].

3.8.2. Role of PKC Isozymes in Cigarette Smoke-Induced Lung Cancer. Cigarette smoke exposure, including secondhand (passive or environmental) smoke exposure, causes damage and/or apoptosis of lung cells and increases the risk of lung cancer [328]. PKC signaling has been shown to be involved in smoke-induced cell damage and apoptosis [328–330], but there is very little data specifically on the role of PKC isozymes in causing cigarette smoke-induced lung cancer. In a recent study, smoke exposure induces the phosphorylation of tumor necrosis factor-convertase (TACE; also known as ADAM17), which is a metalloprotease disintegrin. PKCε expression, activated by c-Src/ROS pathways, is required for TACE phosphorylation and EGFR activation, leading to the hyperproliferation of lung cells [329]. Further, nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1 butanone (NNK) is the most potent carcinogen that is formed by nitrosation of nicotine. A recent study has suggested that NNK can induce migration and invasion of human lung cancer cells through the cooperation with c-Src/PKCι and PKCι/focal

adhesion kinase (FAK) pathways [331]. PKCι can also stimulate nicotine-induced migration and invasion of human lung cancer cells through phosphorylation of μ- and m-calpains that are major members of the calpain family and can regulate cell motility [309]. Therefore, although there is not an overwhelming amount of evidence, it is likely that cigarette smoke can in fact promote invasion and migration of lung cancer cells through PKC signaling [309, 331, 332].

3.9. Melanoma. PKCα, δ, ε, ζ, and λ/ι are the PKC isozymes expressed in melanoma [333, 334]. Among them, PKCα is the most important as it is involved in differentiation, proliferation, survival, metastasis, and antiapoptosis of melanoma cells [333, 335]. Further, αv-integrin expression and αv-mediated relocalization of p53 by PKCα enhance melanoma cell survival [336]. In addition, expression of PKCα plays a critical role in the invasion and migration of melanoma cells [337, 338] as it can stimulate $\alpha v\beta 3$-integrin-mediated invasion of melanoma cells by increasing the GTPase activity of Rac [337]. PKCα also induces melanoma vasculogenic mimicry [339] or the formation of de novo vascular networks by highly aggressive cancer cells thereby promoting the aggressive, metastatic phenotype of cancer cells [340]. However, the cellular activity of PKCα may vary, even in the same melanoma tissues (e.g., samples collected from the center of a B16 melanoma compared to those from its edge show lower PKCα activity) [341].

PKCε can participate in antiapoptosis of melanoma cells. For example, expression of PKCε attenuates the sensitization of melanoma cells to TRAIL-induced apoptosis [342], docetaxel-induced apoptosis through the activation of ERK1/2 pathway [343], and genotoxic stress-induced apoptosis by blocking the transcription factor ATF2 nuclear export and localization in the mitochondria [344].

PKCβ is detected in normal melanocytes, but is not found in isolated primary or metastatic melanoma cells [333, 334]. Introduction of PKCβII into melanoma cells suppresses HGF-induced activation of PI3K, tyrosine phosphorylation of adapter protein Gab1, and invasion activity of melanoma cells [345]. Reexpression of PKCβ in melanoma cells inhibits melanoma growth and elevates UV-induced ROS production [346]. These results indicate that PKCβ has cancer suppressive functions and its activation in melanoma can be a potential treatment option for melanoma.

Melanoma cells overexpressing PKCδ have enhanced cell metastatic capacity, likely through the release and activation of TGF-β1 [347, 348], but reduce proliferative capacity because of reduced sphingomyelinase activity [348, 349]. Furthermore, high levels of activated PKCδ enhance docetaxel-induced apoptosis via JNK activation [350].

3.10. Myeloid and Lymphocytic Leukemia. Leukemia is cancer of the blood cells and is classified as lymphocytic (lymphoid or lymphoblastic) or myeloid (myelogenous or myeloblastic) leukemia according to the type of cell that it starts in. These classifications are further broken down into four types, acute lymphocytic leukemia (ALL), CLL, AML, and chronic myeloid leukemia (CML).

3.10.1. CLL and ALL. Several PKC isozymes (PKCα, βI, βII, δ, ε, ζ, and ι) are detected in CLL, but PKCβII shows the highest expression [351–353] and plays a more important role in cell proliferation, differentiation, survival, and anticancer drug resistance. Overexpression of PKCβII in CLL is also associated with poor prognosis and patient survival [354–357]. For these reasons, PKCβII is considered a useful therapeutic target for the treatment of CLL; however, inhibition of a PKCβII activity with PKCβII-specific inhibitor (e.g., LY379196) has a minimal effect on the viability of CLL cells [351, 358]. The presence of LY379196 also failed to induce a spontaneous decrease of PKCβII mRNA and activity levels in CLL cells [358]. These data strongly suggest the existence of other critical survival signals and PKCβII activation signals in CLL cells. In fact, treatment with the PKC inhibitor RO32-0432, which can inhibit cPKCs, nPKCs, and aPKCs, markedly reduced the cell viability [351]. Further, growth factors, such as VEGF and bFGF, also appear to play an important role in maintaining PKCβII activity, because while LY379196 does not inhibit PKCβII under normal (i.e., growth factor rich) cellular condition, PKCβII is inhibited by this drug in the absence of VEGF [358].

Increased PKCβII expression also induces Akt phosphorylation, known to be a survival signal, independent of PI3K [359, 360], and controls the B cell-activating factor of the TNF family (BAFF; also known as BLyS) that is responsible for the Akt activation in response to PI3K activation [361]. During apoptosis, PKCβII downregulates proapoptotic B-cell receptor signaling in CLL cells [351]. Further, phosphorylation of antiapoptotic Bcl-2 protein at serine 70 by PKCβII increases the survival of CLL cells, but PKCβII-mediated phosphorylation of a proapoptotic BH3 only protein, Bim_{EL}, which is essential for the initial stimulation of apoptosis, leads to its proteasomal degradation [362]. A recent study has demonstrated that PKCβ-dependent activation of NF-κB in bone marrow stromal cells is also essential for the survival of CLL cells [363]. Taken together, PKCβII appears to participate in CLL cell survival by inhibiting proapoptotic signals and activating prosurvival signals.

PKCδ also plays an important role in CLL survival through the activation of PI3K [364], stabilization of Mcl-1 [365], and activation of NOTCH2 with an antiapoptotic function [366].

In ALL, PKCβ-specific inhibitors reduce cell viability in a dose-dependent manner [357]. Overexpression of PKCα has no influence on cell proliferation or cell cycle in the ALL cell line REH, but does induce anticancer drug resistance via Bcl-2 phosphorylation [367].

3.10.2. CML and AML. High levels of PKCα and PKCβII expression have been reported in myeloid leukemia and both isozymes have been shown to regulate cell differentiation, proliferation, and survival [368–370]. In CML cells, PKCβII activation is essential for cell proliferation and survival [362]. A recent study has reported that WK234, an inhibitor of PKCβ, decreases proliferation of CML K562 cells and enhances their apoptosis [371]. Furthermore, a farnesyltransferase inhibitor, BMS-214662, was determined to stimulate

mitochondrial apoptosis in $CD34^+$ CML cells during the early upregulation of PKCβ [372].

CML K562 cells can resist ionizing radiation through activation of the PKCδ/NF-κB pathway [373]. PKCδ is also involved in IFN-α-induced growth inhibition of CML cells through phosphorylation of Stat1 [374]. On the other hand, PKCδ may also participate in K562 cell death because of a close relationship between activation of the PKCδ/ERK pathway and high levels of Bax at hypoxia-induced apoptosis [375].

In AML cells, PKCα may play an important role in the inhibition of anticancer drug-induced apoptosis. Blocking PKCα activation enhances apoptosis in the AML cell line OCI-AML3 [370] and NB cells [376]. Furthermore, AML patients with active PKCα and PKCα-mediated Bcl-2 phosphorylation, which modulates the antiapoptotic ability of Bcl-2, have much shorter survival [377–379]. However, PKCβ may not be involved in AML cell death because PKCβ inhibitors show no effect on AML cell apoptosis [380].

Expression of PKCδ in AML cells induces cell death through the downregulation of heterogeneous nuclear ribonucleoprotein K [380], phosphorylation of eIF2α [381] and β-actin [382], and activation of MAPKs (JNK and p38) [383] and caspase-3 [384, 385]. In addition, when wogonin, a natural monoflavonoid, is added to AML U937 cells, cell differentiation and G_1 phase arrest are induced through PKCδ-mediated upregulation of p21 proteins [386]. Statin-induced AML NB4 cell differentiation [387] and ATRA-induced antileukemic responses in AML cells also require activation of PKCδ [387, 388].

3.11. Ovarian Cancer. Expression of PKCα, ι, and ζ has been found in ovarian cancer. PKCα can activate cell growth and DNA synthesis through follicle-stimulating hormone [389] and lysophosphatidic acid-induction in ovarian cancer cell invasion [390]. PKCι shows a significant correlation with cancer stage, histopathological grading, and proliferation index, but PKCα is only correlated (negatively) with histopathological grading [391]. PKCι does not directly affect ovarian cancer cell response to chemotherapy and proliferation, but it may indirectly participate in cell proliferation [392, 393].

On the other hand, PKCζ in ovarian cancer cells can act as a negative regulator of cell survival via regulation of the proapoptotic functions of protein phosphatase 2A (a survival phosphatase) and HRSL3 (a class II tumor suppressor family; also known as H-REV107-1) [394].

PKCδ is not expressed in primary and recurrent ovarian cancers [391]. However, gonadotropin-induced ovarian cancer cell proliferation requires PKCδ-mediated activation of ERK1/2 signaling [395]. Furthermore, activation of PKCδ may be associated with enhanced apoptosis in the ovarian cancer cell line COC1 [392].

3.12. Pancreatic Cancer. As mentioned above, EMT plays a critical role in promoting metastasis and invasion of cancer cells [253, 396]. Overexpression of PKCα in poorly differentiated human pancreatic cancer tissues and cell line PANC1 downregulates the activation of claudin-1 through Snail- and ERK-dependent pathways during EMT. In the well-differentiated pancreatic cancer cell line HPAC, PKCα activation reduces not only claudin-1 but also claudin-4, -7, and occludin, while Snail signaling is not changed. These signaling responses stimulated by PKCα activation lead to the downregulation of tight junction functions and enhanced antiapoptosis capabilities, which may increase cell invasion and metastasis [397, 398]. TGF-β1-mediated PKCα activation reduces the sensitivity of pancreatic cancer cells to cisplatin through overexpression of P-gp [399], stimulates cell migration, and reduces the expression of a putative tumor suppressor, phosphatase, and tensin homology [400]. In addition, PKCα has been shown to be involved in growth and differentiation of pancreatic cancer cells as the selective downregulation of PKCα enhances TNFα-induced growth arrest and differentiation in HPAC cells [401] and blocks retinoic acid-stimulated growth of the pancreatic cancer cell line AsPc1 [402]. PKCα-selective inhibition reduces carcinogenesis of pancreatic cancer and enhances the survival of tumor-bearing animals [403]. However, one study has shown that activation of PKCα can inhibit growth of the pancreatic cancer cell line DanG through the inhibition of $p21^{Cip1}$-mediated G_1/S cell-cycle transition [404].

PKCζ participates in survival and metastasis of pancreatic cancer cells through the Stat3-dependent pathway [405–407] and Sp1-dependent VPE/VEGF expression, which is associated with cancer angiogenesis [408].

Pancreatic ductal adenocarcinoma (PDAC), the most common type of pancreatic cancer, shows higher expression of PKCι than intraductal papillary mucinous neoplasm. Overexpression of PKCι has also been correlated with poor survival in PDAC patients [409]. High expression of PKCι in intraductal papillary mucinous neoplasm is also significantly associated with a worsening histological grade and advanced stage cancer [410]. PKCι is required for angiogenesis and metastasis of PDAC through Rac1-MEK/ERK1/2 pathway [409] and TGF-α- and $K\text{-}Ras^{G12D}$-mediated pancreatic acinar-to-ductal metaplasia [411].

PKCβ1 may play an important role in migration and antiapoptosis of pancreatic cancer cells [412]. Treatment with the PKCβ inhibitor enzastaurin reduces cancer growth, phosphorylation of GSK3β, and microvessel density in pancreatic cancer-bearing mice when combined with radiation therapy, but enzastaurin alone failed to affect cell survival, proliferation, or xenograft growth [413, 414]. On the other hand, in a study using the pancreatic endocrine cancer cell line DON1, enzastaurin (5 and 10 μM) increased caspase-mediated apoptosis, reduced phosphorylation of GSK3β and Akt, and blocked cell proliferation through the inhibition of insulin-like growth factor-1 (IGF-1) [415].

PKCδ can increase anchorage-independent growth, resistance to treatment of cytotoxic drugs, and metastasis of PANC1 [416]. Activation of the PKCδ/TG2 signaling pathway is also associated with enhanced drug resistance, metastatic phenotype, and poor patient prognosis with pancreatic cancer cells [417].

3.13. Prostate Cancer. In early prostate cancer specimens, PKCα and ζ are significantly increased, but PKCι expression shows no difference between the benign and malignant groups. Attenuation of PKCβ in early prostate cancer is associated with an increase in PKCε expression [418]. High expression of PKCδ in both low- and high grade prostate cancer has been reported [419, 420]. Furthermore, significantly high levels of PKCα, β, ε, and η have been detected in malignant prostatic carcinoma [421].

The levels of PKCα are lower in hormone-sensitive cell lines (e.g., LNCaP) compared to hormone-insensitive cell lines (e.g., PC3 or DU145) [422, 423]. PKCα activation by the arachidonic acid metabolite 12(*S*)-hydroxyeicosatetraenoic acid induces the motility of AT2.1 rat prostate cancer cells [424], but the reduced activation of PKCα by TGF-β1 leads to the inhibition of PC3 cell growth [425]. PKCα is also required for EGFR transactivation and ERK1/2 activation in androgen-independent human prostate cancer cells [426]. Further, these signaling responses are linked to multiple biological responses, such as proliferation, migration, and antiapoptosis, occurring in prostate cancer cells [427]. In prostate cancer progression and angiogenesis, osteopontin, a multifunctional glycosylated phosphoprotein, activates PKCα, which then plays a critical role in COX-2 expression, ultimately resulting in enhanced cell migration and invasion and angiogenesis [428].

Prostate cancer cells show PKCα-dependent proapoptotic and antiapoptotic functions. When the anticancer drug cisplatin introduced to prostate cancer cells, PCPH/ENTPD5 expression increases antiapoptosis through PKCα-mediated Bcl-2 stabilization [429]. In addition, resveratrol (3,4′,5-trihydroxystilbene), a natural stilbene with anticancer activity, induces p53-mediated apoptosis, but this apoptotic process is inhibited by PKCα activation via EGF [430].

On the other hand, PKCα activation by TPA or a methoxyflavanone derivative WJ9708012 was shown to enhance apoptosis of the prostate cancer cells through the downregulation of the serine/threonine kinase ataxia telangiectasia mutated [431], Bcl-2, and Bcl-XL in association with the degradation of the proapoptotic proteins Bid and Bad [432]. However, removal of TPA leads to the downregulation of PKCα [422]. Furthermore, LNCaP cells overexpressing PKCα had increasd sensitivity to bryostatin 1-induced apoptosis [433]. Toll-like receptors (TLRs) have important roles in host defense and tissue homeostasis during carcinogenesis through the immune system [434, 435]. The TLR3-specific ligand poly (I:C) induces apoptosis of human prostate cancer cell lines through the upregulation of JNK and p38 MAPK by PKCα activation, resulting in caspase-8-dependent apoptosis [436].

However, in a phase II clinical trial, PKCα-specific antisense oligonucleotides, ISIS 3521 and ISIS 5132, did not show clinical significant anticancer efficacy in patients with hormone-refractory prostate cancer [437].

PKCε may be the most useful therapeutic target to treat prostate cancers because it plays a key role in growth, survival, and antiapoptosis in this type of cancer. When PKCε is genetically deleted in the transgenic mouse model of prostate adenocarcinoma, proliferation, antiapoptosis, and metastasis of prostate cancer cells are dramatically reduced [438]. PKCε promotes growth and enhances survival of protein kinase D3-induced prostate cancer cells through stimulation of Akt and ERK1/2 [439], enhances cell survival of recurrent CWR-R1 prostate cancer cells through activation of the Akt survival pathway [440], and promotes growth and enhances survival of androgen-independent prostate cells through stimulation of cell proliferation-related protein synthesis (e.g., caceolin-1) and signaling (e.g., Raf1/ERK1/2) [441, 442]. In contrast, one study suggested that overexpression of PKCε does not alter the sensitivity of LNCaP cells to either PMA or androgen and the expression of caceolin-1 [423]. In addition, PKCε is required for constitutive activation of Stat3 through phosphorylation at serine 727 that is essential for prostate cancer cell invasion [438, 443].

Furthermore, PKCε-mediated antiapoptotic properties are obtained through the effects on multiple signaling pathways, such as phosphorylation and inactivation of proapoptotic Bad [444], inhibition of TNFα-induced JNK activation [444], inhibition of IκBα phosphorylation and degradation [445], and interaction of PKCε with proapoptotic Bax, all of which result in the neutralization of apoptotic signals [446]. Furthermore, PKCε increases P-gp-mediated drug resistance [447].

Several groups have also demonstrated that anticancer agents that downregulate PKCε can efficiently induce apoptosis in prostate cancer cells and inhibit their growth *in vivo* and *in vitro*. These drugs include wedelolactone, a medicinal plant-derived coumestan [448]; a second-generation selenium compound, methylseleninic acid [449]; a specific inhibitor of 5-LOX activity, MK591 [450]; and plumbagin (5-hydroxy-2-methyl-1,4-naphthoquinone) [451]. One study, however, has suggested that prostate cancer cells overexpressing PKCε exhibit sensitivity to bryostatin 1-induced cell death [423].

In prostate cancer cells, PKCζ acts as a cancer suppressor through the regulation of c-Myc function [452]. Spisulosine (ES-285), which is a marine compound that has an anticancer activity, induces the death of prostate cancer cells through ceramide accumulation and PKCζ activation [453]. In a recent study, PKCζ was also shown to be involved in promoting the aggressive phenotype of LNCaP cells [454], while another study postulated that its overexpression inhibits invasive and metastatic activity in Dunning R-3327 rat prostate cancer cells [455]. Further, PKCζ activation is required for androgen-dependent cell proliferation in prostate cancer LNCaP cells and during the transition of androgen-dependent to androgen-independent prostate cancer cells [456].

In addition, downregulation of PKCη efficiently enhances TRAIL-induced apoptosis [457] and inhibition of centrosomal PKCβII expression reduces angiogenesis and prostate cancer cell growth [458].

PKCδ expression is associated with apoptosis of prostate cancer cells. The proapoptotic role of the protein tyrosine phosphatase PTPL1 in PC3 and LNCaP prostate cancer cells is PKCδ-dependent and induces inhibition of IκBα degradation and suppression of NF-κB activity [420]. Several mechanisms are involved in PKCδ-dependent apoptosis, which is

triggered by PMA, anticancer drugs, or androgens; these mechanisms include upregulation of DRs (e.g., DR5) [459], activation of DR downstream effectors (e.g., caspase-8 and -3, p38, and JNK) [459–462], enhanced release of death factors (e.g., TNFα and/or TRAIL) [463, 464], upregulation of ROCK (mediated by depletion of type I transmembrane protein p23/Tmp21) [460], and ROCK-mediated upregulation of $p21^{Cip1}$ [465]. Furthermore, activation of neutral endopeptidase (NEP) and PKCδ correlates with TPA-induced apoptosis of androgen-independent prostate cancer cells. The NEP inhibits neuropeptide-induced and c-Src-mediated PKCδ degradation [466]. In anticancer drug-induced apoptosis, PKCδ and ceramide are required for cytochrome C release and caspase-9 activation in mitochondria [467].

In addition, PKCδ is overexpressed in invasive prostate cancer cell lines (e.g., DU145) and plays a critical role in migration and invasion [468]. BK-mediated migration of prostate cancer cells involves upregulation of MMP-9 and activation of the B2 receptor/PKCδ/c-Src/NF-κB signaling pathway [469]. PCPH/ENTPD5-mediated invasion of prostate cancer cells is also PKCδ-dependent [419]. Furthermore, activation of PKCδ in mice xenografted with PC3 cells can increase angiogenic activity through enhanced NADPH oxidase activity and increased levels of hypoxia-inducible factor (HIF)-1α [470].

3.14. Renal Cell Carcinoma (Kidney Cancer). Renal cell carcinomas (RCCs) are divided into four types: clear cell (70~80%), papillary (10~20%), chromophobe (5%), and collecting duct (1%) [471, 472]. Different types of RCC show significantly different patterns in the expression of PKC isozymes. PKCβI, βII, δ, and ε are expressed in RCCs, while PKCα, βI, βII, η, and ι are found in oncocytoma, the most common benign solid renal tumor [473]. Moreover, PKCα, βI, βII, γ, δ, ε, η, θ, and λ have been detected in the human RCC cell line CCF-RC1 [474]. In human clear cell RCC cell lines clearCa-5, clearCa-19, clearCa-28, and clearCa-39 and PKCα, ε, ζ, and ι are found, while PKCβI, βII, γ, δ, η, and θ are absent [475]. Notably, lower levels of PKCα are detected in clear cell RCCs than in normal tissue [473, 476]. Furthermore, clear cell RCCs collected from patients show expression of PKCα, βI, βII, δ, ε, η, ζ, and ι, but not PKCγ and θ. A 3-fold increase in PKCη and a slight increase in PKC ζ (20%) in grades III and IV carcinomas are common in all clear cell RCCs, suggesting that these PKCs are correlated with increased cancer progression [476]. On the other hand, Pu et al. [477] have reported a significant increase of PKCζ as cancer grade increases in addition to a significant association between increased PKCζ and poor patient survival, likely because of increased resistance to the anticancer drug cisplatin. PKCζ can also activate HIF-2/HIF-α in the RCC cell line 786-O by inhibiting mRNA expression of FIH-1 [478].

PKCε is involved in growth, migration, and invasion in the clear cell RCC 769P cell line. Further, inhibition of PKCε has been shown to induce the activity of caspase-3 after adding chemotherapeutic drugs (sunitinib or 5-fluorouracil) [479]. PKCε is also associated with the regulation of β1-integrin expression [473]. PKCα and ε both play a key role in invasion of human clear cell RCC cell lines, especially the more highly invasive RCC cell lines clearCa-5 and clearCa-19 [475]. In addition, expression of netrin-1 is higher in the invasive human RCC cell line ACHN than in the weakly invasive cell line 769P, but expression of UNC5B is found to be the opposite. Stimulation of PKCα by PMA increases the expression of netrin-1 and netrin receptor UNC5B in ACHN cells, but expression of netrin-1 is much higher than that of UNC5B [480]. These results may be related with to the enhanced antiapoptosis, cell proliferation, and migration observed in these cells [481].

Expression of CUB-domain-containing protein 1 can elevate RCC migrations through PKCδ activation and correlates with poor survival of patients [482]. PKCδ activation also increases RCC migration by reducing expression and activity of β1-integrin and FAK [483]. Similar to its role in pancreatic cancer cells, IGF-1 receptor activation via PKCδ induces IGF-1-mediated invasion of RCC cells, but this invasion can be blocked by the tumor suppressor von Hippel-Lindau [484].

3.15. Thyroid Cancer. Sphingosine 1-phosphate (S1P)-mediated migration of thyroid cancer ML-1 cells is dependent on PKCα, ERK1/2, and sphingosine kinase 1 (SK1). SK1 activates S1P secretion and the activated S1P stimulates ERK1/2 phosphorylation through PKCα and βI signaling. Downregulation of PKCα reduces both VEGF-A- and S1P-induced haptotaxis, while downregulation of PKCβI only reduces S1P-induced haptotaxis [485, 486]. Furthermore, the PKCα-D294G mutant in the V3 region is found not only in thyroid cancers with more invasive phenotype [487–489], but also in pituitary adenomas [487, 489] and breast cancers [490]. This mutant reduces the transduction of extracellular signals that can suppress cancer cell growth and increase apoptosis thereby leading to a more malignant phenotype [487]. However, to date, the pituitary mutants PKCα-A294G [491] and PKCα-A881G [492] have not been identified in thyroid cancers.

Similar to the microRNA functions mentioned for other cancers (e.g., miR-31 in breast cancer or miR-203 in lung cancer), overexpression of miR-146a in the papillary thyroid cancer cell line NPA-187 decreases cell survival and induces apoptosis by suppressing PKCε expression [493]. In contrast, inhibition of PKCε in PCCL3 cells blocks p53 expression and increases the levels of murine double minute clone 2, while it has an oncogene function and antiapoptosis activity through the activation of Bcl-2 expression and reduction of Bax expression [494]. In addition, downregulation of PKCε by prolonged expression of RET/PTC increases cell survival and resistance to DOX-induced apoptosis in the thyroid cancer cell line PCCL3, while acute expression of RET/PTC activates PKCε [495]. Reduction of PKCε in papillary thyroid cancers can occur through either translational or posttranslational mechanisms [492].

Furthermore, PKCβII inhibition by enzastaurin leads to the reduction of medullary thyroid carcinoma cell proliferation and survival, indicating that PKCβII is required in these processes [496].

PKCδ activation shows an arrest in papillary thyroid cancer cell (NPA) growth at G_1 phase through the ERK/$p27^{Kip1}$/cyclin E/pRb pathway [497] as well as antiproliferative effects in the anaplastic (FRO and ARO) and follicular (ML-1) thyroid cancer cell lines through MAPK/Akt and FOXO signaling [498]. Enhanced FRO cell migration through phosphorylation of Bcl-2 associated athanogene 3 (BAG3) was also observed in some cases [498, 499].

4. PKC Isozymes as Diagnostic or Prognostic Biomarkers

PKC isozymes that are overexpressed or hyperactivated in cancer tissues can be used as immunohistochemical biomarkers during cancer diagnosis by comparing the expression in cancer tissues to that in normal tissues. For example, PKCθ has been used as a biomarker for GIST, especially GIST that is immunohistochemically negative for KIT and/or DOG1 [176–178]. Furthermore, PKCι has been used as a diagnostic biomarker for ovarian [500] and NSCLC [306], while PKCα and PKCβII have been used for breast cancer [49, 60] and diffuse large B-cell lymphoma (DLBCL; also known as non-Hodgkin's lymphoma) [354–356], respectively.

However, in spite of usefulness of immunohistochemical biomarkers, cancer biomarkers in blood, urine, feces, or saliva have received much greater interest recently as they are easier to sample and handle; the amount of pain is reduced in patients during sampling, and the detection techniques are, overall, much less invasive compared to the analysis of tissue samples. There is currently very little data on the existence of PKC isozymes in blood, urine, feces, or saliva, but recently activated PKCα, which can act as a biomarker for cancer, was identified in blood samples collected from cancer-bearing mice as well as human patients [22, 501, 502]. Furthermore, fecal PKCβII and ζ mRNA levels significantly increase in these types of samples collected from colon cancer-bearing rats as compared with normal rats, meaning that the detection of PKCβII and ζ mRNA may apply to the diagnosis of colon cancer [503, 504].

Overexpression of PKC biomarkers is closely related to poor prognosis, poor response to chemotherapy, and poor survival. In breast cancer progression, PKCα overexpression in breast cancer exhibits poor prognosis and survival because of a decreased response to chemotherapy and the high aggressiveness of the cancer [49, 60]. Further, after endocrine therapy of breast cancer, PKCα expression ($PKC\alpha^+/PKC\delta^-$) correlates to estrogen receptor negativity and poor endocrine responsiveness and patient survival, but PKCδ expression ($PKC\alpha^-/PKC\delta^+$) increases endocrine responsiveness and patient survival [49]. A previous study has also reported that increase in PKCε correlates to positive Her2/neu receptor status, negative estrogen and progesterone receptor status, and poor survival [505]; however, this finding has recently been challenged by another study suggesting that there is no correlation between PKCε expression and clinicopathological parameters (tumor grade and estrogen/progesterone receptor negativity) and recurrence-free or 10-year survival [60]. In DLBCL, PKCβII expression is significantly associated with low response to chemotherapy and poor survival in patients [354–357]. Furthermore, PKCι can be used as a prognostic indicator in NSCLC and ovarian cancer [306, 500]. Interestingly, PKCι expression is associated with tumor stage in ovarian cancer [500], but not in NSCLS that shows an increase in PKCι expression in both early- and late-stage cancers [306].

5. PKC Isozymes and MDR

The ATP-binding cassette transporter family plays a very important role in the relationship between PKC isozymes and MDR. P-gp is a well-studied ATP-binding cassette transporter protein encoded by the *MDR1* (as known as *ABCB1*) gene and is broadly distributed in both cancers and various normal tissues, such as kidney, adrenal, brain vessels, muscle, lung, pancreas, liver, intestine, placenta, and testis [506–508]. Since overexpression of P-gp is typical in cancer cells, P-gp-mediated MDR is one of the most serious problems facing cancer treatment. P-gp-mediated MDR is maintained by several prosurvival and antiapoptosis signals and their targets, including JNK [55], p38 [509], ERK1/2 [509], and Janus kinase [510]. Although inhibition of P-gp may increase the therapeutic effects of anticancer drugs in MDR cancer cells, P-gp inhibitors have been associated with several potential side effects [511, 512].

As mentioned in Section 3. PKC isozymes and cancer, PKC isozymes, especially PKCα and ε, are involved in the P-gp-mediated MDR in several types of cancer, such as colon cancer [119–121], pancreatic cancer [399], gastric cancer [157], breast cancer [55], leukemia [513], and prostate cancer [447]. In general, inhibition of PKC isozymes that regulate P-gp leads to reduced MDR and enhanced cancer cell apoptosis. For instance, the membrane translocation and expression levels of PKCα are significantly increased in DOX-treated human colon cancer HCT15 cells, but PKCα inhibition leads to reduced MDR and increased DOX-induced apoptosis [120]. The MDR breast cancer cell line MCF-7/ADR also exhibits higher PKCα levels and lower cell growth inhibition and apoptosis after TAM treatment, compared with untreated MCF-7 cells. However, addition of PKCα inhibitor into TAM treated MCF-7/ADR cells results in reduced MDR and enhanced apoptosis through increased JNK activity [55].

6. PKC Isozymes and Cancer Stem Cells

Cancer stem cells (CSCs) have several interesting properties, such as self-renewal, clonal formation, and chemoresistance [514, 515]. Although there is very little data regarding the role of PKC isozymes in CSC function, several studies have recently demonstrated the involvement of PKC isozymes in controlling cellular signaling in these cells.

The interaction between HA and CD44 increases PKCε-dependent phosphorylation of the stem cell marker, Nanog, in the breast cancer cell line MCF-7 [38]. Nanog activation by HA-CD44 interaction is also known to occur in ovarian cancers and HNSCCs [516–518]. The activated Nanog induces antiapoptotic and proliferative factors, such as P-gp and

the inhibitor of the apoptosis protein (IAP) family (e.g., cIAP-1, cIAP-2, and XIAP), and reduces cancer suppressor proteins, such as PDCD4, resulting in enhanced antiapoptosis and anticancer drug resistance [516–518]. On the other hand, a recent study has suggested that Nanog expression is also upregulated by inhibition of PKC activity, especially PKCα and δ activity, in human cancer cell lines [519].

In glioma, combination treatment using proteasome inhibitors and TRAIL decreases the levels of PKCε mRNA and protein while also reducing PKCε-dependent activation of Akt and XIAP, resulting in cancer cell (and CSC) apoptosis. These results mean that PKCε is involved in antiapoptosis and survival of glioma stem cells [206]. Furthermore, PKCε participates in UV-radiation-induced development of SCC from precursor hair follicle stem cells [520].

As mentioned in Section 3.8. lung cancer PKCι plays a critical role in K-*Ras*-mediated bronchioalveolar stem cell expansion and lung cancer growth. Importantly, the small molecule PKCι inhibitor aurothiomalate can target the cancer-initiating stem cell niche and efficiently inhibit these K-*Ras*-mediated cellular responses [318].

Notch4 signaling activity is higher in breast cancer stem-like cells compared with differentiated cells and increases stem cell activity and cancer formation [521]. PKCα overexpression upregulates activator protein 1, which in turn mediates Notch4 activity. The activated Notch4 is closely associated with the promotion of estrogen-independent, TAM-resistant growth and chemotherapy resistance in breast cancer cells [522]. In a recent study, breast CSCs and nonbreast CSCs show differential utilization of signaling pathways during the EMT. Non-CSCs utilize c-Fos, while CSCs utilize Fra-1 to act as an effector of the EMT program. Phosphorylation of Fra-1 is performed by PKCα. High PKCα and Fra-1 expression is, therefore associated with aggressive triple-negative breast cancers, while high c-Fos expression is associated with better survival [523].

7. Summary and Overall Conclusions

In cancer, PKC isozymes play a critical role in cell proliferation, survival, invasion, migration, apoptosis, angiogenesis, and anticancer drug resistance. PKC isozymes can exhibit similar expression patterns and roles in multiple types of cancer, but in some case, they can show context specific expression and function that is dependent on the type of cancer. Among PKC isozymes, PKCα, β, ε, and δ have been the most broadly studied isozymes in relation to cancer. This may be associated with their ubiquitous expression in many tissues [524]. However, several recent studies have reported that aPKCs may also act as novel therapeutic targets for cancer treatment (e.g., PKCι in lung, ovarian, and colon cancer).

In general, overexpression of PKC isozymes is closely related to poor prognosis, poor response to chemotherapy, and poor patient survival. These results are likely caused by the high levels of cancer cell migration, invasion, survival, and anticancer drug resistance stimulated by PKC isozymes. Therefore, the overexpression of several PKC isozymes can serve as a potential cancer diagnostic marker and could be utilized as therapeutic targets.

Several PKC isozyme-specific or broad, nonspecific inhibitors have been developed and applied in phases II and III clinical trials. For example, PKCα-specific inhibitors have been used in combination with anticancer drugs in clinical trials, but satisfactory results have not yet been obtained [296–298, 437]. However, I suspect that these combination therapy trials will most likely be the only way to overcome the problem of MDR. Thus, the development of new PKC isozyme-specific inhibitors, in association with combination treatment to inhibit other non-PKC related cancer signals (e.g., c-Src signal) [45], is required.

Furthermore, there has been increasing interest in CSCs-targeted therapies as a novel treatment of cancers. Recent studies demonstrate the important role of PKC isozymes in controlling cellular signaling of CSCs. However, there is a paucity of data on the role of PKC isozymes in CSCs and further studies are required.

Abbreviations

ALL: Acute lymphocytic leukemia
AML: Acute myeloid leukemia
APC: Adenomatous polyposis coli
aPKC: Atypical PKC isozyme
ATM: Ataxia telangiectasia mutated
ATP: Adenosine triphosphate
bFGF: Basic fibroblast growth factor
BK: Bradykinin
Cdk: Cyclin dependent kinase
CEC: Colon epithelial cell
CLL: Chronic lymphocytic leukemia
CML: Chronic myeloid leukemia
Cox-2: Cyclooxygenase type 2
cPKC: Conventional or classic PKC isozyme
CSC: Cancer stem cell
DAG: Diacylglycerol
DLBCL: Diffuse large B-cell lymphoma
DOX: Doxorubicin
DR5: Death receptor 5
Ect2: Epithelial cell transforming sequence 2
EGF: Epidermal growth factor
EGFR: EGF receptor
ER: Estrogen receptor
ERK: Extracellular signal-regulated kinase
FAK: Focal adhesion kinase
FGF: Fibroblast growth factor
FOXO: Forkhead box class-O
GIST: Gastrointestinal stromal tumor
GR: Glucocorticoid receptor
GSK3β: Glycogen synthetase kinase 3β
HA: Hyaluronic acid
HBV: Hepatitis B virus
HCC: Hepatocellular carcinoma
HGF: Hepatocyte growth factor
HIF: Hypoxia-inducible factor
HNSCC: Head and neck squamous cell carcinomas

HSP: Heat shock protein
IAP: Inhibitor of the apoptosis protein
IFIT: Interferon-induced protein with tetratricopeptide repeats
IGF: Insulin-like growth factor
IP_6: Inositol hexaphosphate
JNK: c-Jun N-terminal kinase
MAPK: Mitogen-activated protein kinase
MDR: Multidrug resistant
MEK: MAPK kinase
MMP: Matrix metalloproteinase
mRNA: Messenger RNA
mTOR: Mammalian target of rapamycin
NEP: Neutral endopeptidase
NNK: Nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl-1 butanone)
nPKC: Novel or non-classic PKC isozyme
NSCLC: Nonsmall cell lung cancer
PAR: Proteinase-activated receptor
PDAC: Pancreatic ductal adenocarcinoma
P-gp: P-glycoprotein
PI3K: Phosphatidylinositol 3-kinase
PKC: protein kinase C
PLC: Phospholipase C
PMA: Phorbol-myristate-acetate
pRb: Retinoblastoma protein
PS: Phosphatidylserine
Raf1: v-raf-1 murine leukemia viral oncogene homolog 1
Rb: See pRb
RCC: Renal cell carcinoma
ROS: Reactive oxygen species
SCC: Squamous cell carcinomas
SCLC: Small cell lung cancer
S1P: Sphingosine 1-phosphate
SK: Sphingosine kinase
Stat3: Signal transducers and activators of trancription3
TACE: Tumor necrosis factor-convertase
TAM: Tamoxifen
TGF: Transforming growth factor
TLR: Toll-like receptor
TNF: Tumor necrosis factor
TPA: 12-O-tetradecanolyphorbol 13-acetate
TRAIL: TNF-related apoptosis-inducing ligand
uPA: Urokinase-type plasminogen activator
UV: Ultraviolet
VEGF: Vascular endothelial growth factor
XIAP: X-linked inhibitor of apoptosis.

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this paper.

Acknowledgment

This work was financially supported by a Grant-in-Aid for Scientific Research (B) (KAKENHI Grant no. 23310085) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan.

References

[1] S. F. Steinberg, "Structural basis of protein kinase C isoform function," *Physiological Reviews*, vol. 88, no. 4, pp. 1341–1378, 2008.

[2] E. M. Griner and M. G. Kazanietz, "Protein kinase C and other diacylglycerol effectors in cancer," *Nature Reviews Cancer*, vol. 7, no. 4, pp. 281–294, 2007.

[3] E. Churchill, G. Budas, A. Vallentin, T. Koyanagi, and D. Mochly-Rosen, "PKC isozymes in chronic cardiac disease: possible therapeutic targets?" *Annual Review of Pharmacology and Toxicology*, vol. 48, pp. 569–599, 2008.

[4] S. S. Palaniyandi, L. Sun, J. C. B. Ferreira, and D. Mochly-Rosen, "Protein kinase C in heart failure: a therapeutic target?" *Cardiovascular Research*, vol. 82, no. 2, pp. 229–239, 2009.

[5] M. R. Lee, W. Duan, and S. Tan, "Protein kinase C isozymes as potential therapeutic targets in immune disorders," *Expert Opinion on Therapeutic Targets*, vol. 12, no. 5, pp. 535–552, 2008.

[6] D. H. Boschelli, "Small molecule inhibitors of PKCθ as potential antiinflammatory therapeutics," *Current Topics in Medicinal Chemistry*, vol. 9, no. 7, pp. 640–654, 2009.

[7] C. A. Zarate and H. K. Manji, "Protein kinase C inhibitors: rationale for use and potential in the treatment of bipolar disorder," *CNS Drugs*, vol. 23, no. 7, pp. 569–582, 2009.

[8] A. Pascale, M. Amadio, S. Govoni, and F. Battaini, "The aging brain, a key target for the future: the protein kinase C involvement," *Pharmacological Research*, vol. 55, no. 6, pp. 560–569, 2007.

[9] R. V. Farese and M. P. Sajan, "Atypical protein kinase C in cardiometabolic abnormalities," *Current Opinion in Lipidology*, vol. 23, no. 3, pp. 175–181, 2012.

[10] M. Clarke and P. M. Dodson, "PKC inhibition and diabetic microvascular complications," *Best Practice and Research: Clinical Endocrinology and Metabolism*, vol. 21, no. 4, pp. 573–586, 2007.

[11] N. Das Evcimen and G. L. King, "The role of protein kinase C activation and the vascular complications of diabetes," *Pharmacological Research*, vol. 55, no. 6, pp. 498–510, 2007.

[12] J. H.. Kang, R. Toita, C. W. Kim, and Y. Katayama, "Protein kinase C, (PKC) isozyme-specific substrates and their design," *Biotechnology Advances*, vol. 30, no. 6, pp. 1662–1672, 2012.

[13] H. J. Mackay and C. J. Twelves, "Targeting the protein kinase C family: are we there yet?" *Nature Reviews Cancer*, vol. 7, no. 7, pp. 554–562, 2007.

[14] R. P. Danis and M. J. Sheetz, "Ruboxistaurin: PKC-β inhibition for complications of diabetes," *Expert Opinion on Pharmacotherapy*, vol. 10, no. 17, pp. 2913–2925, 2009.

[15] M. E. Sobhia, B. K. Grewal, S. P. Ml et al., "Protein kinase C inhibitors: a patent review (2008-2009)," *Expert Opinion on Therapeutic Patents*, vol. 23, no. 10, pp. 1297–1315, 2013.

[16] M. E. Sobhia, B. K. Grewal, M. L. Paul et al., "Protein kinase C inhibitors: a patent review (2010—present)," *Expert Opinion on Therapeutic Patents*, vol. 23, no. 11, pp. 1451–1468, 2013.

[17] K. Kielbassa, H.-J. Müller, H. E. Meyer, F. Marks, and M. Gschwendt, "Protein kinase Cδ-specific phosphorylation of the elongation factor eEF- 1α and an eEF-1α peptide at threonine 431," *The Journal of Biological Chemistry*, vol. 270, no. 11, pp. 6156–6162, 1995.

[18] J. H. Kang, D. Asai, S. Yamada et al., "A short peptide is a protein kinase C (PKC) α-specific substrate," *Proteomics*, vol. 8, no. 10, pp. 2006–2011, 2008.

[19] T. Kajimoto, S. Sawamura, Y. Tohyama, Y. Mori, and A. C. Newton, "Protein kinase C δ-specific activity reporter reveals agonist-evoked nuclear activity controlled by Src family of kinases," *The Journal of Biological Chemistry*, vol. 285, no. 53, pp. 41896–41910, 2010.

[20] Y. Serulle, G. Morfini, G. Pigino et al., "1-methyl-4-phenylpyridinium induces synaptic dysfunction through a pathway involving caspase and PKCδ enzymatic activities," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 104, no. 7, pp. 2437–2441, 2007.

[21] V. O. Rybin, A. Sabri, J. Short, J. C. Braz, J. D. Molkentin, and S. F. Steinberg, "Cross-regulation of novel protein kinase C (PKC) isoform function in cardiomyocytes: role of PKCε in activation loop phosphorylations and PKCδ in hydrophobic motif phosphorylations," *The Journal of Biological Chemistry*, vol. 278, no. 16, pp. 14555–14564, 2003.

[22] J. H. Kang, D. Asai, R. Toita, H. Kitazaki, and Y. Katayama, "Plasma protein kinase C (PKC)α as a biomarker for the diagnosis of cancers," *Carcinogenesis*, vol. 30, no. 11, pp. 1927–1931, 2009.

[23] J. H. Kang, Y. Asami, M. Murata et al., "Gold nanoparticle-based colorimetric assay for cancer diagnosis," *Biosensors and Bioelectronics*, vol. 25, no. 8, pp. 1869–1874, 2010.

[24] J. H. Kang, J. Oishi, J. Kim et al., "Hepatoma-targeted gene delivery using a tumor cell-specific gene regulation system combined with a human liver cell-specific bionanocapsule," *Nanomedicine: Nanotechnology, Biology, and Medicine*, vol. 6, no. 4, pp. 583–589, 2010.

[25] J. H. Kang, D. Asai, J. Kim et al., "Design of polymeric carriers for cancer-specific gene targeting: utilization of abnormal protein kinase Cα activation in cancer cells," *Journal of the American Chemical Society*, vol. 130, no. 45, pp. 14906–14907, 2008.

[26] R. Toita, J. H.. Kang, T. Tomiyama et al., "Gene carrier showing all-or-none response to cancer cell signaling," *Journal of the American Chemical Society*, vol. 134, no. 37, pp. 15410–15417, 2012.

[27] C.-C. Chen, J. Chang, and W.-C. Chen, "Role of protein kinase C subtypes α and δ in the regulation of bradykinin-stimulated phosphoinositide breakdown in astrocytes," *Molecular Pharmacology*, vol. 48, no. 1, pp. 39–47, 1995.

[28] A. Varga, G. Czifra, B. Tállai et al., "Tumor grade-dependent alterations in the protein kinase C isoform pattern in urinary bladder carcinomas," *European Urology*, vol. 46, no. 4, pp. 462–465, 2004.

[29] L. Langzam, R. Koren, R. Gal et al., "Patterns of protein kinase C isoenzyme expression in transitional cell carcinoma of bladder relation to degree of malignancy," *American Journal of Clinical Pathology*, vol. 116, no. 3, pp. 377–385, 2001.

[30] R. Koren, L. Langzam, A. Paz, P. M. Livne, R. Gal, and S. R. Sampson, "Protein kinase C (PKC) isoenzymes immunohistochemistry in lymph node revealing solution-fixed, paraffin-embedded bladder tumors," *Applied Immunohistochemistry and Molecular Morphology*, vol. 8, no. 2, pp. 166–171, 2000.

[31] C. Kong, Y. Zhu, D. Liu et al., "Role of protein kinase C-alpha in superficial bladder carcinoma recurrence," *Urology*, vol. 65, no. 6, pp. 1228–1232, 2005.

[32] A. V. Smrcka, J. H.. Brown, and G. G. Holz, "Role of phospholipase Cε in physiological phosphoinositide signaling networks," *Cellular Signalling*, vol. 24, no. 6, pp. 1333–1343, 2012.

[33] L. Yan, C. Luo, X. Wu, and Q. Zhang, "Involvement of the PLCε/PKCα pathway in human BIU-87 bladder cancer cell proliferation," *Cell Biology International*, vol. 35, no. 10, pp. 1031–1036, 2011.

[34] V. Aaltonen and J. Peltonen, "PKCα/β I inhibitor Go6976 induces dephosphorylation of constitutively hyperphosphorylated Rb and G1 arrest in T24 cells," *Anticancer Research*, vol. 30, no. 10, pp. 3995–3999, 2010.

[35] J. Koivunen, V. Aaltonen, S. Koskela, P. Lehenkar, M. Laato, and J. Peltonen, "Protein kinase C α/β inhibitor Go6976 promotes formation of cell junctions and inhibits invasion of urinary bladder carcinoma cells," *Cancer Research*, vol. 64, no. 16, pp. 5693–5701, 2004.

[36] K. A. Fitzgerald, A. G. Bowie, B. S. Skeffington, and L. A. J. O'Neill, "Ras, protein kinase Cζ, and IκB kinases 1 and 2 are downstream effectors of CD44 during the activation of NF-κB by hyaluronic acid fragments in T-24 carcinoma cells," *Journal of Immunology*, vol. 164, no. 4, pp. 2053–2063, 2000.

[37] M. Kim, H. Kwak, J. Lee et al., "17-allylamino-17-demethoxygeldanamycin down-regulates hyaluronic acid-induced glioma invasion by blocking matrix metalloproteinase-9 secretion," *Molecular Cancer Research*, vol. 6, no. 11, pp. 1657–1665, 2008.

[38] L. Y. W. Bourguignon, C. C. Spevak, G. Wong, W. Xia, and E. Gilad, "Hyaluronan-CD44 interaction with protein kinase Cε promotes oncogenic signaling by the stem cell marker nanog and the production of microRNA-21, leading to down-regulation of the tumor suppressor protein PDCD4, anti-apoptosis, and chemotherapy resistance in breast tumor cells," *The Journal of Biological Chemistry*, vol. 284, no. 39, pp. 26533–26546, 2009.

[39] C. Chen, P. Chan, S. Wang, Y. Pan, and H. Chen, "Elevated expression of protein kinase Cδ induces cell scattering upon serum deprivation," *Journal of Cell Science*, vol. 123, no. 17, pp. 2901–2913, 2010.

[40] A. K. Gupta, S. S. Galoforo, C. M. Berns et al., "Elevated levels of ERK2 in human breast carcinoma MCF-7 cells transfected with protein kinase Cα," *Cell Proliferation*, vol. 29, no. 12, pp. 655–663, 1996.

[41] H. Li, L. Zhao, Z. Yang, J. W. Funder, and J. Liu, "Telomerase is controlled by protein kinase Cα in human breast cancer cells," *The Journal of Biological Chemistry*, vol. 273, no. 50, pp. 33436–33442, 1998.

[42] J. Kim, S. H. Thorne, L. Sun, B. Huang, and D. Mochly-Rosen, "Sustained inhibition of PKCα reduces intravasation and lung seeding during mammary tumor metastasis in an *in vivo* mouse model," *Oncogene*, vol. 30, no. 3, pp. 323–333, 2011.

[43] S. Kim, J. Han, S. K. Lee et al., "Berberine suppresses the TPA-induced MMP-1 and MMP-9 expressions through the inhibition of PKC-α in breast cancer cells," *Journal of Surgical Research*, vol. 176, no. 1, pp. e21–e29, 2012.

[44] J. M. Connolly and D. P. Rose, "Expression of the invasive phenotype by MCF-7 human breast cancer cells transfected to overexpress protein kinase C-α or the erbB2 proto-oncogene," *International Journal of Oncology*, vol. 10, no. 1, pp. 71–76, 1997.

[45] M. Tan, P. Li, M. Sun, G. Yin, and D. Yu, "Upregulation and activation of PKCα by ErbB2 through Src promotes breast

cancer cell invasion that can be blocked by combined treatment with PKCα and Src inhibitors," *Oncogene*, vol. 25, no. 23, pp. 3286–3295, 2006.

[46] J. D. Noti, "Adherence to osteopontin via alphavbeta3 suppresses phorbol ester-mediated apoptosis in MCF-7 breast cancer cells that overexpress protein kinase C-alpha," *International Journal of Oncology*, vol. 17, no. 6, pp. 1237–1243, 2000.

[47] D. B. Fournier, M. Chisamore, J. R. Lurain, A. W. Rademaker, V. C. Jordan, and D. A. Tonetti, "Protein kinase C alpha expression is inversely related to ER status in endometrial carcinoma: possible role in AP-1-mediated proliferation of ER-negative endometrial cancer," *Gynecologic Oncology*, vol. 81, no. 3, pp. 366–372, 2001.

[48] Z. Li, N. A. Wang, J. Fang et al., "Role of PKC-ERK signaling in tamoxifen-induced apoptosis and tamoxifen resistance in human breast cancer cells," *Oncology Reports*, vol. 27, no. 6, pp. 1879–1886, 2012.

[49] J. W. Assender, J. M. W. Gee, I. Lewis, I. O. Ellis, J. F. R. Robertson, and R. I. Nicholson, "Protein kinase C isoform expression as a predictor of disease outcome on endocrine therapy in breast cancer," *Journal of Clinical Pathology*, vol. 60, no. 11, pp. 1216–1221, 2007.

[50] D. A. Tonetti, W. Gao, D. Escarzaga, K. Walter, A. Szafran, and J. S. Coon, "PKCα and ERβ are associated with triple-negative breast cancers in African American and Caucasian patients," *International Journal of Breast Cancer*, vol. 2012, Article ID 740353, 9 pages, 2012.

[51] W. L. Tam, H. Lu, J. Buikhuisen et al., "Protein kinase C α is a central signaling node and therapeutic target for breast cancer stem cells," *Cancer Cell*, vol. 24, no. 3, pp. 347–364, 2013.

[52] D. A. Tonetti, M. Morrow, N. Kidwai, A. Gupta, and S. Badve, "Elevated protein kinase C alpha expression may be predictive of tamoxifen treatment failure," *British Journal of Cancer*, vol. 88, no. 9, pp. 1400–1402, 2003.

[53] L. B. Frankel, A. E. Lykkesfeldt, J. B. Hansen, and J. Stenvang, "Protein kinase C α is a marker for antiestrogen resistance and is involved in the growth of tamoxifen resistant human breast cancer cells," *Breast Cancer Research and Treatment*, vol. 104, no. 2, pp. 165–179, 2007.

[54] X. Lin, Y. Yu, H. Zhao, Y. Zhang, J. Manela, and D. A. Tonetti, "Overexpression of PKCα is required to impart estradiol inhibition and tamoxifen-resistance in a T47D human breast cancer tumor model," *Carcinogenesis*, vol. 27, no. 8, pp. 1538–1546, 2006.

[55] N. Wang, Z. Li, F. Tian et al., "PKCα inhibited apoptosis by decreasing the activity of JNK in MCF-7/ADR cells," *Experimental and Toxicologic Pathology*, vol. 64, no. 5, pp. 459–464, 2012.

[56] X.-F. Le, M. Marcelli, A. McWatters et al., "Heregulin-induced apoptosis is mediated by down-regulation of Bcl-2 and activation of caspase-7 and is potentiated by impairment of protein kinase C α activity," *Oncogene*, vol. 20, no. 57, pp. 8258–8269, 2001.

[57] P. K. Gill, A. Gescher, and T. W. Gant, "Regulation of MDR1 promoter activity in human breast carcinoma cells by protein kinase C isozymes α and θ," *European Journal of Biochemistry*, vol. 268, no. 15, pp. 4151–4157, 2001.

[58] S. Ahmad and R. I. Glazer, "Expression of the antisense cDNA for protein kinase Cα attenuates resistance in doxorubicin-resistant MCF-7 breast carcinoma cells," *Molecular Pharmacology*, vol. 43, no. 6, pp. 858–862, 1993.

[59] I. Carey, C. L. Williams, D. K. Ways, and J. D. M. Noti, "Overexpression of protein kinase C-α in MCF-7 breast cancer cells results in differential regulation and expression of αvβ3 and αvβ5," *International Journal of Oncology*, vol. 15, no. 1, pp. 127–136, 1999.

[60] G. K. Lønne, L. Cornmark, I. O. Zahirovic, G. Landberg, K. Jirström, and C. Larsson, "PKCα expression is a marker for breast cancer aggressiveness," *Molecular Cancer*, vol. 9, article 76, 2010.

[61] H. Li and I. B. Weinstein, "Protein kinase C β enhances growth and expression of cyclin D1 in human breast cancer cells," *Cancer Research*, vol. 66, no. 23, pp. 11399–11408, 2006.

[62] V. C. Grossoni, L. B. Todaro, M. G. Kazanietz, E. D. Bal de Lier Joffé, and A. J. Urtreger, "Opposite effects of protein kinase C beta1 (PKCβ1) and PKCε in the metastatic potential of a breast cancer murine model," *Breast Cancer Research and Treatment*, vol. 118, no. 3, pp. 469–480, 2009.

[63] C. Körner, I. Keklikoglou, C. Bender, A. Wörner, and E. Münstermann, "MicroRNA-31 sensitizes human breast cells to apoptosis by direct targeting of protein kinase C ϵ (PKCϵ)," *The Journal of Biological Chemistry*, vol. 288, no. 12, pp. 8750–8761, 2013.

[64] M. H. Aziz, H. Shen, and C. G. Maki, "Glucocorticoid receptor activation inhibits p53-induced apoptosis of MCF10Amyc cells via induction of protein kinase Cε," *The Journal of Biological Chemistry*, vol. 287, no. 35, pp. 29825–29836, 2012.

[65] D. Lu, J. Huang, and A. Basu, "Protein kinase Cε activates protein kinase B/Akt via DNA-PK to protect against tumor necrosis factor-α-induced cell death," *The Journal of Biological Chemistry*, vol. 281, no. 32, pp. 22799–22807, 2006.

[66] E. Shankar, U. Sivaprasad, and A. Basu, "Protein kinase Cε confers resistance of MCF-7 cells to TRAIL by Akt-dependent activation of Hdm2 and downregulation of p53," *Oncogene*, vol. 27, no. 28, pp. 3957–3966, 2008.

[67] L. Huang, H. Cheng, R. Isom, C. Chen, R. A. Levine, and B. U. Pauli, "Protein kinase Cε mediates polymeric fibronectin assembly on the surface of blood-borne rat breast cancer cells to promote pulmonary metastasis," *The Journal of Biological Chemistry*, vol. 283, no. 12, pp. 7616–7627, 2008.

[68] D. Pal, S. P. Outram, and A. Basu, "Upregulation of PKCη by PKCε and PDK1 involves two distinct mechanisms and promotes breast cancer cell survival," *Biochimica et Biophysica Acta*, vol. 1830, no. 8, pp. 4040–4045, 2013.

[69] G. Karp, A. Maissel, and E. Livneh, "Hormonal regulation of PKC: estrogen up-regulates PKCη expression in estrogen-responsive breast cancer cells," *Cancer Letters*, vol. 246, no. 1-2, pp. 173–181, 2007.

[70] G. Karp, S. Abu-Ghanem, V. Novack et al., "Localization of PKCη in cell membranes as a predictor for breast cancer response to treatment," *Onkologie*, vol. 35, no. 5, pp. 260–266, 2012.

[71] N. Rotem-Dai, G. Oberkovitz, S. Abu-Ghanem, and E. Livneh, "PKCη confers protection against apoptosis by inhibiting the pro-apoptotic JNK activity in MCF-7 cells," *Experimental Cell Research*, vol. 315, no. 15, pp. 2616–2623, 2009.

[72] G. R. Akkaraju and A. Basu, "Overexpression of protein kinase C-η attenuates caspase activation and tumor necrosis factor-α-induced cell death," *Biochemical and Biophysical Research Communications*, vol. 279, no. 1, pp. 103–107, 2000.

[73] P. A. Masso-Welch, J. S. Winston, S. Edge et al., "Altered expression and localization of PKC eta in human breast tumors,"

Breast Cancer Research and Treatment, vol. 68, no. 3, pp. 211–223, 2001.

[74] S. Huang, N. Ouyang, L. Lin et al., "HGF-induced PKCζ activation increases functional CXCR4 expression in human breast cancer cells," *PLoS ONE*, vol. 7, no. 1, Article ID e29124, 2012.

[75] P. Yi, Q. Feng, L. Amazit et al., "Atypical protein kinase C regulates dual pathways for degradation of the oncogenic coactivator SRC-3/ AIB1," *Molecular Cell*, vol. 29, no. 4, pp. 465–476, 2008.

[76] M. Mao, X. Fang, Y. Lu, R. LaPushin, R. C. Bast Jr., and G. B. Mills, "Inhibition of growth-factor-induced phosphorylation and activation of protein kinase B/Akt by atypical protein kinase C in breast cancer cells," *Biochemical Journal*, vol. 352, no. 2, pp. 475–482, 2000.

[77] K. Belguise, S. Milord, F. Galtier, G. Moquet-Torcy, M. Piechaczyk, and D. Chalbos, "The PKCθ pathway participates in the aberrant accumulation of Fra-1 protein in invasive ER-negative breast cancer cells," *Oncogene*, vol. 31, no. 47, pp. 4889–4897, 2012.

[78] K. Belguise and G. E. Sonenshein, "PKCθ promotes c-Rel-driven mammary tumorigenesis in mice and humans by repressing estrogen receptor α synthesis," *The Journal of Clinical Investigation*, vol. 117, no. 12, pp. 4009–4021, 2007.

[79] E. McKiernan, K. O'Brien, N. Grebenchtchikov et al., "Protein kinase Cδ expression in breast cancer as measured by real-time PCR, western blotting and ELISA," *British Journal of Cancer*, vol. 99, no. 10, pp. 1644–1650, 2008.

[80] S. Yin, S. Sethi, and K. B. Reddy, "Protein kinase Cδ and caspase-3 modulate TRAIL-induced apoptosis in breast tumor cells," *Journal of Cellular Biochemistry*, vol. 111, no. 4, pp. 979–987, 2010.

[81] J. Zhang, N. Liu, J. Zhang, S. Liu, Y. Liu, and D. Zheng, "PKCδ protects human breast tumor MCF-7 cells against tumor necrosis factor-related apoptosis-inducing ligand-mediated apoptosis," *Journal of Cellular Biochemistry*, vol. 96, no. 3, pp. 522–532, 2005.

[82] M. Kim, J. Ju, K. Jang et al., "Protein kinase Cδ negatively regulates Notch1-dependent transcription via a kinase-independent mechanism *in vitro*," *Biochimica et Biophysica Acta*, vol. 1823, no. 2, pp. 387–397, 2012.

[83] Y. S. Kim, H. T. An, J. Kim, and J. Ko, "Effects of protein kinase Cδ and phospholipase C-γ1 on monocyte chemoattractant protein-1 expression in taxol-induced breast cancer cell death," *International Journal of Molecular Medicine*, vol. 24, no. 6, pp. 853–858, 2009.

[84] M. I. Díaz Bessone, D. E. Berardi, P. B. Campodónico et al., "Involvement of PKC delta (PKCδ) in the resistance against different doxorubicin analogs," *Breast Cancer Research and Treatment*, vol. 126, no. 3, pp. 577–587, 2011.

[85] V. C. Grossoni, K. B. Falbo, M. G. Kazanietz, E. D. Bal de Lier Joffé, and A. J. Urtreger, "Protein kinase C δ enhances proliferation and survival of murine mammary cells," *Molecular Carcinogenesis*, vol. 46, no. 5, pp. 381–390, 2007.

[86] S. M. Nabha, S. Glaros, M. Hong et al., "Upregulation of PKC-δ contributes to antiestrogen resistance in mammary tumor cells," *Oncogene*, vol. 24, no. 19, pp. 3166–3176, 2005.

[87] G. K. Lønne, K. C. Masoumi, J. Lennartsson, and C. Larsson, "Protein kinase Cδ supports survival of MDA-MB-231 breast cancer cells by suppressing the ERK1/2 pathway," *The Journal of Biological Chemistry*, vol. 284, no. 48, pp. 33456–33465, 2009.

[88] Y. H. Zeidan, B. X. Wu, R. W. Jenkins, L. M. Obeid, and Y. A. Hannun, "A novel role for protein kinase Cδ-mediated phosphorylation of acid sphingomyelinase in UV light-induced mitochondrial injury," *The FASEB Journal*, vol. 22, no. 1, pp. 183–193, 2008.

[89] S. A. Lee and M. Jung, "The nucleoside analog sangivamycin induces apoptotic cell death in breast carcinoma MCF7/ adriamycin-resistant cells via protein kinase Cδ and JNK activation," *The Journal of Biological Chemistry*, vol. 282, no. 20, pp. 15271–15283, 2007.

[90] I. Vucenik, G. Ramakrishna, K. Tantivejkul, L. M. Anderson, and D. Ramljak, "Inositol hexaphosphate (IP_6) blocks proliferation of human breast cancer cells through a PKCδ-dependent increase in $p27^{Kip1}$ and decrease in retinoblastoma protein (pRb) phosphorylation," *Breast Cancer Research and Treatment*, vol. 91, no. 1, pp. 35–45, 2005.

[91] G. Yokoyama, T. Fujii, K. Tayama, H. Yamana, M. Kuwano, and K. Shirouzu, "PKCδ and MAPK mediate G1 arrest induced by PMA in SKBR-3 breast cancer cells," *Biochemical and Biophysical Research Communications*, vol. 327, no. 3, pp. 720–726, 2005.

[92] B. L. Allen-Petersen, C. J. Carter, A. M. Ohm, and M. E. Reyland, "Protein kinase Cδ is required for ErbB2-driven mammary gland tumorigenesis and negatively correlates with prognosis in human breast cancer," *Oncogene*, vol. 33, no. 10, pp. 1306–1315, 2014.

[93] S. Greco, C. Storelli, and S. Marsigliante, "Protein kinase C (PKC)-δ/-ε mediate the PKC/Akt-dependent phosphorylation of extracellular signal-regulated kinases 1 and 2 in MCF-7 cells stimulated by bradykinin," *Journal of Endocrinology*, vol. 188, no. 1, pp. 79–89, 2006.

[94] B. de Servi, A. Hermani, S. Medunjanin, and D. Mayer, "Impact of PKCδ on estrogen receptor localization and activity in breast cancer cells," *Oncogene*, vol. 24, no. 31, pp. 4946–4955, 2005.

[95] V. G. Keshamouni, R. R. Mattingly, and K. B. Reddy, "Mechanism of 17-β-estradiol-induced Erk1/2 activation in breast cancer cells. A role for HER2 and PKC-δ," *The Journal of Biological Chemistry*, vol. 277, no. 25, pp. 22558–22565, 2002.

[96] M. Shanmugam, N. L. Krett, E. T. Maizels, F. M. Murad, S. T. Rosen, and M. Hunzicker-Dunn, "A role for protein kinase C δ in the differential sensitivity of MCF-7 and MDA-MB 231 human breast cancer cells to phorbol ester-induced growth arrest and $p21^{WAFI/CIP1}$ induction," *Cancer Letters*, vol. 172, no. 1, pp. 43–53, 2001.

[97] Y. Zuo, Y. Wu, and C. Chakraborty, "Cdc42 negatively regulates intrinsic migration of highly aggressive breast cancer cells," *Journal of Cellular Physiology*, vol. 227, no. 4, pp. 1399–1407, 2012.

[98] C. Lin, W. Hou, S. Shen et al., "Quercetin inhibition of tumor invasion via suppressing PKCδ/ERK/ AP-1-dependent matrix metalloproteinase-9 activation in breast carcinoma cells," *Carcinogenesis*, vol. 29, no. 9, pp. 1807–1815, 2008.

[99] S. K. Park, Y. S. Hwang, K. Park, H. Park, J. Y. Seo, and W. Chung, "Kalopanaxsaponin A inhibits PMA-induced invasion by reducing matrix metalloproteinase-9 via PI3K/Akt- and PKCδ-mediated signaling in MCF-7 human breast cancer cells," *Carcinogenesis*, vol. 30, no. 7, pp. 1225–1233, 2009.

[100] D. Alonso-Escolano, C. Medina, K. Cieslik et al., "Protein kinase Cδ mediates platelet-induced breast cancer cell invasion," *Journal of Pharmacology and Experimental Therapeutics*, vol. 318, no. 1, pp. 373–380, 2006.

[101] D. Jackson, Y. Zheng, D. Lyo et al., "Suppression of cell migration by protein kinase Cδ," *Oncogene*, vol. 24, no. 18, pp. 3067–3072, 2005.

[102] L. A. Davidson, Y.-H. Jiang, J. N. Derr, H. M. Aukema, J. R. Lupton, and R. S. Chapkin, "Protein kinase C isoforms in human and rat colonic mucosa," *Archives of Biochemistry and Biophysics*, vol. 312, no. 2, pp. 547–553, 1994.

[103] S. Doi, D. Goldstein, H. Hug, and I. B. Weinstein, "Expression of multiple isoforms of protein kinase C in normal human colon mucosa and colon tumors and decreased levels of protein kinase C β and η mRNAs in the tumors," *Molecular Carcinogenesis*, vol. 11, no. 4, pp. 197–203, 1994.

[104] J. Pongracz, P. Clark, J. P. Neoptolemos, and J. M. Lord, "Expression of protein kinase C isoenzymes in colorectal cancer tissue and their differential activation by different bile acids," *International Journal of Cancer*, vol. 61, no. 1, pp. 35–39, 1995.

[105] G. Gobbi, D. di Marcantonio, C. Micheloni et al., "TRAIL up-regulation must be accompanied by a reciprocal PKCε down-regulation during differentiation of colonic epithelial cell: implications for colorectal cancer cell differentiation," *Journal of Cellular Physiology*, vol. 227, no. 2, pp. 630–638, 2012.

[106] I. Heider, B. Schulze, E. Oswald, P. Henklein, J. Scheele, and R. Kaufmann, "PAR_1-type thrombin receptor stimulates migration and matrix adhesion of human colon carcinoma cells by a PKCε-dependent mechanism," *Oncology Research*, vol. 14, no. 10, pp. 475–482, 2004.

[107] M. L. Saxon, X. Zhao, and J. D. Black, "Activation of protein kinase C isozymes is associated with post-mitotic events in intestinal epithelial cells in situ," *The Journal of Cell Biology*, vol. 126, no. 3, pp. 747–763, 1994.

[108] G. Verstovsek, A. Byrd, M. R. Frey, N. J. Petrelli, and J. D. Black, "Colonocyte differentiation is associated with increased expression and altered distribution of protein kinase C isozymes," *Gastroenterology*, vol. 115, no. 1, pp. 75–85, 1998.

[109] B. Scaglione-Sewell, C. Abraham, M. Bissonnette et al., "Decreased PKC-α expression increases cellular proliferation, decreases differentiation, and enhances the transformed phenotype of CaCo-2 cells," *Cancer Research*, vol. 58, no. 5, pp. 1074–1081, 1998.

[110] H. Oster and M. Leitges, "Protein kinase C α but not PKCζ suppresses intestinal tumor formation in $Apc^{Min/+}$ mice," *Cancer Research*, vol. 66, no. 14, pp. 6955–6963, 2006.

[111] M. A. Pysz, O. V. Leontieva, N. W. Bateman et al., "PKCα tumor suppression in the intestine is associated with transcriptional and translational inhibition of cyclin D1," *Experimental Cell Research*, vol. 315, no. 8, pp. 1415–1428, 2009.

[112] F. Hao, M. A. Pysz, K. J. Curry et al., "Protein kinase Cα signaling regulates inhibitor of DNA binding 1 in the intestinal epithelium," *The Journal of Biological Chemistry*, vol. 286, no. 20, pp. 18104–18117, 2011.

[113] J. Gwak, S. Jung, D. Kang et al., "Stimulation of protein kinase C-α suppresses colon cancer cell proliferation by down-regulation of β-catenin," *Journal of Cellular and Molecular Medicine*, vol. 13, no. 8B, pp. 2171–2180, 2009.

[114] J. M. Lee, I. S. Kim, H. Kim et al., "RORα attenuates Wnt/β-catenin signaling by PKCα-dependent phosphorylation in colon cancer," *Molecular Cell*, vol. 37, no. 2, pp. 183–195, 2010.

[115] B. Wu, H. Zhou, L. Hu, Y. Mu, and Y. Wu, "Involvement of PKCα activation in TF/VIIa/PAR2-induced proliferation, migration, and survival of colon cancer cell SW620," *Tumor Biology*, vol. 34, no. 2, pp. 837–846, 2013.

[116] K. Masur, K. Lang, B. Niggemann, K. S. Zanker, and F. Entschladen, "High PKC α and low E-cadherin expression contribute to high migratory activity of colon carcinoma cells," *Molecular Biology of the Cell*, vol. 12, no. 7, pp. 1973–1982, 2001.

[117] S. Chakrabarty, S. Rajagopal, and T. L. Moskal, "Protein kinase Cα controls the adhesion but not the antiproliferative response of human colon carcinoma cells to transforming growth factor β1: identification of two distinct branches of post-protein kinase Cα adhesion signal pathway," *Laboratory Investigation*, vol. 78, no. 4, pp. 413–421, 1998.

[118] H. Wang and S. Chakrabarty, "Requirement of protein kinase Cα, extracellular matrix remodeling, and cell-matrix interaction for transforming growth factorβ-regulated expression of E-cadherin and catenins," *Journal of Cellular Physiology*, vol. 187, no. 2, pp. 188–195, 2001.

[119] K. R. Gravitt, N. E. Ward, D. Fan, J. M. Skibber, B. Levin, and C. A. O'Brian, "Evidence that protein kinase C-α activation is a critical event in phorbol ester-induced multiple drug resistance in human colon cancer cells," *Biochemical Pharmacology*, vol. 48, no. 2, pp. 375–381, 1994.

[120] S. K. Lee, A. Shehza, J. C. Jung et al., "Protein kinase Cα protects against multidrug resistance in human colon cancer cells," *Molecules and Cells*, vol. 34, no. 1, pp. 61–69, 2012.

[121] C. A. M. la Porta, E. Dolfini, and R. Comolli, "Inhibition of protein kinase C-α isoform enhances the P-glycoprotein expression and the survival of LoVo human colon adenocarcinoma cells to doxorubicin exposure," *British Journal of Cancer*, vol. 78, no. 10, pp. 1283–1287, 1998.

[122] S. Chakrabarty and S. Huang, "Modulation of chemosensitivity in human colon carcinoma cells by downregulating protein kinase Cα expression," *Journal of Experimental Therapeutics and Oncology*, vol. 1, no. 4, pp. 218–221, 1996.

[123] N. R. Murray, L. A. Davidson, R. S. Chapkin, W. C. Gustafson, D. G. Schattenberg, and A. P. Fields, "Overexpression of protein kinase C β(II) induces colonic hyperproliferation and increased sensitivity to colon carcinogenesis," *The Journal of Cell Biology*, vol. 145, no. 4, pp. 699–711, 1999.

[124] N. R. Murray, C. Weems, L. Chen et al., "Protein kinase C βII and TGFβRII in ω-3 fatty acid-mediated inhibition of colon carcinogenesis," *The Journal of Cell Biology*, vol. 157, no. 6, pp. 915–920, 2002.

[125] Y. Gökmen-Polar, N. R. Murray, M. A. Velasco, Z. Gatalica, and A. P. Fields, "Elevated protein kinase C βII is an early promotive event in colon carcinogenesis," *Cancer Research*, vol. 61, no. 4, pp. 1375–1381, 2001.

[126] Y. Liu, W. Su, E. A. Thompson, M. Leitges, N. R. Murray, and A. P. Fields, "Protein kinase C βII regulates its own expression in rat intestinal epithelial cells and the colonic epithelium *in vivo*," *The Journal of Biological Chemistry*, vol. 279, no. 44, pp. 45556–45563, 2004.

[127] W. Yu, N. R. Murray, C. Weems et al., "Role of cyclooxygenase 2 in protein kinase C βII-mediated colon carcinogenesis," *The Journal of Biological Chemistry*, vol. 278, no. 13, pp. 11167–11174, 2003.

[128] J. Zhang, P. Z. Anastasiadis, Y. Liu, E. A. Thompson, and A. P. Fields, "Protein kinase c (PKC) βII induces cell invasion through a Ras/Mek-, PKCι/Rac 1-dependent signaling pathway," *The Journal of Biological Chemistry*, vol. 279, no. 21, pp. 22118–22123, 2004.

[129] L. A. Davidson, R. E. Brown, W. L. Chang et al., "Morphodensitometric analysis of protein kinase C βII expression in rat colon: modulation by diet and relation to in situ cell proliferation and apoptosis," *Carcinogenesis*, vol. 21, no. 8, pp. 1513–1519, 2000.

[130] P. Cesaro, E. Raiteri, M. Démoz et al., "Expression of protein kinase C β1 confers resistance to TNFα- and paclitaxel-induced

apoptosis in HT-29 colon carcinoma cells," *International Journal of Cancer*, vol. 93, no. 2, pp. 179–184, 2001.

[131] H. Lee, J. Ghose-Dastidar, S. Winawer, and E. Friedman, "Signal transduction through extracellular signal-regulated kinase-like pp57 blocked in differentiated cells having low protein kinase Cβ activity," *The Journal of Biological Chemistry*, vol. 268, no. 7, pp. 5255–5263, 1993.

[132] S. Sauma, Z. Yan, S. Ohno, and E. Friedman, "Protein kinase Cβ1 and protein kinase Cβ2 activate p57 mitogen- activated protein kinase and block differentiation in colon carcinoma cells," *Cell Growth & Differentiation*, vol. 7, no. 5, pp. 587–594, 1996.

[133] A. P. Fields, S. R. Calcagno, M. Krishna, S. Rak, M. Leitges, and N. R. Murray, "Protein kinase cβ is an effective target for chemoprevention of colon cancer," *Cancer Research*, vol. 69, no. 4, pp. 1643–1650, 2009.

[134] N. R. Murray, L. Jamieson, W. Yu et al., "Protein kinase Cι is required for Ras transformation and colon carcinogenesis *in vivo*," *The Journal of Cell Biology*, vol. 164, no. 6, pp. 797–802, 2004.

[135] N. R. Murray, J. Weems, U. Braun, M. Leitges, and A. P. Fields, "Protein kinase C βII and PKCι/λ: collaborating partners in colon cancer promotion and progression," *Cancer Research*, vol. 69, no. 2, pp. 656–662, 2009.

[136] S. I. Oikarinen, A. Pajari, I. Salminen, S. Heinonen, H. Adlercreutz, and M. Mutanen, "Effects of a flaxseed mixture and plant oils rich in α-linolenic acid on the adenoma formation in multiple intestinal neoplasia (Min) mice," *British Journal of Nutrition*, vol. 94, no. 4, pp. 510–518, 2005.

[137] R. Mustafi, S. Cerda, A. Chumsangsri, A. Fichera, and M. Bissonnette, "Protein kinase-ζ inhibits collagen I-dependent and anchorage-independent growth and enhances apoptosis of human Caco-2 cells," *Molecular Cancer Research*, vol. 4, no. 9, pp. 683–694, 2006.

[138] L. Ma, Y. Tao, A. Duran et al., "Control of nutrient stress-induced metabolic reprogramming by PKCζ in tumorigenesis," *Cell*, vol. 152, no. 3, pp. 599–611, 2013.

[139] L. B. Luna-Ulloa, J. G. Hernández-Maqueda, P. Santoyo-Ramos, M. C. Castañeda-Patlán, and M. Robles-Flores, "Protein kinase C ζ is a positive modulator of canonical wnt signaling pathway in tumoral colon cell lines," *Carcinogenesis*, vol. 32, no. 11, pp. 1615–1624, 2011.

[140] Y. Qin, Y. Tang, A. V. Schally, and B. S. Beckman, "Dexniguldipine hydrochloride inhibits growth of human HT-29 colon carcinoma cells and expression of protein kinase C Δ and ζ," *International Journal of Oncology*, vol. 7, no. 5, pp. 1073–1077, 1995.

[141] H. K. Roy, M. Bissonnette, B. P. Frawley Jr. et al., "Selective preservation of protein kinase C-ζ in the chemoprevention of azoxymethane-induced colonic tumors by piroxicam," *FEBS Letters*, vol. 366, no. 2-3, pp. 143–145, 1995.

[142] J. G. Hernández-Maqueda, L. B. Luna-Ulloa, P. Santoyo-Ramos, M. C. Castañeda-Patlán, and M. Robles-Flores, "Protein kinase C delta negatively modulates canonical Wnt pathway and cell proliferation in colon tumor cell lines," *PLoS ONE*, vol. 8, no. 3, Article ID e58540, 2013.

[143] G. Perletti, E. Marras, D. Osti, L. Felici, S. Zaro, and M. de Eguileor, "PKCδ requires p53 for suppression of the transformed phenotype in human colon cancer cells," *Journal of Cellular and Molecular Medicine*, vol. 8, no. 4, pp. 563–569, 2004.

[144] G. Perletti, E. Marras, D. Dondi et al., "$p21^{Waf1/Cip1}$ and p53 are downstream effectors of protein kinase C delta in tumor suppression and differentiation in human colon cancer cells," *International Journal of Cancer*, vol. 113, no. 1, pp. 42–53, 2005.

[145] Y. H. Kim, J. H.. Lim, T. J. Lee, J. W. Park, and T. K. Kwon, "Expression of cyclin D3 through Sp1 sites by histone deacetylase inhibitors is mediated with protein kinase C-δ (PKC-δ) signal pathway," *Journal of Cellular Biochemistry*, vol. 101, no. 4, pp. 987–995, 2007.

[146] S. R. Cerda, R. Mustafi, H. Little et al., "Protein kinase C delta inhibits Caco-2 cell proliferation by selective changes in cell cycle and cell death regulators," *Oncogene*, vol. 25, no. 22, pp. 3123–3138, 2006.

[147] S. R. Cerda, M. Bissonnette, B. Scaglione-Sewell et al., "PKC-δ inhibits anchorage-dependent and -independent growth, enhances differentiation, and increases apoptosis in CaCo-2 cells," *Gastroenterology*, vol. 120, no. 7, pp. 1700–1712, 2001.

[148] A. E. Lewis, R. Susarla, B. C. Y. Wong, M. J. S. Langman, and M. C. Eggo, "Protein kinase C delta is not activated by caspase-3 and its inhibition is sufficient to induce apoptosis in the colon cancer line, COLO 205," *Cellular Signalling*, vol. 17, no. 2, pp. 253–262, 2005.

[149] Q. Wang, X. Wang, and B. M. Evers, "Induction of cIAP-2 in human colon cancer cells through PKCδ/NF-κB," *The Journal of Biological Chemistry*, vol. 278, no. 51, pp. 51091–51099, 2003.

[150] Q. Wang, X. Wang, Y. Zhou, and B. M. Evers, "PKCδ-mediated regulation of FLIP expression in human colon cancer cells," *International Journal of Cancer*, vol. 118, no. 2, pp. 326–334, 2006.

[151] D. H. Kho, J. A. Bae, J. H.. Lee et al., "KITENIN recruits Dishevelled/PKCd to form a functional complex and controls the migration and invasiveness of colorectal cancer cells," *Gut*, vol. 58, no. 4, pp. 509–519, 2009.

[152] M. Park, W. K. Kim, M. Song et al., "Protein kinase C-δ-mediated recycling of active KIT in colon cancer," *Clinical Cancer Research*, vol. 19, no. 18, pp. 4961–4971, 2013.

[153] A. Doller, S. Schulz, J. Pfeilschifter, and W. Eberhardt, "RNA-dependent association with myosin IIA promotes F-actin-guided trafficking of the ELAV-like protein HuR to polysomes," *Nucleic Acids Research*, vol. 41, no. 19, pp. 9152–9167, 2013.

[154] A. Sadok, V. Bourgarel-Rey, F. Gattacceca, C. Penel, M. Lehmann, and H. Kovacic, "Nox1-dependent superoxide production controls colon adenocarcinoma cell migration," *Biochimica et Biophysica Acta*, vol. 1783, no. 1, pp. 23–33, 2008.

[155] S. C. Lin, W. Y. Chen, K. Y. Lin et al., "Clinicopathological correlation and prognostic significance of protein kinase Cα overexpression in human gastric carcinoma," *PLoS ONE*, vol. 8, no. 2, Article ID e56675, 2013.

[156] K. Lin, C. Fang, Y. Uen et al., "Overexpression of protein kinase Cα mRNA may be an independent prognostic marker for gastric carcinoma," *Journal of Surgical Oncology*, vol. 97, no. 6, pp. 538–543, 2008.

[157] Y. Han, Z. Han, X. Zhou et al., "Expression and function of classical protein kinase C isoenzymes in gastric cancer cell line and its drug-resistant sublines," *World Journal of Gastroenterology*, vol. 8, no. 3, pp. 441–445, 2002.

[158] D. Wu, F. Sui, C. Du et al., "Antisense expression of PKCα improved sensitivity of SGC7901/VCR cells to doxorubicin," *World Journal of Gastroenterology*, vol. 15, no. 10, pp. 1259–1263, 2009.

[159] X. Jiang, S. Tu, J. Cui et al., "Antisense targeting protein kinase C α and β1 inhibits gastric carcinogenesis," *Cancer Research*, vol. 64, no. 16, pp. 5787–5794, 2004.

[160] M. J. Redlak, J. J. Power, and T. A. Miller, "Aspirin-induced apoptosis in human gastric cancer epithelial cells: relationship with protein kinase C signaling," *Digestive Diseases and Sciences*, vol. 52, no. 3, pp. 810–816, 2007.

[161] M. J. Atten, E. Godoy-Romero, B. M. Attar, T. Milson, M. Zopel, and O. Holian, "Resveratrol regulates cellular PKC α and δ to inhibit growth and induce apoptosis in gastric cancer cells," *Investigational New Drugs*, vol. 23, no. 2, pp. 111–119, 2005.

[162] H. Okuda, M. Adachi, M. Miyazawa, Y. Hinoda, and K. Imai, "Protein kinase Cα promotes apoptotic cell death in gastric cancer cells depending upon loss of anchorage," *Oncogene*, vol. 18, no. 40, pp. 5604–5609, 1999.

[163] B. Zhang and C. Xia, "12-O-tetradecanoylphorbol-1,3-acetate induces the negative regulation of protein kinase B by protein kinase Cα during gastric cancer cell apoptosis," *Cellular and Molecular Biology Letters*, vol. 15, no. 3, pp. 377–394, 2010.

[164] G. H. Zhu, B. C. Y. Wong, E. D. Slosberg et al., "Overexpression of protein kinase C-β1 isoenzyme suppresses indomethacin-induced apoptosis in gastric epithelial cells," *Gastroenterology*, vol. 118, no. 3, pp. 507–514, 2000.

[165] X. Jiang, S. Lam, M. C. M. Lin et al., "Novel target for induction of apoptosis by cyclo-oxygenase-2 inhibitor SC-236 through a protein kinase C-β_1-dependent pathway," *Oncogene*, vol. 21, no. 39, pp. 6113–6122, 2002.

[166] K. W. Lee, S. G. Kim, H. P. Kim et al., "Enzastaurin, a protein kinase Cβ inhibitor, suppresses signaling through the ribosomal S6 kinase and bad pathways and induces apoptosis in human gastric cancer cells," *Cancer Research*, vol. 68, no. 6, pp. 1916–1926, 2008.

[167] M. Lisovsky, F. Ogawa, K. Dresser, B. Woda, and G. Y. Lauwers, "Loss of cell polarity protein Lgl2 in foveolar-type gastric dysplasia: correlation with expression of the apical marker aPKC-zeta," *Virchows Archiv*, vol. 457, no. 6, pp. 635–642, 2010.

[168] R. Takagawa, K. Akimoto, Y. Ichikawa et al., "High expression of atypical protein kinase C λ/ι in gastric cancer as a prognostic factor for recurrence," *Annals of Surgical Oncology*, vol. 17, no. 1, pp. 81–88, 2010.

[169] Y. Yoshihama, Y. Izumisawa, K. Akimoto et al., "High expression of KIBRA in low atypical protein kinase C-expressing gastric cancer correlates with lymphatic invasion and poor prognosis," *Cancer Science*, vol. 104, no. 2, pp. 259–265, 2013.

[170] Y. Iioka, K. Mishima, N. Azuma et al., "Overexpression of protein kinase Cδ enhances cisplatin-induced cytotoxicity correlated with p53 in gastric cancer cell line," *Pathobiology*, vol. 72, no. 3, pp. 152–159, 2005.

[171] T. Kanno, T. Nishimoto, Y. Fujita, A. Gotoh, T. Nakano, and T. Nishizaki, "Sphingosine induces apoptosis in MKN-28 human gastric cancer cells in an SDK-dependent manner," *Cellular Physiology and Biochemistry*, vol. 30, pp. 987–994, 2012.

[172] M. Lee, T. Y. Kim, Y. Kim et al., "The signaling network of transforming growth factor β1, protein kinase Cδ and integrin underlies the spreading and invasiveness of gastric carcinoma cells," *Molecular and Cellular Biology*, vol. 25, no. 16, pp. 6921–6936, 2005.

[173] H. E. Lee, M. A. Kim, H. S. Lee, B. L. Lee, and W. H. Kim, "Characteristics of KIT-negative gastrointestinal stromal tumours and diagnostic utility of protein kinase C theta immunostaining," *Journal of Clinical Pathology*, vol. 61, no. 6, pp. 722–729, 2008.

[174] P. Blay, A. Astudillo, J. M. Buesa et al., "Protein kinase C θ is highly expressed in gastrointestinal stromal tumors but not in other mesenchymal neoplasias," *Clinical Cancer Research*, vol. 10, no. 12, part 1, pp. 4089–4095, 2004.

[175] W.-B. Ou, M.-J. Zhu, G. D. Demetri, C. D. M. Fletcher, and J. A. Fletcher, "Protein kinase C-θ regulates KIT expression and proliferation in gastrointestinal stromal tumors," *Oncogene*, vol. 27, no. 42, pp. 5624–5634, 2008.

[176] A. Motegi, S. Sakurai, H. Nakayama, T. Sano, T. Oyama, and T. Nakajima, "PKC theta, a novel immunohistochemical marker for gastrointestinal stromal tumors (GIST), especially useful for identifying KIT-negative tumors," *Pathology International*, vol. 55, no. 3, pp. 106–112, 2005.

[177] G. Kang, A. Srivastava, Y. E. Kim et al., "DOG1 and PKC-θ-are useful in the diagnosis of KIT-negative gastrointestinal stromal tumors," *Modern Pathology*, vol. 24, no. 6, pp. 866–875, 2011.

[178] C. Wang, M. S. Jin, Y. B. Zou et al., "Diagnostic significance of DOG-1 and PKC-θ expression and c-Kit/PDGFRA mutations in gastrointestinal stromal tumours," *Scandinavian Journal of Gastroenterology*, vol. 48, no. 9, pp. 1055–1065, 2013.

[179] K. Kim, D. W. Kang, W. S. Moon et al., "PKCθ expression in gastrointestinal stromal tumor," *Modern Pathology*, vol. 19, no. 11, pp. 1480–1486, 2006.

[180] M. J. Ríos-Moreno, S. Jaramillo, S. Pereira Gallardo et al., "Gastrointestinal stromal tumors (GISTs): CD117, DOG-1 and PKCθ expression. Is there any advantage in using several markers?" *Pathology Research and Practice*, vol. 208, no. 2, pp. 74–81, 2012.

[181] P. Y. Wen and S. Kesari, "Malignant gliomas in adults," *The New England Journal of Medicine*, vol. 359, no. 5, pp. 492–507, 2008.

[182] C.-C. Chen, "Protein kinase Cα, δ, ε and ζ in C6 glioma cells. TPA induces translocation and down-regulation of conventional and new PKC isoforms but not atypical PKC ζ," *FEBS Letters*, vol. 332, no. 1-2, pp. 169–173, 1993.

[183] M. I. González, B. T. S. Susarla, and M. B. Robinson, "Evidence that protein kinase Cα interacts with and regulates the glial glutamate transporter GLT-1," *Journal of Neurochemistry*, vol. 94, no. 5, pp. 1180–1188, 2005.

[184] H. Xiao, D. A. Goldthwait, and T. Mapstone, "The identification of four protein kinase C isoforms in human glioblastoma cell lines: PKC alpha, gamma, epsilon, and zeta," *Journal of Neurosurgery*, vol. 81, no. 5, pp. 734–740, 1994.

[185] A. Misra-Press, A. P. Fields, D. Samols, and D. A. Goldthwait, "Protein kinase C isoforms in human glioblastoma cells," *Glia*, vol. 6, no. 3, pp. 188–197, 1992.

[186] R. Mandil, E. Ashkenazi, M. Blass et al., "Protein kinase Cα and protein kinase Cδ play opposite roles in the proliferation and apoptosis of glioma cells," *Cancer Research*, vol. 61, no. 11, pp. 4612–4619, 2001.

[187] T. Todo, N. Shitara, H. Nakamura, K. Takakura, and K. Ikeda, "Immunohistochemical demonstration of protein kinase C isozymes in human brain tumors," *Neurosurgery*, vol. 29, no. 3, pp. 399–404, 1991.

[188] D. L. Benzil, S. D. Finkelstein, M. H. Epstein, and P. W. Finch, "Expression pattern of α-protein kinase C in human astrocytomas indicates a role in malignant progression," *Cancer Research*, vol. 52, no. 10, pp. 2951–2956, 1992.

[189] M. Leirdal and M. Sioud, "Protein kinase Cα isoform regulates the activation of the MAP kinase ERK1/2 in human glioma cells: involvement in cell survival and gene expression," *Molecular Cell Biology Research Communications*, vol. 4, no. 2, pp. 106–110, 2000.

[190] Q. Fan, C. Cheng, Z. A. Knight et al., "EGFR signals to mTOR through PKC and independently of Akt in glioma," *Science Signaling*, vol. 2, no. 55, article ra4, 2009.

[191] A. J. Cameron, K. J. Procyk, M. Leitges, and P. J. Parker, "PKC alpha protein but not kinase activity is critical for glioma cell proliferation and survival," *International Journal of Cancer*, vol. 123, no. 4, pp. 769–779, 2008.

[192] R. Sattler, B. Tyler, B. Hoover et al., "Increased expression of glutamate transporter GLT-1 in peritumoral tissue associated with prolonged survival and decreases in tumor growth in a rat model of experimental malignant glioma," *Journal of Neurosurgery*, vol. 119, no. 4, pp. 878–886, 2013.

[193] M. I. González, P. G. Bannerman, and M. B. Robinson, "Phorbol myristate acetate-dependent interaction of protein kinase Cα and the neuronal glutamate transporter EAAC1," *Journal of Neuroscience*, vol. 23, no. 13, pp. 5589–5593, 2003.

[194] Y. Huang and Z. Zuo, "Isoflurane induces a protein kinase C α-dependent increase in cell-surface protein level and activity of glutamate transporter type 3," *Molecular Pharmacology*, vol. 67, no. 5, pp. 1522–1533, 2005.

[195] A. M. Donson, A. Banerjee, F. Gamboni-Robertson, J. M. Fleitz, and N. K. Foreman, "Protein kinase C ζ isoform is critical for proliferation in human glioblastoma cell lines," *Journal of Neuro-Oncology*, vol. 47, no. 2, pp. 109–115, 2000.

[196] S. Singh, T. Okamura, and F. Ali-Osman, "Serine phosphorylation of glutathione S-transferase P1 (GSTP1) by PKCα enhances GSTP1-dependent cisplatin metabolism and resistance in human glioma cells," *Biochemical Pharmacology*, vol. 80, no. 9, pp. 1343–1355, 2010.

[197] D. R. Sorensen, M. Leirdal, P. O. Iversen, and M. Sioud, "Combination of endostatin and a protein kinase Cα DNA enzyme improves the survival of rats with malignant glioma," *Neoplasia*, vol. 4, no. 6, pp. 474–479, 2002.

[198] M. Leirdal and M. Sioud, "Ribozyme inhibition of the protein kinase Cα triggers apoptosis in glioma cells," *British Journal of Cancer*, vol. 80, no. 10, pp. 1558–1564, 1999.

[199] S. A. Grossman, J. B. Alavi, J. G. Supko et al., "Efficacy and toxicity of the antisense oligonucleotide aprinocarsen directed against protein kinase C-α delivered as a 21-day continuous intravenous infusion in patients with recurrent high-grade astrocytomas," *Neuro-Oncology*, vol. 7, no. 1, pp. 32–40, 2005.

[200] C. Lin, S. Shen, C. Chien, L. Yang, L. Shia, and Y. Chen, "12-O-tetradecanoylphorbol-13-acetate-induced invasion/migration of glioblastoma cells through activating PKCα/ERK/NF-κB-dependent MMP-9 expression," *Journal of Cellular Physiology*, vol. 225, no. 2, pp. 472–481, 2010.

[201] S. Amos, M. Mut, C. G. diPierro et al., "Protein kinase C-α-mediated regulation of low-density lipoprotein receptor-related protein and urokinase increases astrocytoma invasion," *Cancer Research*, vol. 67, no. 21, pp. 10241–10251, 2007.

[202] Z. A. Kohutek, C. G. diPierro, G. T. Redpath, and I. M. Hussaini, "ADAM-10-mediated N-cadherin cleavage is protein kinase C-α dependent and promotes glioblastoma cell migration," *Journal of Neuroscience*, vol. 29, no. 14, pp. 4605–4615, 2009.

[203] I. T. Makagiansar, S. Williams, T. Mustelin, and W. B. Stallcup, "Differential phosphorylation of NG2 proteoglycan by ERK and PKCα helps balance cell proliferation and migration," *The Journal of Cell Biology*, vol. 178, no. 1, pp. 155–165, 2007.

[204] A. Ziv-Av, D. Taller, M. Attia et al., "RTVP-1 expression is regulated by SRF downstream of protein kinase C and contributes to the effect of SRF on glioma cell migration," *Cellular Signalling*, vol. 23, no. 12, pp. 1936–1943, 2011.

[205] T. R. Sharif and M. Sharif, "Overexpression of protein kinase C epsilon in astroglial brain tumor derived cell lines and primary tumor samples," *International Journal of Oncology*, vol. 15, no. 2, pp. 237–243, 1999.

[206] S. Kahana, S. Finniss, S. Cazacu et al., "Proteasome inhibitors sensitize glioma cells and glioma stem cells to TRAIL-induced apoptosis by PKCε-dependent downregulation of AKT and XIAP expressions," *Cellular Signalling*, vol. 23, no. 8, pp. 1348–1357, 2011.

[207] H. Shinohara, N. Kayagaki, H. Yagita et al., "A protective role of PKCε against TNF-related apoptosis-inducing ligand (TRAIL)-induced apoptosis in glioma cells," *Biochemical and Biophysical Research Communications*, vol. 284, no. 5, pp. 1162–1167, 2001.

[208] M. H. Aziz, B. B. Hafeez, J. M. Sand et al., "Protein kinase Cε mediates Stat3Ser727 phosphorylation, Stat3-regulated gene expression, and cell invasion in various human cancer cell lines through integration with MAPK cascade (RAF-1, MEK1/2, and ERK1/2)," *Oncogene*, vol. 29, no. 21, pp. 3100–3109, 2010.

[209] S. Fortin, M. le Mercier, I. Camby et al., "Galectin-1 is implicated in the protein kinase c ε/vimentin-controlled trafficking of integrin-β1 in glioblastoma cells," *Brain Pathology*, vol. 20, no. 1, pp. 39–49, 2010.

[210] A. Besson, A. Davy, S. M. Robbins, and V. W. Yong, "Differential activation of ERKs to focal adhesions by PKC ε is required for PMA-induced adhesion and migration of human glioma cells," *Oncogene*, vol. 20, no. 50, pp. 7398–7407, 2001.

[211] T. R. Sharif, N. Sasakawa, and M. Sharif, "Regulated expression of a dominant negative protein kinase C epsilon mutant inhibits the proliferation of U-373MG human astrocytoma cells," *International Journal of Molecular Medicine*, vol. 7, no. 4, pp. 373–380, 2001.

[212] K. Alapati, S. Gopinath, R. Malla, V. R. Dasari, and J. Rao, "uPAR and cathepsin B knockdown inhibits radiation-induced PKC integrated integrin signaling to the cytoskeleton of glioma-initiating cells," *International Journal of Oncology*, vol. 41, no. 2, pp. 599–610, 2012.

[213] H. Guo, F. Gu, W. Li et al., "Reduction of protein kinase C ζ inhibits migration and invasion of human glioblastoma cells," *Journal of Neurochemistry*, vol. 109, no. 1, pp. 203–213, 2009.

[214] H. Huang, C. Huang, S. Lin-Shiau, and J. Lin, "Ursolic acid inhibits IL-1β or TNF-α-induced C6 glioma invasion through suppressing the association ZIP/p62 with PKC-ζ and downregulating the MMP-9 expression," *Molecular Carcinogenesis*, vol. 48, no. 6, pp. 517–531, 2009.

[215] P. O. Estève, É. Chicoine, O. Robledo et al., "Protein kinase C-ζ regulates transcription of the matrix metalloproteinase-9 gene induced by IL-1 and TNF-α in glioma cells via NF-κB," *The Journal of Biological Chemistry*, vol. 277, no. 38, pp. 35150–35155, 2002.

[216] K. van Kolen and H. Slegers, "Atypical PKCζ is involved in RhoA-dependent mitogenic signaling by the P2Y12 receptor in C6 cells," *The FEBS Journal*, vol. 273, no. 8, pp. 1843–1854, 2006.

[217] M. Guizzetti and L. G. Costa, "Effect of ethanol on protein kinase Cζ and p70S6 kinase activation by carbachol: a possible mechanism for ethanol-induced inhibition of glial cell proliferation," *Journal of Neurochemistry*, vol. 82, no. 1, pp. 38–46, 2002.

[218] R. Patel, H. Win, S. Desai, K. Patel, J. A. Matthews, and M. Acevedo-Duncan, "Involvement of PKC-ι in glioma proliferation," *Cell Proliferation*, vol. 41, no. 1, pp. 122–135, 2008.

[219] E. Bicaku, R. Patel, and M. Acevedo-Duncan, "Cyclin-dependent kinase activating kinase/Cdk7 co-localizes with PKC-ι in human glioma cells," *Tissue and Cell*, vol. 37, no. 1, pp. 53–58, 2005.

[220] S. R. Desai, P. P. Pillai, R. S. Patel, A. N. McCray, H. Y. Win-Piazza, and M. E. Acevedo-Duncan, "Regulation of Cdk7 activity through a phosphatidylinositol (3)-kinase/PKC-ι-mediated signaling cascade in glioblastoma," *Carcinogenesis*, vol. 33, no. 1, pp. 10–19, 2012.

[221] S. Desai, P. Pillai, H. Win-Piazza, and M. Acevedo-Duncan, "PKC-3 promotes glioblastoma cell survival by phosphorylating and inhibiting BAD through a phosphatidylinositol 3-kinase pathway," *Biochimica et Biophysica Acta*, vol. 1813, no. 6, pp. 1190–1197, 2011.

[222] R. M. Baldwin, M. Garratt-Lalonde, D. A. E. Parolin, P. M. Krzyzanowski, M. A. Andrade, and I. A. J. Lorimer, "Protection of glioblastoma cells from cisplatin cytotoxicity via protein kinase Cι-mediated attenuation of p38 MAP kinase signaling," *Oncogene*, vol. 25, no. 20, pp. 2909–2919, 2006.

[223] R. M. Baldwin, D. A. E. Parolin, and I. A. J. Lorimer, "Regulation of glioblastoma cell invasion by PKCι and RhoB," *Oncogene*, vol. 27, no. 25, pp. 3587–3595, 2008.

[224] R. M. Uht, S. Amos, P. M. Martin, A. E. Riggan, and I. M. Hussaini, "The protein kinase C-η isoform induces proliferation in glioblastoma cell lines through an ERK/Elk-1 pathway," *Oncogene*, vol. 26, no. 20, pp. 2885–2893, 2007.

[225] S. E. Aeder, P. M. Martin, J. Soh, and I. M. Hussaini, "PKC-η mediates glioblastoma cell proliferation through the Akt and mTOR signaling pathways," *Oncogene*, vol. 23, no. 56, pp. 9062–9069, 2004.

[226] P. M. Martin, S. E. Aeder, C. A. Chrestensen, T. W. Sturgill, and I. M. Hussaini, "Phorbol 12-myristate 13-acetate and serum synergize to promote rapamycin-insensitive cell proliferation via protein kinase C-eta," *Oncogene*, vol. 26, no. 3, pp. 407–414, 2007.

[227] I. M. Hussaini, J. E. Carpenter, G. T. Redpath, J. J. Sando, M. E. Shaffrey, and S. R. VandenBerg, "Protein kinase C-η regulates resistance to UV- and γ-irradiation-induced apoptosis in glioblastoma cells by preventing caspase-9 activation," *Neuro-Oncology*, vol. 4, no. 1, pp. 9–21, 2002.

[228] W. Lu, H. Lee, C. Xiang, S. Finniss, and C. Brodie, "The phosphorylation of tyrosine 332 is necessary for the caspase 3-dependent cleavage of PKCδ and the regulation of cell apoptosis," *Cellular Signalling*, vol. 19, no. 10, pp. 2165–2173, 2007.

[229] W. Lu, S. Finnis, C. Xiang et al., "Tyrosine 311 is phosphorylated by c-Abl and promotes the apoptotic effect of PKCδ in glioma cells," *Biochemical and Biophysical Research Communications*, vol. 352, no. 2, pp. 431–436, 2007.

[230] R. Gomel, C. Xiang, S. Finniss et al., "The localization of protein kinase Cδ in different subcellular sites affects its proapoptotic and antiapoptotic functions and the activation of distinct downstream signaling pathways," *Molecular Cancer Research*, vol. 5, no. 6, pp. 627–639, 2007.

[231] H. Okhrimenko, W. Lu, C. Xiang et al., "Roles of tyrosine phosphorylation and cleavage of protein kinase Cδ in its protective effect against tumor necrosis factor-related apoptosis inducing ligand-induced apoptosis," *The Journal of Biological Chemistry*, vol. 280, no. 25, pp. 23643–23652, 2005.

[232] A. Zrachia, M. Dobroslav, M. Blass et al., "Infection of glioma cells with Sindbis virus induces selective activation and tyrosine phosphorylation of protein kinase C δ: implications for sindbis virus-induced apoptosis," *The Journal of Biological Chemistry*, vol. 277, no. 26, pp. 23693–23701, 2002.

[233] M. Blass, I. Kronfeld, G. Kazimirsky, P. M. Blumberg, and C. Brodie, "Tyrosine phosphorylation of protein kinase Cδ is essential for its apoptotic effect in response to etoposide," *Molecular and Cellular Biology*, vol. 22, no. 1, pp. 182–195, 2002.

[234] R. Mandil, E. Ashkenazi, M. Blass et al., "Protein kinase Cα and protein kinase Cδ play opposite roles in the proliferation and apoptosis of glioma cells," *Cancer Research*, vol. 61, no. 11, pp. 4612–4619, 2001.

[235] S. L. Lomonaco, S. Kahana, M. Blass et al., "Phosphorylation of protein kinase Cδ on distinct tyrosine residues induces sustained activation of Erk1/2 via down-regulation of MKP-1: role in the apoptotic effect of etoposide," *The Journal of Biological Chemistry*, vol. 283, no. 25, pp. 17731–17739, 2008.

[236] C. Peng, T. Tseng, J. Liu et al., "Penta-acetyl geniposide-induced C6 glioma cell apoptosis was associated with the activation of protein kinase C-delta," *Chemico-Biological Interactions*, vol. 147, no. 3, pp. 287–296, 2004.

[237] C. Peng, C. Huang, S. Hsu, and C. Wang, "Penta-acetyl geniposide induce apoptosis in C6 glioma cells by modulating the activation of neutral sphingomyelinase-induced p75 nerve growth factor receptor and protein kinase Cδ pathway," *Molecular Pharmacology*, vol. 70, no. 3, pp. 997–1004, 2006.

[238] S. Kim, J. Hwang, W. Lee, D. Y. Hwang, and K. Suk, "Role of protein kinase Cδ in paraquat-induced glial cell death," *Journal of Neuroscience Research*, vol. 86, no. 9, pp. 2062–2070, 2008.

[239] M. Kim, R. Kim, C. Yoon et al., "Importance of PKCδ signaling in fractionatedradiation-induced expansion of glioma-initiating cells and resistance to cancer treatment," *Journal of Cell Science*, vol. 124, no. 18, pp. 3084–3094, 2011.

[240] S. Amos, P. M. Martin, G. A. Polar, S. J. Parsons, and I. M. Hussaini, "Phorbol 12-myristate 13-acetate induces epidermal growth factor receptor transactivation via protein kinase Cδ/c-Src pathways in glioblastoma cells," *The Journal of Biological Chemistry*, vol. 280, no. 9, pp. 7729–7738, 2005.

[241] B. S. Paugh, S. W. Paugh, L. Bryan et al., "EGF regulates plasminogen activator inhibitor-1 (PAI-1) by a pathway involving c-Src, PKCδ, and sphingosine kinase 1 in glioblastoma cells," *The FASEB Journal*, vol. 22, no. 2, pp. 455–465, 2008.

[242] S. Sarkar and V. W. Yong, "Reduction of protein kinase C delta attenuates tenascin-C stimulated glioma invasion in three-dimensional matrix," *Carcinogenesis*, vol. 31, no. 2, pp. 311–317, 2010.

[243] A. Forastiere, W. Koch, A. Trotti, and D. Sidransky, "Head and neck cancer," *The New England Journal of Medicine*, vol. 345, no. 26, pp. 1890–1900, 2001.

[244] R. I. Haddad and D. M. Shin, "Recent advances in head and neck cancer," *The New England Journal of Medicine*, vol. 359, no. 11, pp. 1096–1154, 2008.

[245] E. E. W. Cohen, H. Zhu, M. W. Lingen et al., "A feed-forward loop involving protein kinase Cα and microRNAs regulates tumor cell cycle," *Cancer Research*, vol. 69, no. 1, pp. 65–74, 2009.

[246] F. Liu, Z. Zhao, P. Li et al., "NF-κB participates in chemokine receptor 7-mediated cell survival in metastatic squamous cell carcinoma of the head and neck," *Oncology Reports*, vol. 25, no. 2, pp. 383–391, 2011.

[247] Z. J. Zhao, P. Li, F. Y. Liu, L. Sun, and C. F. Sun, "PKCα take part in CCR7/NF-κB autocrine signaling loop in CCR7-positive squamous cell carcinoma of head and neck," *Molecular and Cellular Biochemistry*, vol. 357, no. 1-2, pp. 181–187, 2011.

[248] Q. Pan, L. W. Bao, T. N. Teknos, and S. D. Merajver, "Targeted disruption of protein kinase Cε reduces cell invasion and motility through inactivation of RhoA and RhoC GTPases in head and neck squamous cell carcinoma," *Cancer Research*, vol. 66, no. 19, pp. 9379–9384, 2006.

[249] J. Datta, A. Smith, J. C. Lang et al., "microRNA-107 functions as a candidate tumor-suppressor gene in head and neck squamous cell carcinoma by downregulation of protein kinase Ceopen," *Oncogene*, vol. 31, no. 36, pp. 4045–4053, 2012.

[250] E. E. W. Cohen, M. W. Lingen, B. Zhu et al., "Protein kinase Cζ mediates epidermal growth factor-induced growth of head and neck tumor cells by regulating mitogen-activated protein kinase," *Cancer Research*, vol. 66, no. 12, pp. 6296–6303, 2006.

[251] C. Valkova, C. Mertens, S. Weisheit, D. Imhof, and C. Liebmann, "Activation by tyrosine phosphorylation as a prerequisite for protein kinase Cζ to mediate epidermal growth factor receptor signaling to ERK," *Molecular Cancer Research*, vol. 8, no. 5, pp. 783–797, 2010.

[252] Z. Xie, Y. Jiang, E. Liao et al., "PIKE mediates EGFR proliferative signaling in squamous cell carcinoma cells," *Oncogene*, vol. 31, no. 49, pp. 5090–5098, 2012.

[253] K. C. Lai, C. J. Liu, K. W. Chang, and T. C. Lee, "Depleting IFIT2 mediates atypical PKC signaling to enhance the migration and metastatic activity of oral squamous cell carcinoma cells," *Oncogene*, vol. 32, no. 32, pp. 3686–3697, 2013.

[254] C.-C. Yu, S.-C. Lo, and T.-C. V. Wang, "Telomerase is regulated by protein kinase C-ζ in human nasopharyngeal cancer cells," *Biochemical Journal*, vol. 355, no. 2, pp. 459–464, 2001.

[255] M. J. Frederick, A. J. VanMeter, M. A. Gadhikar et al., "Phosphoproteomic analysis of signaling pathways in head and neck squamous cell carcinoma patient samples," *American Journal of Pathology*, vol. 178, no. 2, pp. 548–571, 2011.

[256] Y. Yang, J. Chu, M. Luo et al., "Amplification of *PRKCI*, located in 3q26, is associated with lymph node metastasis in esophageal squamous cell carcinoma," *Genes Chromosomes and Cancer*, vol. 47, no. 2, pp. 127–136, 2008.

[257] S. Liu, B. Wang, Y. Jiang et al., "Atypical protein kinase Cι (PKCι) promotes metastasis of esophageal squamous cell carcinoma by enhancing resistance to anoikis via PKCι-SKP2-AKT Pathway," *Molecular Cancer Research*, vol. 9, no. 4, pp. 390–402, 2011.

[258] B. S. Wang, Y. Yang, H. Yang et al., "PKCι counteracts oxidative stress by regulating Hsc70 in an esophageal cancer cell line," *Cell Stress and Chaperones*, vol. 18, no. 3, pp. 359–366, 2013.

[259] P. Chu, N. C. Hsu, H. Tai et al., "High nuclear protein kinase Cθ expression may correlate with disease recurrence and poor survival in oral squamous cell carcinoma," *Human Pathology*, vol. 43, no. 2, pp. 276–281, 2012.

[260] P. Y. Chu, N. C. H. Hsu, S. H. Lin, M. F. How, and K. T. Yeh, "High nuclear protein kinase C βII expression is a marker of disease recurrence in oral squamous cell carcinoma," *Anticancer Research*, vol. 32, no. 9, pp. 3987–3991, 2012.

[261] L. Ducher, F. Croquet, S. Gil, J. Davy, J. Féger, and A. Bréhier, "Differential expression of five protein kinase C isoenzymes in FAO and HepG2 hepatoma cell lines compared with normal rat hepatocytes," *Biochemical and Biophysical Research Communications*, vol. 217, no. 2, pp. 546–553, 1995.

[262] S. Hsu, Y. Chou, S. Yin, and J. Liu, "Differential effects of phorbol ester on growth and protein kinase C isoenzyme regulation in human hepatoma Hep3B cells," *Biochemical Journal*, vol. 333, part 1, pp. 57–64, 1998.

[263] T. Ohigashi, C. S. Mallia, E. McGary et al., "Protein kinase C α protein expression is necessary for sustained erythropoietin production in human hepatocellular carcinoma (Hep3B) cells exposed to hypoxia," *Biochimica et Biophysica Acta*, vol. 1450, no. 2, pp. 109–118, 1999.

[264] H. Lu, F. Chou, K. Yeh, Y. Chang, N. C. Hsu, and J. Chang, "Expression of protein kinase C family in human hepatocellular carcinoma," *Pathology and Oncology Research*, vol. 16, no. 3, pp. 385–391, 2010.

[265] J. Wang, Q. Li, G. Du, J. Lu, and S. Zou, "Significance and expression of atypical protein kinase C-ι in human hepatocellular carcinoma," *Journal of Surgical Research*, vol. 154, no. 1, pp. 143–149, 2009.

[266] G. Du, J. Wang, J. Lu et al., "Expression of P-aPKC-ι, E-cadherin, and β-catenin related to invasion and metastasis in hepatocellular carcinoma," *Annals of Surgical Oncology*, vol. 16, no. 6, pp. 1578–1586, 2009.

[267] H. Lu, F. Chou, K. Yeh, Y. Chang, N. C. Hsu, and J. Chang, "Analysing the expression of protein kinase C eta in human hepatocellular carcinoma," *Pathology*, vol. 41, no. 7, pp. 626–629, 2009.

[268] T. Wu, Y. Hsieh, Y. Hsieh, and J. Liu, "Reduction of PKCα decreases cell proliferation, migration, and invasion of human malignant hepatocellular carcinoma," *Journal of Cellular Biochemistry*, vol. 103, no. 1, pp. 9–20, 2008.

[269] Y. Hsieh, T. Wu, C. Huang, Y. Hsieh, J. Hwang, and J. Liu, "p38 mitogen-activated protein kinase pathway is involved in protein kinase Cα-regulated invasion in human hepatocellular carcinoma cells," *Cancer Research*, vol. 67, no. 9, pp. 4320–4327, 2007.

[270] J. Tsai, Y. Hsieh, S. Kuo et al., "Alteration in the expression of protein kinase C isoforms in human hepatocellular carcinoma," *Cancer Letters*, vol. 161, no. 2, pp. 171–175, 2000.

[271] W. Wu, R. K. Tsai, C. H. Chang, S. Wang, J. Wu, and Y. Chang, "Reactive oxygen species mediated sustained activation of protein kinase C α and extracellular signal-regulated kinase for migration of human hepatoma cell Hepg2," *Molecular Cancer Research*, vol. 4, no. 10, pp. 747–758, 2006.

[272] W. S. Wu, "Protein kinase C α trigger Ras and Raf-independent MEK/ERK activation for TPA-induced growth inhibition of human hepatoma cell HepG2," *Cancer Letters*, vol. 239, no. 1, pp. 27–35, 2006.

[273] W. S. Wu and J. M. Huang, "Activation of protein kinase C alpha is required for TPA-triggered ERK (MAPK) signaling and growth inhibition of human hepatoma cell HepG2," *Journal of Biomedical Science*, vol. 12, no. 2, pp. 289–296, 2005.

[274] C. Chiang, Y. Huang, K. Leong et al., "PKCalpha mediated induction of miR-101 in human hepatoma HepG2 cells," *Journal of Biomedical Science*, vol. 17, article 35, 2010.

[275] H. F. Bunn, "Erythropoietin," *Cold Spring Harbor Perspectives in Medicine*, vol. 3, no. 3, Article ID a011619, 2013.

[276] C. T. Hu, C. C. Cheng, S. M. Pan, J. R. Wu, and W. S. Wu, "PKC mediates fluctuant ERK-paxillin signaling for hepatocyte growth factor-induced migration of hepatoma cell HepG2," *Cellular Signalling*, vol. 25, no. 6, pp. 1457–1467, 2013.

[277] T. Wu, Y. Hsieh, C. Wu, Y. Hsieh, C. Huang, and J. Liu, "Overexpression of protein kinase Cα mRNA in human hepatocellular carcinoma: a potential marker of disease prognosis," *Clinica Chimica Acta*, vol. 382, no. 1-2, pp. 54–58, 2007.

[278] C. Seeger and W. S. Mason, "Hepatitis B virus biology," *Microbiology and Molecular Biology Reviews*, vol. 64, no. 1, pp. 51–68, 2000.

[279] E. Hildt, B. Munz, G. Saher, K. Reifenberg, and P. H. Hofschneider, "The PreS2 activator MHBs^t of hepatitis B virus activates c-raf-1/Erk2 signaling in transgenic mice," *The EMBO Journal*, vol. 21, no. 4, pp. 525–535, 2002.

[280] H. Liu, J. Xu, L. Zhou et al., "Hepatitis B virus large surface antigen promotes liver carcinogenesis by activating the Src/

PI3K/Akt pathway," *Cancer Research*, vol. 71, no. 24, pp. 7547–7557, 2011.

[281] J. Hung, Y. Lu, Y. Wang et al., "FTY720 induces apoptosis in hepatocellular carcinoma cells through activation of protein kinase C δ signaling," *Cancer Research*, vol. 68, no. 4, pp. 1204–1212, 2008.

[282] C. Yoon, M. Kim, M. Park et al., "Claudin-1 acts through c-Abl-protein kinase Cδ (PKCδ) signaling and has a causal role in the acquisition of invasive capacity in human liver cells," *The Journal of Biological Chemistry*, vol. 285, no. 1, pp. 226–233, 2010.

[283] S. Takai, R. Matsushima-Nishiwaki, H. Tokuda et al., "Protein kinase C δ regulates the phosphorylation of heat shock protein 27 in human hepatocellular carcinoma," *Life Sciences*, vol. 81, no. 7, pp. 585–591, 2007.

[284] K. Guo, N. X. Kang, Y. Li et al., "Regulation of HSP27 on NF-κB pathway activation may be involved in metastatic hepatocellular carcinoma cells apoptosis," *BMC Cancer*, vol. 9, article 100, 2009.

[285] Y. Wang, D. Sun, and D. Liu, "Tumor suppression by RNA from C/EBPβ 3′UTR through the inhibition of protein kinase Cε activity," *PLoS ONE*, vol. 6, no. 1, Article ID e16543, 2011.

[286] K. Guo, Y. Li, X. Kang et al., "Role of PKCβ in hepatocellular carcinoma cells migration and invasion *in vitro*: a potential therapeutic target," *Clinical and Experimental Metastasis*, vol. 26, no. 3, pp. 189–195, 2009.

[287] R. S. Herbst, J. V. Heymach, and S. M. Lippman, "Molecular origins of cancer: lung cancer," *The New England Journal of Medicine*, vol. 359, no. 13, pp. 1367–1380, 2008.

[288] S. S. Singhal, S. Yadav, J. Singhal, K. Drake, Y. C. Awasthi, and S. Awasthi, "The role of PKCα and RLIP76 in transport-mediated doxorubicin-resistance in lung cancer," *FEBS Letters*, vol. 579, no. 21, pp. 4635–4641, 2005.

[289] W. Lang, H. Wang, L. Ding, and L. Xiao, "Cooperation between PKC-α and PKC-ε in the regulation of JNK activation in human lung cancer cells," *Cellular Signalling*, vol. 16, no. 4, pp. 457–467, 2004.

[290] M. Lahn, C. Su, S. Li et al., "Expression levels of protein kinase C-α in non-small-cell lung cancer," *Clinical Lung Cancer*, vol. 6, no. 3, pp. 184–189, 2004.

[291] A. K. O'Neill, L. L. Gallegos, V. Justilien et al., "Protein kinase Cα promotes cell migration through a PDZ-dependent interaction with its novel substrate discs large homolog 1 (DLG1)," *The Journal of Biological Chemistry*, vol. 286, no. 50, pp. 43559–43568, 2011.

[292] C. A. M. la Porta, L. Tessitore, and R. Comolli, "Changes in protein kinase C α,δ and in nuclear β isoform expression in tumour and lung metastatic nodules induced by diethylnitrosamine in the rat," *Carcinogenesis*, vol. 18, no. 4, pp. 715–719, 1997.

[293] C. Wang, X. Wang, H. Liang et al., "miR-203 inhibits cell proliferation and migration lung cancer cells by targeting PKCα," *PLoS ONE*, vol. 8, no. 9, Article ID e73985, 2013.

[294] D. Xiao, K. Wang, J. Zhou et al., "Inhibition of fibroblast growth factor 2-induced apoptosis involves survivin expression, protein kinase Cα activation and subcellular translocation of Smac in human small cell lung cancer cells," *Acta Biochimica et Biophysica Sinica*, vol. 40, no. 4, pp. 297–303, 2008.

[295] K. S. Hill, E. Erdogan, A. Khoor et al., "Protein kinase Cα suppresses Kras-mediated lung tumor formation through activation of a p38 MAPK-TGFβ signaling axis," *Oncogene*, 2013.

[296] L. Paz-Ares, J. Douillard, P. Koralewski et al., "Phase III study of gemcitabine and cisplatin with or without aprinocarsen, a protein kinase C-alpha antisense oligonucleotide, in patients with advanced-stage non-small-cell lung cancer," *Journal of Clinical Oncology*, vol. 24, no. 9, pp. 1428–1434, 2006.

[297] P. Ritch, C. M. Rudin, J. D. Bitran et al., "Phase II study of PKC-α antisense oligonucleotide aprinocarsen in combination with gemcitabine and carboplatin in patients with advanced non-small cell lung cancer," *Lung Cancer*, vol. 52, no. 2, pp. 173–180, 2006.

[298] M. A. Villalona-Calero, P. Ritch, J. A. Figueroa et al., "A phase I/II study of LY900003, an antisense inhibitor of protein kinase C-α, in combination with cisplatin and gemcitabine in patients with advanced non-small cell lung cancer," *Clinical Cancer Research*, vol. 10, no. 18, part 1, pp. 6086–6093, 2004.

[299] K. Bae, H. Wang, G. Jiang, M. G. Chen, L. Lu, and L. Xiao, "Protein kinase Cε is overexpressed in primary human non-small cell lung cancers and functionally required for proliferation of non-small cell lung cancer cells in a p21/Cip1-dependent manner," *Cancer Research*, vol. 67, no. 13, pp. 6053–6063, 2007.

[300] M. C. Caino, C. Lopez-Haber, J. Kim, D. Mochly-Rosen, and M. G. Kazanietz, "Protein kinase Cε is required for non-small cell lung carcinoma growth and regulates the expression of apoptotic genes," *Oncogene*, vol. 31, no. 20, pp. 2593–2600, 2012.

[301] M. Felber, J. Sonnemann, and J. F. Beck, "Inhibition of novel protein kinase Cε augments TRAIL-induced cell death in A549 lung cancer cells," *Pathology and Oncology Research*, vol. 13, no. 4, pp. 295–301, 2007.

[302] L. Ding, H. Wang, W. Lang, and L. Xiao, "Protein kinase C-ε promotes survival of lung cancer cells by suppressing apoptosis through dysregulation of the mitochondrial caspase pathway," *The Journal of Biological Chemistry*, vol. 277, no. 38, pp. 35305–35313, 2002.

[303] O. E. Pardo, C. Wellbrock, U. K. Khanzada et al., "FGF-2 protects small cell lung cancer cells from apoptosis through a complex involving PKCε, B-Raf and S6K2," *The EMBO Journal*, vol. 25, no. 13, pp. 3078–3088, 2006.

[304] M. C. Caino, C. Lopez-Haber, J. L. Kissil, and M. G. Kazanietz, "Non-small cell lung carcinoma cell motility, Rac activation and metastatic dissemination are mediated by protein kinase C epsilon," *PLoS ONE*, vol. 7, no. 2, Article ID e31714, 2012.

[305] S. Tuomi, A. Mai, J. Nevo et al., "PKCε regulation of an α5 integrin-ZO-1 complex controls lamellae formation in migrating cancer cells," *Science Signaling*, vol. 2, no. 77, article ra32, 2009.

[306] R. P. Regala, C. Weems, L. Jamieson et al., "Atypical protein kinase Cι is an oncogene in human non-small cell lung cancer," *Cancer Research*, vol. 65, no. 19, pp. 8905–8911, 2005.

[307] R. P. Regala, C. Weems, L. Jamieson, J. A. Copland, E. A. Thompson, and A. P. Fields, "Atypical protein kinase Cτ plays a critical role in human lung cancer cell growth and tumorigenicity," *The Journal of Biological Chemistry*, vol. 280, no. 35, pp. 31109–31115, 2005.

[308] S. Liu, B. Wang, Y. Jiang et al., "Atypical protein kinase Cι (PKCι) promotes metastasis of esophageal squamous cell carcinoma by enhancing resistance to anoikis via PKCι-SKP2-AKT pathway," *Molecular Cancer Research*, vol. 9, no. 4, pp. 390–402, 2011.

[309] L. Xu and X. Deng, "Protein kinase Cι promotes nicotine-induced migration and invasion of cancer cells via phosphorylation of μ- and m-calpains," *The Journal of Biological Chemistry*, vol. 281, no. 7, pp. 4457–4466, 2006.

[310] J. C. Shultz, N. Vu, M. D. Shultz, M. U. U. Mba, B. A. Shapiro, and C. E. Chalfant, "The proto-oncogene PKCι regulates the alternative splicing of Bcl-x pre-mRNA," *Molecular Cancer Research*, vol. 10, no. 5, pp. 660–669, 2012.

[311] R. P. Regala, E. A. Thompson, and A. P. Fields, "Atypical protein kinase Cι expression and aurothiomalate sensitivity in human lung cancer cells," *Cancer Research*, vol. 68, no. 14, pp. 5888–5895, 2008.

[312] V. Justilien, L. Jameison, C. J. Der, K. L. Rossman, and A. P. Fields, "Oncogenic activity of Ect2 is regulated through protein kinase Cι-mediated phosphorylation," *The Journal of Biological Chemistry*, vol. 286, no. 10, pp. 8149–8157, 2011.

[313] L. A. Frederick, J. A. Matthews, L. Jamieson et al., "Matrix metalloproteinase-10 is a critical effector of protein kinase Cι-Par6α-mediated lung cancer," *Oncogene*, vol. 27, no. 35, pp. 4841–4853, 2008.

[314] E. Erdogan, E. W. Klee, E. A. Thompson, and A. P. Fields, "Meta-analysis of oncogenic protein kinase Cι signaling in lung adenocarcinoma," *Clinical Cancer Research*, vol. 15, no. 5, pp. 1527–1533, 2009.

[315] D. Meng, M. Yuan, X. Li et al., "Prognostic value of K-RAS mutations in patients with non-small cell lung cancer: a systematic review with meta-analysis," *Lung Cancer*, vol. 81, no. 1, pp. 1–10, 2013.

[316] N. Karachaliou, C. Mayo, C. Costa et al., "KRAS mutations in lung cancer," *Clinical Lung Cancer*, vol. 14, no. 3, pp. 205–214, 2013.

[317] M. Stailings-Mann, L. Jamieson, R. P. Regala, C. Weems, N. R. Murray, and A. P. Fields, "A novel small-molecule inhibitor of protein kinase Cι blocks transformed growth of non-small-cell lung cancer cells," *Cancer Research*, vol. 66, no. 3, pp. 1767–1774, 2006.

[318] R. P. Regala, R. K. Davis, A. Kunz, A. Khoor, M. Leitges, and A. P. Fields, "Atypical protein kinase Cι is required for bronchioalveolar stem cell expansion and lung tumorigenesis," *Cancer Research*, vol. 69, no. 19, pp. 7603–7611, 2009.

[319] W. Guo, S. Wu, J. Liu, and B. Fang, "Identification of a small molecule with synthetic lethality for K-Ras and protein kinase C iota," *Cancer Research*, vol. 68, no. 18, pp. 7403–7408, 2008.

[320] E. Krasnitsky, Y. Baumfeld, J. Freedman et al., "PKCη is a novel prognostic marker in non-small cell lung cancer," *Anticancer Research*, vol. 32, no. 4, pp. 1507–1513, 2012.

[321] J. Sonnemann, V. Gekeler, K. Ahlbrecht et al., "Down-regulation of protein kinase Cη by antisense oligonucleotides sensitises A549 lung cancer cells to vincristine and paclitaxel," *Cancer Letters*, vol. 209, no. 2, pp. 177–185, 2004.

[322] Y. Liu, B. Wang, J. Wang et al., "Down-regulation of PKCζ expression inhibits chemotaxis signal transduction in human lung cancer cells," *Lung Cancer*, vol. 63, no. 2, pp. 210–218, 2009.

[323] J. M. Symonds, A. M. Ohm, C. J. Carter et al., "Protein kinase C δ is a downstream effector of oncogenic K-ras in lung tumors," *Cancer Research*, vol. 71, no. 6, pp. 2087–2097, 2011.

[324] A. S. Clark, K. A. West, P. M. Blumberg, and P. A. Dennis, "Altered protein kinase C (PKC) isoforms in non-small cell lung cancer cells: PKCδ promotes cellular survival and chemotherapeutic resistance," *Cancer Research*, vol. 63, no. 4, pp. 780–786, 2003.

[325] E. Kim, H. Lee, D. Lee et al., "Inhibition of heat shock protein 27-mediated resistance to DNA damaging agents by a novel PKCδ-V5 heptapeptide," *Cancer Research*, vol. 67, no. 13, pp. 6333–6341, 2007.

[326] L. Xu, L. Su, and X. Liu, "PKCδ regulates death receptor 5 expression induced by PS-341 through ATF4-ATF3/CHOP axis in human lung cancer cells," *Molecular Cancer Therapeutics*, vol. 11, no. 10, pp. 2174–2182, 2012.

[327] M. Nakagawa, J. L. Oliva, D. Kothapalli, A. Fournier, R. K. Assoian, and M. G. Kazanietz, "Phorbol ester-induced G1 phase arrest selectively mediated by protein kinase Cδ-dependent induction of p21," *The Journal of Biological Chemistry*, vol. 280, no. 40, pp. 33926–33934, 2005.

[328] S. S. Hecht, "Tobacco carcinogens, their biomarkers and tobacco-induced cancer," *Nature Reviews Cancer*, vol. 3, no. 10, pp. 733–744, 2003.

[329] H. Lemjabbar-Alaoui, S. S. Sidhu, A. Mengistab, M. Gallup, and C. Basbaum, "TACE/ADAM-17 phosphorylation by PKC-epsilon mediates premalignant changes in Tobacco smoke-exposed lung cells," *PLoS ONE*, vol. 6, no. 3, Article ID e17489, 2011.

[330] Y. M. Whang, U. Jo, J. S. Sung et al., "Wnt5a is associated with cigarette smoke-related lung carcinogenesis via protein kinase C," *PLoS ONE*, vol. 8, no. 1, Article ID e53012, 2013.

[331] J. Shen, L. Xu, T. K. Owonikoko et al., "NNK promotes migration and invasion of lung cancer cells through activation of c-Src/PKCι/FAK loop," *Cancer Letters*, vol. 318, no. 1, pp. 106–113, 2012.

[332] R. Gopalakrishna, Z. Chen, and U. Gundimeda, "Tobacco smoke tumor promoters, catechol and hydroquinone, induce oxidative regulation of protein kinase C and influence invasion and metastasis of lung carcinoma cells," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 91, no. 25, pp. 12233–12237, 1994.

[333] M. Oka and U. Kikkawa, "Protein kinase C in melanoma," *Cancer and Metastasis Reviews*, vol. 24, no. 2, pp. 287–300, 2005.

[334] M. F. Denning, "Specifying protein kinase C functions in melanoma," *Pigment Cell & Melanoma Research*, vol. 25, no. 4, pp. 466–476, 2012.

[335] M. M. Lahn and K. L. Sundell, "The role of protein kinase C-alpha (PKC-α) in melanoma," *Melanoma Research*, vol. 14, no. 2, pp. 85–89, 2004.

[336] S. D. Smith, M. Enge, W. Bao et al., "Protein kinase Cα (PKCα) regulates p53 localization and melanoma cell survival downstream of integrin αv in three-dimensional collagen and *in vivo*," *The Journal of Biological Chemistry*, vol. 287, no. 35, pp. 29336–29347, 2012.

[337] A. J. Putnam, V. V. Schulz, E. M. Freiter, H. M. Bill, and C. K. Miranti, "Src, PKCα, and PKCδ are required for αvβ3 integrin-mediated metastatic melanoma invasion," *Cell Communication and Signalling*, vol. 7, article 10, 2009.

[338] H. R. Byers, S. J. S. Boissel, C. Tu, and H. Park, "RNAi-mediated knockdown of protein kinase C-alpha inhibits cell migration in MM-RU human metastatic melanoma cell line," *Melanoma Research*, vol. 20, no. 3, pp. 171–178, 2010.

[339] A. Vartanian, E. Stepanova, I. Grigorieva, E. Solomko, A. Baryshnikov, and M. Lichinitser, "VEGFR1 and PKCα signaling control melanoma vasculogenic mimicry in a VEGFR2 kinase-independent manner," *Melanoma Research*, vol. 21, no. 2, pp. 91–98, 2011.

[340] R. E. B. Seftor, A. R. Hess, E. A. Seftor et al., "Tumor cell vasculogenic mimicry: from controversy to therapeutic promise," *The American Journal of Pathology*, vol. 181, no. 4, pp. 1115–1125, 2012.

[341] J. H. Kang, D. Asai, J. Oishi et al., "Role of plasma as activator and cofactor in phosphorylation catalyzed by protein kinase C," *Cell Biochemistry and Function*, vol. 26, no. 1, pp. 70–75, 2008.

[342] S. Gillespie, X. D. Zhang, and P. Hersey, "Variable expression of protein kinase Cε in human melanoma cells regulates sensitivity

to TRAIL-induced apoptosis," *Molecular Cancer Therapeutics*, vol. 4, no. 4, pp. 668–676, 2005.

[343] N. M. Mhaidat, R. F. Thorne, X. D. Zhang, and P. Hersey, "Regulation of docetaxel-induced apoptosis of human melanoma cells by different isoforms of protein kinase C," *Molecular Cancer Research*, vol. 5, no. 10, pp. 1073–1081, 2007.

[344] E. Lau, H. Kluger, T. Varsano et al., "PKCε promotes oncogenic functions of ATF2 in the nucleus while blocking its apoptotic function at mitochondria," *Cell*, vol. 148, no. 3, pp. 543–555, 2012.

[345] M. Oka, U. Kikkawa, and C. Nishigori, "Protein kinase C-βII represses hepatocyte growth factor-induced invasion by preventing the association of adapter protein Gab1 and phosphatidylinositol 3-kinase in melanoma cells," *Journal of Investigative Dermatology*, vol. 128, no. 1, pp. 188–195, 2008.

[346] J. P. Voris, L. A. Sitailo, H. R. Rahn et al., "Functional alterations in protein kinase C beta II expression in melanoma," *Pigment Cell and Melanoma Research*, vol. 23, no. 2, pp. 216–224, 2010.

[347] C. A. M. la Porta and R. Comolli, "Overexpression of nPKCδ in BL6 murine melanoma cells enhances TGFβ1 release into the plasma of metastasized animals," *Melanoma Research*, vol. 10, no. 6, pp. 527–534, 2000.

[348] C. A. M. la Porta, A. di Dio, D. Porro, and R. Comolli, "Overexpression of novel protein kinase C δ in BL6 murine melanoma cells inhibits the proliferative capacity *in vitro* but enhances the metastatic potential *in vivo*," *Melanoma Research*, vol. 10, no. 2, pp. 93–102, 2000.

[349] E. Albi, C. A. M. la Porta, S. Cataldi, and M. V. Magni, "Nuclear sphingomyelin-synthase and protein kinase C δ in melanoma cells," *Archives of Biochemistry and Biophysics*, vol. 438, no. 2, pp. 156–161, 2005.

[350] N. M. Mhaidat, R. F. Thorne, D. Z. Xu, and P. Hersey, "Regulation of docetaxel-induced apoptosis of human melanoma cells by different isoforms of protein kinase C," *Molecular Cancer Research*, vol. 5, no. 10, pp. 1073–1081, 2007.

[351] S. T. Abrams, T. Lakum, K. Lin et al., "B-cell receptor signaling in chronic lymphocytic leukemia cells is regulated by overexpressed active protein kinase CβII," *Blood*, vol. 109, no. 3, pp. 1193–1201, 2007.

[352] N. N. Kabir, L. Rönnstrand, and J. U. Kazi, "Protein kinase C expression is deregulated in chronic lymphocytic leukemia," *Leukemia & Lymphoma*, vol. 54, no. 10, pp. 2288–2290, 2013.

[353] J. U. Kazi, N. N. Kabir, and L. Rönnstrand, "Protein kinase C, (PKC) as a drug target in chronic lymphocytic leukemia," *Medical Oncology*, vol. 30, no. 4, article 757, 2013.

[354] I. Espinosa, J. Briones, R. Bordes et al., "Membrane PKC-beta 2 protein expression predicts for poor response to chemotherapy and survival in patients with diffuse large B-cell lymphoma," *Annals of Hematology*, vol. 85, no. 9, pp. 597–603, 2006.

[355] R. Schaffel, J. C. Morais, I. Biasoli et al., "PKC-beta II expression has prognostic impact in nodal diffuse large B-cell lymphoma," *Modern Pathology*, vol. 20, no. 3, pp. 326–330, 2007.

[356] S. Riihijärvi, S. Koivula, H. Nyman, K. Rydström, M. Jerkeman, and S. Leppä, "Prognostic impact of protein kinase C βII expression in R-CHOP-treated diffuse large B-cell lymphoma patients," *Modern Pathology*, vol. 23, no. 5, pp. 686–693, 2010.

[357] N. S. Saba and L. S. Levy, "Apoptotic induction in B-cell acute lymphoblastic leukemia cell lines treated with a protein kinase Cβ inhibitor," *Leukemia & Lymphoma*, vol. 52, no. 5, pp. 877–886, 2011.

[358] S. T. Abrams, B. R. B. Brown, M. Zuzel, and J. R. Slupsky, "Vascular endothelial growth factor stimulates protein kinase C βII expression in chronic lymphocytic leukemia cells," *Blood*, vol. 115, no. 22, pp. 4447–4454, 2010.

[359] M. Barragán, M. de Frias, D. Iglesias-Serret et al., "Regulation of Akt/PKB by phosphatidylinositol 3-kinase-dependent and -independent pathways in B-cell chronic lymphocytic leukemia cells: role of protein kinase Cβ," *Journal of Leukocyte Biology*, vol. 80, no. 6, pp. 1473–1479, 2006.

[360] C. Holler, J. D. Piñón, U. Denk et al., "PKCβ is essential for the development of chronic lymphocytic leukemia in the TCL1 transgenic mouse model: validation of PKCβ as a therapeutic target in chronic lymphocytic leukemia," *Blood*, vol. 113, no. 12, pp. 2791–2794, 2009.

[361] A. Patke, I. Mecklenbräuker, H. Erdjument-Bromage, P. Tempst, and A. Tarakhovsky, "BAFF controls B cell metabolic fitness through a PKCβ- and Akt-dependent mechanism," *Journal of Experimental Medicine*, vol. 203, no. 11, pp. 2551–2562, 2006.

[362] C. M. zum Büschenfelde, M. Wagner, G. Lutzny et al., "Recruitment of PKC-βII to lipid rafts mediates apoptosis-resistance in chronic lymphocytic leukemia expressing ZAP-70," *Leukemia*, vol. 24, no. 1, pp. 141–152, 2010.

[363] G. Lutzny, T. Kocher, M. Schmidt-Supprian et al., "Protein kinase C-β-dependent activation of NF-κB in stromal cells is indispensable for the survival of chronic lymphocytic leukemia B cells *in vivo*," *Cancer Cell*, vol. 23, no. 1, pp. 77–92, 2013.

[364] I. Ringshausen, F. Schneller, C. Bogner et al., "Constitutively activated phosphatidylinositol-3 kinase (PI-3K) is involved in the defect of apoptosis in B-CLL: association with protein kinase Cδ," *Blood*, vol. 100, no. 10, pp. 3741–3748, 2002.

[365] A. D. Baudot, P. Y. Jeandel, X. Mouska et al., "The tyrosine kinase Syk regulates the survival of chronic lymphocytic leukemia B cells through PKC and proteasome-dependent regulation of Mcl-1 expression," *Oncogene*, vol. 28, no. 37, pp. 3261–3273, 2009.

[366] R. Hubmann, M. Düchler, S. Schnabl et al., "NOTCH2 links protein kinase C delta to the expression of CD23 in chronic lymphocytic leukaemia (CLL) cells: research paper," *British Journal of Haematology*, vol. 148, no. 6, pp. 868–878, 2010.

[367] T. Jiffar, S. Kurinna, G. Suck et al., "PKC α mediates chemoresistance in acute lymphoblastic leukemia through effects on Bcl2 phosphorylation," *Leukemia*, vol. 18, no. 3, pp. 505–512, 2004.

[368] N. R. Murray, G. P. Baumgardner, D. J. Burns, and A. P. Fields, "Protein kinase C isotypes in human erythroleukemia (K562) cell proliferation and differentiation. Evidence that β(II) protein kinase C is required for proliferation," *The Journal of Biological Chemistry*, vol. 268, no. 21, pp. 15847–15853, 1993.

[369] M. Kaneki, S. Kharbanda, P. Pandey et al., "Functional role for protein kinase Cβ as a regulator of stress- activated protein kinase activation and monocytic differentiation of myeloid leukemia cells," *Molecular and Cellular Biology*, vol. 19, no. 1, pp. 461–470, 1999.

[370] P. P. Ruvolo, L. Zhou, J. C. Watt et al., "Targeting PKC-mediated signal transduction pathways using enzastaurin to promote apoptosis in acute myeloid leukemia-derived cell lines and blast cells," *Journal of Cellular Biochemistry*, vol. 112, no. 6, pp. 1696–1707, 2011.

[371] X. Li, Y. Li, Y. Zhang et al., "A novel bisindolymaleimide derivative (WK234) inhibits proliferation and induces apoptosis through the protein kinase Cβ pathway, in chronic myelogenous leukemia K562 cells," *Leukemia & Lymphoma*, vol. 52, no. 7, pp. 1312–1320, 2011.

[372] F. Pellicano, M. Copland, H. G. Jorgensen, J. Mountford, B. Leber, and T. L. Holyoake, "BMS-214662 induces mitochondrial apoptosis in chronic myeloid leukemia (CML) stem/progenitor cells, including $CD34^{+}38^{-}$ cells, through activation of protein kinase Cβ," *Blood*, vol. 114, no. 19, pp. 4186–4196, 2009.

[373] A. Cataldi, M. Rapino, L. Centurione et al., "NF-κB activation plays an antiapoptotic role in human leukemic K562 cells exposed to ionizing radiation," *Journal of Cellular Biochemistry*, vol. 89, no. 5, pp. 956–963, 2003.

[374] S. Kaur, S. Parmar, J. Smith et al., "Role of protein kinase C-δ (PKC-δ) in the generation of the effects of IFN-α in chronic myelogenous leukemia cells," *Experimental Hematology*, vol. 33, no. 5, pp. 550–557, 2005.

[375] V. di Giacomo, M. Rapino, S. Miscia, C. di Giulio, and A. Cataldi, "Dual role of HIF-1α in delivering a survival or death signal in hypoxia exposed human K562 erythroleukemia cells," *Cell Biology International*, vol. 33, no. 1, pp. 49–56, 2009.

[376] Z. Li, K. Shi, L. Guan, Q. Jiang, Y. Yang, and C. Xu, "Downregulation of protein kinase Cα was involved in selenite-induced apoptosis of NB4 cells," *Oncology Research*, vol. 19, no. 2, pp. 77–83, 2010.

[377] S. Kurinna, M. Konopleva, S. L. Palla et al., "Bcl2 phosphorylation and active PKC α are associated with poor survival in AML," *Leukemia*, vol. 20, no. 7, pp. 1316–1319, 2006.

[378] S. M. Kornblau, H. T. Vu, P. Ruvolo et al., "BAX and PKCα modulate the prognostic impact of BCL2 expression in acute myelogenous leukemia," *Clinical Cancer Research*, vol. 6, no. 4, pp. 1401–1409, 2000.

[379] P. P. Ruvolo, X. Deng, B. K. Carr, and W. S. May, "A functional role for mitochondrial protein kinase Cα in Bcl2 phosphorylation and suppression of apoptosis," *The Journal of Biological Chemistry*, vol. 273, no. 39, pp. 25436–25442, 1998.

[380] F. Gao, Y. Wu, M. Zhao, C. Liu, L. Wang, and G. Chen, "Protein kinase C-δ mediates down-regulation of heterogeneous nuclear ribonucleoprotein K protein: involvement in apoptosis induction," *Experimental Cell Research*, vol. 315, no. 19, pp. 3250–3258, 2009.

[381] B. Ozpolat, U. Akar, I. Tekedereli et al., "PKCδ regulates translation initiation through PKR and eIF2α in response to retinoic acid in acute myeloid leukemia cells," *Leukemia Research and Treatment*, vol. 2012, Article ID 482905, 17 pages, 2012.

[382] S. Wang, Y. Zheng, Y. Yu et al., "Phosphorylation of β-actin by protein kinase C-delta in camptothecin analog-induced leukemic cell apoptosis," *Acta Pharmacologica Sinica*, vol. 29, no. 1, pp. 135–142, 2008.

[383] H. Yan, Y.-C. Wang, D. Li et al., "Arsenic trioxide and proteasome inhibitor bortezomib synergistically induce apoptosis in leukemic cells: the role of protein kinase Cδ," *Leukemia*, vol. 21, no. 7, pp. 1488–1495, 2007.

[384] M. Song, S. Gao, K. Du et al., "Nanomolar concentration of NSC606985, a camptothecin analog, induces leukemic-cell apoptosis through protein kinase Cδ-dependent mechanisms," *Blood*, vol. 105, no. 9, pp. 3714–3721, 2005.

[385] B. Jang, K. Lim, J. Paik et al., "Tetrandrine-induced apoptosis is mediated by activation of caspases and PKC-δ in U937 cells," *Biochemical Pharmacology*, vol. 67, no. 10, pp. 1819–1829, 2004.

[386] H. Zhang, Y. Yang, K. Zhang et al., "Wogonin induced differentiation and G1 phase arrest of human U-937 leukemia cells via PKCδ phosphorylation," *European Journal of Pharmacology*, vol. 591, no. 1–3, pp. 7–12, 2008.

[387] A. Sassano, J. K. Altman, L. I. Gordon, and L. C. Platanias, "Statin-dependent activation of protein kinase Cδ in acute promyelocytic leukemia cells and induction of leukemic cell differentiation," *Leukemia & Lymphoma*, vol. 53, no. 9, pp. 1779–1784, 2012.

[388] A. Uruno, N. Noguchi, K. Matsuda et al., "All-trans retinoic acid and a novel synthetic retinoid tamibarotene (Am80) differentially regulate CD38 expression in human leukemia HL-60 cells: possible involvement of protein kinase C-δ," *Journal of Leukocyte Biology*, vol. 90, no. 2, pp. 235–247, 2011.

[389] K. Ohtani, H. Sakamoto, A. Kikuchi et al., "Follicle-stimulating hormone promotes the growth of human epithelial ovarian cancer cells through the protein kinase C-mediated system," *Cancer Letters*, vol. 166, no. 2, pp. 207–213, 2001.

[390] C. Mahanivong, H. M. Chen, S. W. Yee, Z. K. Pan, Z. Dong, and S. Huang, "Protein kinase Cα-CARMA3 signaling axis links Ras to NF-κB for lysophosphatidic acid-induced urokinase plasminogen activator expression in ovarian cancer cells," *Oncogene*, vol. 27, no. 9, pp. 1273–1280, 2008.

[391] W. Weichert, V. Gekeler, C. Denkert, M. Dietel, and S. Hauptmann, "Protein kinase C isoform expression in ovarian carcinoma correlates with indicator of poor prognosis," *International Journal of Oncology*, vol. 23, no. 3, pp. 633–639, 2003.

[392] N. Zhang, H. Zhang, L. Xia et al., "NSC606985 induces apoptosis, exerts synergistic effects with cisplatin, and inhibits hypoxia-stabilized HIF-1α protein in human ovarian cancer cells," *Cancer Letters*, vol. 278, no. 2, pp. 139–144, 2009.

[393] A. M. Eder, X. Sui, D. G. Rosen et al., "Atypical PKCι contributes to poor prognosis through loss of apical-basal polarity and cyclin E overexpression in ovarian cancer," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 102, no. 35, pp. 12519–12524, 2005.

[394] I. Nazarenko, M. Jenny, J. Keil et al., "Atypical protein kinase C ζ exhibits a proapoptotic function in ovarian cancer," *Molecular Cancer Research*, vol. 8, no. 6, pp. 919–934, 2010.

[395] I. Mertens-Walker, C. Bolitho, R. C. Baxter, and D. J. Marsh, "Gonadotropin-induced ovarian cancer cell migration and proliferation require extracellular signal-regulated kinase 1/2 activation regulated by calcium and protein kinase Cδ," *Endocrine-Related Cancer*, vol. 17, no. 2, pp. 335–349, 2010.

[396] J. Yang and R. A. Weinberg, "Epithelial-mesenchymal transition: at the crossroads of development and tumor metastasis," *Developmental Cell*, vol. 14, no. 6, pp. 818–829, 2008.

[397] D. Kyuno, T. Kojima, T. Ito et al., "Protein kinase Cα inhibitor enhances the sensitivity of human pancreatic cancer HPAC cells to Clostridium perfringens enterotoxin via claudin-4," *Cell and Tissue Research*, vol. 346, no. 3, pp. 369–381, 2011.

[398] D. Kyuno, T. Kojima, H. Yamaguchi et al., "Protein kinase Cα inhibitor protects against downregulation of claudin-1 during epithelial-mesenchymal transition of pancreatic cancer," *Carcinogenesis*, vol. 34, no. 6, pp. 1232–1243, 2013.

[399] Y. Chen, G. Yu, D. Yu, and M. Zhu, "PKCα-induced drug resistance in pancreatic cancer cells is associated with transforming growth factor-β1," *Journal of Experimental and Clinical Cancer Research*, vol. 29, no. 1, article 104, 2010.

[400] J. Y. C. Chow, H. Dong, K. T. Quach, P. N. van Nguyen, K. Chen, and J. M. Carethers, "TGF-β mediates PTEN suppression and cell motility through calcium-dependent PKC-α activation in pancreatic cancer cells," *American Journal of Physiology—Gastrointestinal and Liver Physiology*, vol. 294, no. 4, pp. G899–G905, 2008.

[401] M. G. Franz, J. G. Norman, P. J. Fabri, and W. R. Gower Jr., "Differentiation of pancreatic ductal carcinoma cells associated

with selective expression of protein kinase C isoforms," *Annals of Surgical Oncology*, vol. 3, no. 6, pp. 564–569, 1996.

[402] S. Rosewicz, F. Brembeck, A. Kaiser, Z. V. Marschall, and E. Riecken, "Differential growth regulation by all-trans retinoic acid is determined by protein kinase C α in human pancreatic carcinoma cells," *Endocrinology*, vol. 137, no. 8, pp. 3340–3347, 1996.

[403] D. W. Denham, M. G. Franz, W. Denham et al., "Directed antisense therapy confirms the role of protein kinase C-α in the tumorigenicity of pancreatic cancer," *Surgery*, vol. 124, no. 2, pp. 218–224, 1998.

[404] K. M. Detjen, F. H. Brembeck, M. Welzel et al., "Activation of protein kinase Cα inhibits growth of pancreatic cancer cells via $p21^{cip}$-mediated G_1 arrest," *Journal of Cell Science*, vol. 113, no. 17, pp. 3025–3035, 2000.

[405] A. M. Butler, M. L. S. Buzhardt, S. Li, K. E. Smith, A. P. Fields, and N. R. Murray, "Protein kinase C zeta regulates human pancreatic cancer cell transformed growth and invasion through a STAT3-dependent mechanism," *PLoS ONE*, vol. 8, no. 8, Article ID e72061, 2013.

[406] C. Laudanna, C. Sorio, C. Tecchio et al., "Motility analysis of pancreatic adenocarcinoma cells reveals a role for the atypical ζ isoform of protein kinase C in cancer cell movement," *Laboratory Investigation*, vol. 83, no. 8, pp. 1155–1163, 2003.

[407] M. D. Peruta, C. Giagulli, C. Laudanna, A. Scarpa, and C. Sorio, "RHOA and PRKCZ control different aspects of cell motility in pancreatic cancer metastatic clones," *Molecular Cancer*, vol. 9, article 61, 2010.

[408] M. Neid, K. Datta, S. Stephan et al., "Role of insulin receptor substrates and protein kinase C-ζ in vascular permeability factor/vascular endothelial growth factor expression in pancreatic cancer cells," *The Journal of Biological Chemistry*, vol. 279, no. 6, pp. 3941–3948, 2004.

[409] M. L. Scotti, W. R. Bamlet, T. C. Smyrk, A. P. Fields, and N. R. Murray, "Protein kinase Cι is required for pancreatic cancer cell transformed growth and tumorigenesis," *Cancer Research*, vol. 70, no. 5, pp. 2064–2074, 2010.

[410] S. Kato, K. Akimoto, Y. Nagashima et al., "aPKCλ/ι is a beneficial prognostic marker for pancreatic neoplasms," *Pancreatology*, vol. 13, no. 4, pp. 360–368, 2013.

[411] M. L. Scotti, K. E. Smith, A. M. Butler et al., "Protein kinase C iota regulates pancreatic acinar-to-ductal metaplasia," *PLoS ONE*, vol. 7, no. 2, Article ID e30509, 2012.

[412] S. M. Cirigliano, L. V. Mauro, V. C. Grossoni et al., "Modulation of pancreatic tumor potential by overexpression of protein kinase C β1," *Pancreas*, vol. 42, no. 7, pp. 1060–1069, 2013.

[413] A. C. Spalding, R. Watson, M. E. Davis, A. C. Kim, T. S. Lawrence, and E. Ben-Josef, "Inhibition of protein kinase Cβ by enzastaurin enhances radiation cytotoxicity in pancreatic cancer," *Clinical Cancer Research*, vol. 13, no. 22, pp. 6827–6833, 2007.

[414] A. C. Spalding, B. D. Zeitlin, K. Wilder-Romans et al., "Enzastaurin, an inhibitor of PKCβ, enhances antiangiogenic effects and cytotoxicity of radiation against endothelial cells," *Translational Oncology*, vol. 1, no. 4, pp. 195–201, 2008.

[415] D. Molè, T. Gagliano, E. Gentilin et al., "Targeting protein kinase C by Enzastaurin restrains proliferation and secretion in human pancreatic endocrine tumors," *Endocrine-Related Cancer*, vol. 18, no. 4, pp. 439–450, 2011.

[416] L. V. Mauro, V. C. Grossoni, A. J. Urtreger et al., "PKC delta (PKCδ) promotes tumoral progression of human ductal pancreatic cancer," *Pancreas*, vol. 39, no. 1, pp. e31–e41, 2010.

[417] B. Ozpolat, U. Akar, K. Mehta, and G. Lopei-Berestein, "PKCδ and tissue transglutaminase are novel inhibitors of autophagy in pancreatic cancer cells," *Autophagy*, vol. 3, no. 5, pp. 480–483, 2007.

[418] P. Cornford, J. Evans, A. Dodson et al., "Protein kinase C isoenzyme patterns characteristically modulated in early prostate cancer," *American Journal of Pathology*, vol. 154, no. 1, pp. 137–144, 1999.

[419] J. Villar, M. I. Arenas, C. M. MacCarthy, M. J. Blánquez, O. M. Tirado, and V. Notario, "PCPH/ENTPD5 expression enhances the invasiveness of human prostate cancer cells by a protein kinase Cδ-dependent mechanism," *Cancer Research*, vol. 67, no. 22, pp. 10859–10868, 2007.

[420] C. Castilla, D. Chinchón, R. Medina, F. J. Torrubia, M. A. Japón, and C. Sáez, "PTPL1 and PKCδ contribute to proapoptotic signalling in prostate cancer cells," *Cell Death and Disease*, vol. 4, article e576, 2013.

[421] R. Koren, D. Ben Meir, L. Langzam et al., "Expression of protein kinase C isoenzymes in benign hyperplasia and carcinoma of prostate," *Oncology Reports*, vol. 11, no. 2, pp. 321–326, 2004.

[422] C. T. Powell, N. J. Brittis, D. Stec, H. Hug, W. D. W. Heston, and W. R. Fair, "Persistent membrane translocation of protein kinase C α during 12-*O*-tetradecanoylphorbol-13-acetate-induced apoptosis of LNCaP human prostate cancer cells," *Cell Growth & Differentiation*, vol. 7, no. 4, pp. 419–428, 1996.

[423] C. T. Powell and L. Yin, "Overexpression of PKCε sensitizes LNCaP human prostate cancer cells to induction of apoptosis by bryostatin 1," *International Journal of Cancer*, vol. 118, no. 6, pp. 1572–1576, 2006.

[424] B. Liu, R. J. Maher, J. P. de Jonckheere et al., "12(S)-HETE increases the motility of prostate tumor cells through selective activation of PKC(α)," *Advances in Experimental Medicine and Biology*, vol. 400B, pp. 707–718, 1997.

[425] M. L. G. Lamm, D. D. Long, S. M. Goodwin, and C. Lee, "Transforming growth factor-β1 inhibits membrane association of protein kinase Cα in a human prostate cancer cell line, PC3," *Endocrinology*, vol. 138, no. 11, pp. 4657–4664, 1997.

[426] J. R. Stewart and C. A. O'Brian, "Protein kinase C-α mediates epidermal growth factor receptor transactivation in human prostate cancer cells," *Molecular Cancer Therapeutics*, vol. 4, no. 5, pp. 726–732, 2005.

[427] O. M. Fischer, S. Hart, A. Gschwind, and A. Ullrich, "EGFR signal transactivation in cancer cells," *Biochemical Society Transactions*, vol. 31, no. 6, pp. 1203–1208, 2003.

[428] S. Jain, G. Chakraborty, and G. C. Kundu, "The crucial role of cyclooxygenase-2 in osteopontin-induced protein kinase C α/c-Src/IκB kinase α/β-dependent prostate tumor progression and angiogenesis," *Cancer Research*, vol. 66, no. 13, pp. 6638–6648, 2006.

[429] J. Villar, H. S. Quadri, I. Song, Y. Tomita, O. M. Tirado, and V. Notario, "PCPH/ENTPD5 expression confers to prostate cancer cells resistance against cisplatin-induced apoptosis through protein kinase Cα-mediated Bcl-2 stabilization," *Cancer Research*, vol. 69, no. 1, pp. 102–110, 2009.

[430] A. Shih, S. Zhang, H. J. Cao et al., "Inhibitory effect of epidermal growth factor on resveratrol-induced apoptosis in prostate cancer cells is mediated by protien kinase C-α," *Molecular Cancer Therapeutics*, vol. 3, no. 11, pp. 1355–1363, 2004.

[431] J. Truman, S. A. Rotenberg, J. Kang et al., "PKCα activation downregulates ATM and radio-sensitizes androgen-sensitive human prostate cancer cells *in vitro* and *in vivo*," *Cancer Biology and Therapy*, vol. 8, no. 1, pp. 54–63, 2009.

[432] T. Kuo, W. Huang, and J. Guh, "WJ9708012 exerts anticancer activity through PKC-α related crosstalk of mitochondrial and endoplasmic reticulum stresses in human hormone-refractory prostate cancer cells," *Acta Pharmacologica Sinica*, vol. 32, no. 1, pp. 89–98, 2011.

[433] J. E. Gschwend, W. R. Fair, and C. T. Powell, "Bryostatin 1 induces prolonged activation of extracellular regulated protein kinases in and apoptosis of LNCaP human prostate cancer cells overexpressing protein kinase Cα," *Molecular Pharmacology*, vol. 57, no. 6, pp. 1224–1234, 2000.

[434] S. Rakoff-Nahoum and R. Medzhitov, "Toll-like receptors and cancer," *Nature Reviews Cancer*, vol. 9, no. 1, pp. 57–63, 2009.

[435] L. A. Rindour, R. Y. Cheng, C. H. Switzer et al., "Molecular pathways: toll-like receptors in the tumor microenvironment-poor prognosis or new therapeutic opportunity," *Clinical Cancer Research*, vol. 19, no. 6, pp. 1340–1346, 2013.

[436] A. Paone, D. Starace, R. Galli et al., "Toll-like receptor 3 triggers apoptosis of human prostate cancer cells through a PKC-α-dependent mechanism," *Carcinogenesis*, vol. 29, no. 7, pp. 1334–1342, 2008.

[437] A. W. Tolcher, L. Reyno, P. M. Venner et al., "A randomized Phase II and pharmacokinetic study of the antisense oligonucleotides ISIS 3521 and ISIS 5132 in patients with hormone-refractory prostate cancer," *Clinical Cancer Research*, vol. 8, no. 8, pp. 2530–2535, 2002.

[438] B. B. Hafeez, W. Zhong, J. Weichert, N. E. Dreckschmidt, M. S. Jamal, and A. K. Verma, "Genetic ablation of PKC epsilon inhibits prostate cancer development and metastasis in transgenic mouse model of prostate adenocarcinoma," *Cancer Research*, vol. 71, no. 6, pp. 2318–2327, 2011.

[439] J. Chen, F. Deng, S. V. Singh, and Q. J. Wang, "Protein kinase D3 (PKD3) contributes to prostate cancer cell growth and survival through a PKCε/PKD3 pathway downstream of Akt and ERK 1/2," *Cancer Research*, vol. 68, no. 10, pp. 3844–3853, 2008.

[440] D. Wu, C. U. Thakore, G. G. Wescott, J. A. McCubrey, and D. M. Terrian, "Integrin signaling links protein kinase Cε to the protein kinase B/Akt survival pathway in recurrent prostate cancer cells," *Oncogene*, vol. 23, no. 53, pp. 8659–8672, 2004.

[441] D. Wu, T. L. Foreman, C. W. Gregory et al., "Protein kinase Cε has the potential to advance the recurrence of human prostate cancer," *Cancer Research*, vol. 62, no. 8, pp. 2423–2429, 2002.

[442] D. Wu and D. M. Terrian, "Regulation of caveolin-1 expression and secretion by a protein kinase Cε signaling pathway in human prostate cancer cells," *The Journal of Biological Chemistry*, vol. 277, no. 43, pp. 40449–40455, 2002.

[443] M. H. Aziz, H. T. Manoharan, D. R. Church et al., "Protein kinase Cε interacts with signal transducers and activators of transcription 3 (Stat3), phosphorylates Stat3Ser727, and regulates its constitutive activation in prostate cancer," *Cancer Research*, vol. 67, no. 18, pp. 8828–8838, 2007.

[444] J. Meshki, M. C. Caino, V. A. von Burstin, E. Griner, and M. G. Kazanietz, "Regulation of prostate cancer cell survival by protein kinase Cε involves bad phosphorylation and modulation of the TNFα/JNK pathway," *The Journal of Biological Chemistry*, vol. 285, no. 34, pp. 26033–26040, 2010.

[445] R. Garg, J. Blando, C. J. Perez, H. B. Wang, F. J. Benavides, and M. G. Kazaniets, "Activation of nuclear factor κB (NF-κB) in prostate cancer is mediated by protein kinase C ϵ (PKCϵ)," *The Journal of Biological Chemistry*, vol. 287, no. 44, pp. 37570–37582, 2012.

[446] M. A. McJilton, C. van Sikes, G. G. Wescott et al., "Protein kinase Cε interacts with Bax and promotes survival of human prostate cancer cells," *Oncogene*, vol. 22, no. 39, pp. 7958–7968, 2003.

[447] E. Flescher and R. Rotem, "Protein kinase C ε mediates the induction of P-glycoprotein in LNCaP prostate carcinoma cells," *Cellular Signalling*, vol. 14, no. 1, pp. 37–43, 2002.

[448] S. Sarveswaran and J. Ghosh, "Wedelolactone, a medicinal plant-derived coumestan, induces caspase-dependent apoptosis in prostate cancer cells via downregulation of PKCε without inhibiting Akt," *International Journal of Oncology*, vol. 41, no. 6, pp. 2191–2199, 2012.

[449] U. Gundimeda, J. E. Schiffman, D. Chhabra, J. Wong, A. Wu, and R. Gopalakrishna, "Locally generated methylseleninic acid induces specific inactivation of protein kinase C isoenzymes: relevance to selenium-induced apoptosis in prostate cancer cells," *The Journal of Biological Chemistry*, vol. 283, no. 50, pp. 34519–34531, 2008.

[450] S. Sarveswaran, V. Thamilselvan, C. Brodie, and J. Ghosh, "Inhibition of 5-lipoxygenase triggers apoptosis in prostate cancer cells via down-regulation of protein kinase C-epsilon," *Biochimica et Biophysica Acta*, vol. 1813, no. 12, pp. 2108–2117, 2011.

[451] B. B. Hafeez, W. Zhong, A. Mustafa, J. W. Fischer, O. Witkowsky, and A. K. Verma, "Plumbagin inhibits prostate cancer development in TRAMP mice via targeting PKCε, Stat3 and neuroendocrine markers," *Carcinogenesis*, vol. 33, no. 12, pp. 2586–2592, 2012.

[452] J. Y. Kim, T. Valencia, S. Abu-Baker et al., "c-Myc phosphorylation by PKCζ represses prostate tumorigenesis," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 110, no. 16, pp. 6418–6423, 2013.

[453] A. M. Sánchez, S. Malagarie-Cazenave, N. Olea, D. Vara, C. Cuevas, and I. Díaz-Laviada, "Spisulosine (ES-285) induces prostate tumor PC-3 and LNCaP cell death by de novo synthesis of ceramide and PKCζ activation," *European Journal of Pharmacology*, vol. 584, no. 2-3, pp. 237–245, 2008.

[454] S. Yao, A. Bee, D. Brewer et al., "Prkc-ζ expression promotes the aggressive phenotype of human prostate cancer cells and is a novel target for therapeutic intervention," *Genes & Cancer*, vol. 1, no. 5, pp. 444–464, 2010.

[455] C. T. Powell, J. E. Gschwend, W. R. Fair, N. J. Brittis, D. Stec, and R. Huryk, "Overexpression of protein kinase C-zeta (PKC-ζ) inhibits invasive and metastatic abilities of Dunning R-3327 MAT-LyLu rat prostate cancer cells," *Cancer Research*, vol. 56, no. 18, pp. 4137–4141, 1996.

[456] T. Inoue, T. Yoshida, Y. Shimizu et al., "Requirement of androgen-dependent activation of protein kinase Cζ for androgen-dependent cell proliferation in LNCaP cells and its roles in transition to androgen-independent cells," *Molecular Endocrinology*, vol. 20, no. 12, pp. 3053–3069, 2006.

[457] J. Sonnemann, V. Gekeler, A. Sagrauske, C. Müller, H. Hofmann, and J. F. Beck, "Down-regulation of protein kinase Cη potentiates the cytotoxic effects of exogenous tumor necrosis factor-related apoptosis-inducing ligand in PC-3 prostate cancer cells," *Molecular Cancer Therapeutics*, vol. 3, no. 7, pp. 773–781, 2004.

[458] J. Kim, Y. Choi, A. Vallentin et al., "Centrosomal PKCβII and pericentrin are critical for human prostate cancer growth and angiogenesis," *Cancer Research*, vol. 68, no. 16, pp. 6831–6839, 2008.

[459] P. Lu, C. Yu, P. Chiang et al., "Paclitaxel induces apoptosis through activation of nuclear protein kinase C-δ and subsequent activation of Golgi associated Cdk1 in human hormone refractory prostate cancer," *The Journal of Urology*, vol. 186, no. 6, pp. 2434–2441, 2011.

[460] H. Wang, L. Xiao, and M. G. Kazanietz, "p23/Tmp21 associates with protein kinase Cδ (PKCδ) and modulates its apoptotic function," *The Journal of Biological Chemistry*, vol. 286, no. 18, pp. 15821–15831, 2011.

[461] M. V. Gavrielides, A. M. Gonzalez-Guerrico, N. A. Riobo, and M. G. Kazanietz, "Androgens regulate protein kinase Cδ transcription and modulate its apoptotic function in prostate cancer cells," *Cancer Research*, vol. 66, no. 24, pp. 11792–11801, 2006.

[462] A. M. Gonzalez-Guerrico and M. G. Kazanietz, "Phorbol ester-induced apoptosis in prostate cancer cells via autocrine activation of the extrinsic apoptotic cascade: a key role for protein kinase Cδ," *The Journal of Biological Chemistry*, vol. 280, no. 47, pp. 38982–38991, 2005.

[463] V. A. von Burstin, L. Xiao, and M. G. Kazanietz, "Bryostatin 1 inhibits phorbol ester-induced apoptosis in prostate cancer cells by differentially modulating protein kinase C (PKC) δ translocation and preventing PKCδ-mediated release of tumor necrosis factor-α," *Molecular Pharmacology*, vol. 78, no. 3, pp. 325–332, 2010.

[464] L. Xiao, A. Gonzalez-Guerrico, and M. G. Kazanietz, "PKC-mediated secretion of death factors in LNCaP prostate cancer cells is regulated by androgens," *Molecular Carcinogenesis*, vol. 48, no. 3, pp. 187–195, 2009.

[465] L. Xiao, M. Eto, and M. G. Kazanietz, "ROCK mediates phorbol ester-induced apoptosis in prostate cancer cells via $p21^{Cip1}$ up-regulation and JNK," *The Journal of Biological Chemistry*, vol. 284, no. 43, pp. 29365–29375, 2009.

[466] M. Sumitomo, R. Shen, J. S. Goldberg, J. Dai, D. Navarro, and D. M. Nanus, "Neutral endopeptidase promotes phorbol ester-induced apoptosis in prostate cancer cells by inhibiting neuropeptide-induced protein kinase C δ degradation," *Cancer Research*, vol. 60, no. 23, pp. 6590–6596, 2000.

[467] M. Sumitomo, M. Ohba, J. Asakuma et al., "Protein kinase Cδ amplifies ceramide formation via mitochondrial signaling in prostate cancer cells," *The Journal of Clinical Investigation*, vol. 109, no. 6, pp. 827–836, 2002.

[468] S. Kharait, R. Dhir, D. Lauffenburger, and A. Wells, "Protein kinase Cδ signaling downstream of the EGF receptor mediates migration and invasiveness of prostate cancer cells," *Biochemical and Biophysical Research Communications*, vol. 343, no. 3, pp. 848–856, 2006.

[469] H. S. Yu, T. H. Lin, and C. H. Tang, "Bradykinin enhances cell migration in human prostate cancer cells through B2 receptor/PKCδ/c-Src dependent signaling pathway," *Prostate*, vol. 73, no. 1, pp. 89–100, 2013.

[470] J. Kim, T. Koyanagi, and D. Mochly-Rosen, "PKCIδ activation mediates angiogenesis via NADPH oxidase activity in PC-3 prostate cancer cells," *Prostate*, vol. 71, no. 9, pp. 946–954, 2011.

[471] G. Kovacs, M. Akhtar, B. J. Beckwith et al., "The Heidelberg classification of renal cell tumours," *The Journal of Pathology*, vol. 183, no. 2, pp. 131–133, 1997.

[472] J. S. Lam, O. Shvarts, J. T. Leppert, R. A. Figlin, and A. S. Belldegrun, "Renal cell carcinoma 2005: new frontiers in staging, prognostication and targeted molecular therapy," *The Journal of Urology*, vol. 173, no. 6, pp. 1853–1862, 2005.

[473] M. von Brandenstein, J. J. Pandarakalam, L. Kroon et al., "MicroRNA 15a, inversely correlated to PKCα, is a potential marker to differentiate between benign and malignant renal tumors in biopsy and urine samples," *American Journal of Pathology*, vol. 180, no. 5, pp. 1787–1797, 2012.

[474] W. Brenner, F. Benzing, J. Gudejko-Thiel et al., "Regulation of β1 integrin expression by PKCε in renal cancer cells," *International Journal of Oncology*, vol. 25, no. 4, pp. 1157–1163, 2004.

[475] R. Engers, S. Mrzyk, E. Springer et al., "Protein kinase C in human renal cell carcinomas: role in invasion and differential isoenzyme expression," *British Journal of Cancer*, vol. 82, no. 5, pp. 1063–1069, 2000.

[476] W. Brenner, G. Färber, T. Herget, C. Wiesner, J. G. Hengstler, and J. W. Thüroff, "Protein kinase C η is associated with progression of Renal Cell Carcinoma (RCC)," *Anticancer Research*, vol. 23, no. 5A, pp. 4001–4006, 2003.

[477] Y. S. Pu, C. Y. Huang, J. Y. Chen et al., "Down-regulation of PKCζ in renal cell carcinoma and its clinicopathological implications," *Journal of Biomedical Science*, vol. 19, article 39, 2012.

[478] K. Datta, J. Li, R. Bhattacharya, L. Gasparian, E. Wang, and D. Mukhopadhyay, "Protein kinase C ζ transactivates hypoxia-inducible factor α by promoting its association with p300 in renal cancer," *Cancer Research*, vol. 64, no. 2, pp. 456–462, 2004.

[479] B. Huang, K. Cao, X. Li et al., "The expression and role of protein kinase C (PKC) epsilon in clear cell renal cell carcinoma," *Journal of Experimental and Clinical Cancer Research*, vol. 30, no. 1, article 88, 2011.

[480] B. Zhan, C. Kong, K. Guo, and Z. Zhang, "PKCα is involved in the progression of kidney carcinoma through regulating netrin-1/UNC5B signaling pathway," *Tumor Biology*, vol. 34, no. 3, pp. 1759–1766, 2013.

[481] D. Lv, W. Zhao, D. Dong et al., "Genetic and epigenetic control of UNC5C expression in human renal cell carcinoma," *European Journal of Cancer*, vol. 47, no. 13, pp. 2068–2076, 2011.

[482] O. V. Razorenova, E. C. Finger, R. Colavitti et al., "*VHL* loss in renal cell carcinoma leads to up-regulation of CUB domain-containing protein 1 to stimulate PKCδ-driven migration," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 108, no. 5, pp. 1931–1936, 2011.

[483] W. Brenner, I. Greber, J. Gudejko-Thiel et al., "Migration of renal carcinoma cells is dependent on protein kinase Cδ via β1 integrin and focal adhesion kinase," *International Journal of Oncology*, vol. 32, no. 5, pp. 1125–1131, 2008.

[484] K. Datta, R. Nambudripad, S. Pal, M. Zhou, H. T. Cohen, and D. Mukhopadhyay, "Inhibition of insulin-like growth factor-I-mediated cell signaling by the von Hippel-Lindau gene product in renal cancer," *The Journal of Biological Chemistry*, vol. 275, no. 27, pp. 20700–20706, 2000.

[485] N. Bergelin, C. Löf, S. Balthasar, V. Kalhori, and K. Törnquist, "$S1P_1$ and VEGFR-2 form a signaling complex with extracellularly regulated kinase 1/2 and protein kinase C-α regulating ML-1 thyroid carcinoma cell migration," *Endocrinology*, vol. 151, no. 7, pp. 2994–3005, 2010.

[486] N. Bergelin, T. Blom, J. Heikkilä et al., "Sphingosine kinase as an oncogene: autocrine sphingosine 1-phoshate modulates ML-1 thyroid carcinoma cell migration by a mechanism dependent on protein kinase C-α and ERK1/2," *Endocrinology*, vol. 150, no. 5, pp. 2055–2063, 2009.

[487] Y. Zhu, Q. Dong, B. J. Tan, W. G. Lim, S. Zhou, and W. Duan, "The PKCα-D294G mutant found in pituitary and thyroid

tumors fails to transduce extracellular signals," *Cancer Research*, vol. 65, no. 11, pp. 4520–4524, 2005.

[488] C. Prévostel, V. Alvaro, F. de Boisvilliers, A. Martin, C. Jaffiol, and D. Joubert, "The natural protein kinase Cα mutant is present in human thyroid neoplasms," *Oncogene*, vol. 11, no. 4, pp. 669–674, 1995.

[489] C. Prévostel, A. Martin, V. Alvaro, C. Jaffiol, and D. Joubert, "Protein kinase C alpha and tumorigenesis of the endocrine gland," *Hormone Research*, vol. 47, no. 4–6, pp. 140–144, 1997.

[490] A. Vallentin, T.-C. Lo, and D. Joubert, "A single point mutation in the V3 region affects protein kinase Cα targeting and accumulation at cell-cell contacts," *Molecular and Cellular Biology*, vol. 21, no. 10, pp. 3351–3363, 2001.

[491] R. Assert, R. Kötter, U. Schiemann, P. Goretzki, and A. F. H. Pfeiffer, "Effects of the putatively oncogenic protein kinase Cα D294G mutation on enzymatic activity and cell growth and its occurrence in human thyroid neoplasias," *Hormone and Metabolic Research*, vol. 34, no. 6, pp. 311–317, 2002.

[492] J. A. Knauf, L. S. Ward, Y. E. Nikiforov et al., "Isozyme-specific abnormalities of PKC in thyroid cancer: evidence for post-transcriptional changes in PKC epsilon," *The Journal of Clinical Endocrinology and Metabolism*, vol. 87, no. 5, pp. 2150–2159, 2002.

[493] X. Zhang, D. Li, M. Li et al., "MicroRNA-146a targets PRKCE to modulate papillary thyroid tumor development," *International Journal of Cancer*, vol. 134, no. 2, pp. 257–267, 2014.

[494] J. A. Knauf, R. Elisei, D. Mochly-Rosen et al., "Involvement of protein kinase Cε (PKCε) in thyroid cell death. A truncated chimeric PKCε cloned from a thyroid cancer cell line protects thyroid cells from apoptosis," *The Journal of Biological Chemistry*, vol. 274, no. 33, pp. 23414–23425, 1999.

[495] J. A. Knauf, B. Ouyang, M. Croyle, E. Kimura, and J. A. Fagin, "Acute expression of RET/PTC induces isozyme-specific activation and subsequent downregulation of PKCε in PCCL3 thyroid cells," *Oncogene*, vol. 22, no. 44, pp. 6830–6838, 2003.

[496] D. Molè, E. Gentilin, T. Gagliano et al., "Protein kinase C: a putative new target for the control of human medullary thyroid carcinoma cell proliferation *in vitro*," *Endocrinology*, vol. 153, no. 5, pp. 2088–2098, 2012.

[497] K. Koike, T. Fujii, A. M. Nakamura et al., "Activation of protein kinase C δ induces growth arrest in NPA thyroid cancer cells through extracellular signal-regulated kinase mitogen-activated protein kinase," *Thyroid*, vol. 16, no. 4, pp. 333–341, 2006.

[498] E. Afrasiabi, J. Ahlgren, N. Bergelin, and K. Törnquist, "Phorbol 12-myristate 13-acetate inhibits FRO anaplastic human thyroid cancer cell proliferation by inducing cell cycle arrest in G1/S phase: evidence for an effect mediated by PKCδ," *Molecular and Cellular Endocrinology*, vol. 292, no. 1-2, pp. 26–35, 2008.

[499] N. Li, Z. X. Du, Z. H. Zong et al., "PKCδ-mediated phosphorylation of BAG3 at Ser187 site induces epithelial-mesenchymal transition and enhances invasiveness in thyroid cancer FRO cells," *Oncogene*, vol. 32, no. 88, pp. 4539–4548, 2013.

[500] L. Zhang, J. Huang, N. Yang et al., "Integrative genomic analysis of protein kinase C (PKC) family identifies PKCι as a biomarker and potential oncogene in ovarian carcinoma," *Cancer Research*, vol. 66, no. 9, pp. 4627–4635, 2006.

[501] J. H.. Kang, T. Mori, H. Kitazaki et al., "Kinase activity of protein kinase cα in serum as a diagnostic biomarker of human lung cancer," *Anticancer Research*, vol. 33, no. 2, pp. 485–488, 2013.

[502] J. H.. Kang, T. Mori, H. Kitazaki et al., "Serum protein kinase Cα as a diagnostic biomarker of cancers," *Cancer Biomarkers*, vol. 13, no. 2, pp. 99–103, 2013.

[503] L. A. Davidson, C. M. Aymond, Y. Jiang, N. D. Turner, J. R. Lupton, and R. S. Chapkin, "Non-invasive detection of fecal protein kinase C βII and ζ messenger RNA: putative biomarkers for colon cancer," *Carcinogenesis*, vol. 19, no. 2, pp. 253–257, 1998.

[504] L. A. Davidson, Y. Jiang, J. R. Lupton, and R. S. Chapkin, "Noninvasive detection of putative biomarkers for colon cancer using fecal messenger RNA," *Cancer Epidemiology Biomarkers & Prevention*, vol. 4, no. 6, pp. 643–647, 1995.

[505] Q. Pan, L. W. Bao, C. G. Kleer et al., "Protein kinase Cε is a predictive biomarker of aggressive breast cancer and a validated target for RNA interference anticancer therapy," *Cancer Research*, vol. 65, no. 18, pp. 8366–8371, 2005.

[506] C. Cordon-Cardo, J. P. O'Brien, J. Boccia, D. Casals, J. R. Bertino, and M. R. Melamed, "Expression of the multidrug resistance gene product (*P*-glycoprotein) in human normal and tumor tissues," *Journal of Histochemistry and Cytochemistry*, vol. 38, no. 9, pp. 1277–1287, 1990.

[507] I. Sugawara, S. Akiyama, R. J. Scheper, and S. Itoyama, "Lung resistance protein (LRP) expression in human normal tissues in comparison with that of MDR1 and MRP," *Cancer Letters*, vol. 112, no. 1, pp. 23–31, 1997.

[508] D. S. Cox, K. R. Scott, H. Gao, and N. D. Eddington, "Effect of P-glycoprotein on the pharmacokinetics and tissue distribution of enaminone anticonvulsants: analysis by population and physiological approaches," *Journal of Pharmacology and Experimental Therapeutics*, vol. 302, no. 3, pp. 1096–1104, 2002.

[509] C. Sauvant, M. Nowak, C. Wirth et al., "Acidosis induces multidrug resistance in rat prostate cancer cells (AT1) *in vitro* and *in vivo* by increasing the activity of the p-glycoprotein via activation of p38," *International Journal of Cancer*, vol. 123, no. 11, pp. 2532–2542, 2008.

[510] C. R. Carmo, J. Lyons-Lewis, M. J. Seckl, and A. P. Costa-Pereira, "A novel requirement for Janus Kinases as mediators of drug resistance induced by fibroblast growth factor-2 in human cancer cells," *PLoS ONE*, vol. 6, no. 5, Article ID e19861, 2011.

[511] S. Daenen, B. van der Holt, G. E. G. Verhoef et al., "Addition of cyclosporin A to the combination of mitoxantrone and etoposide to overcome resistance to chemotherapy in refractory or relapsing acute myeloid leukaemia: a randomised phase II trial from HOVON, the Dutch-Belgian Haemato-Oncology Working Group for adults," *Leukemia Research*, vol. 28, no. 10, pp. 1057–1067, 2004.

[512] M. R. Baer, S. L. George, R. K. Dodge et al., "Phase 3 study of the multidrug resistance modulator PSC-833 in previously untreated patients 60 years of age and older with acute myeloid leukemia: cancer and Leukemia Group B study 9720," *Blood*, vol. 100, no. 4, pp. 1224–1232, 2002.

[513] M. Hu, Y. Liu, C. Deng et al., "Enhanced invasiveness in multidrug resistant leukemic cells is associated with overexpression of P-glycoprotein and cellular inhibitor of apoptosis protein," *Leukemia & Lymphoma*, vol. 52, no. 7, pp. 1302–1311, 2011.

[514] T. Reya, S. J. Morrison, M. F. Clarke, and I. L. Weissman, "Stem cells, cancer, and cancer stem cells," *Nature*, vol. 414, no. 6859, pp. 105–111, 2001.

[515] L. V. Nguyen, R. Vanner, P. Dirks, and C. J. Eaves, "Cancer stem cells: an evolving concept," *Nature Reviews Cancer*, vol. 12, no. 2, pp. 133–143, 2012.

[516] L. Y. W. Bourguignon, C. Earle, G. Wong, C. C. Spevak, and K. Krueger, "Stem cell marker (Nanog) and Stat-3 signaling promote MicroRNA-21 expression and chemoresistance in hyaluronan/CD44-activated head and neck squamous cell carcinoma cells," *Oncogene*, vol. 31, no. 2, pp. 149–160, 2012.

[517] L. Y. W. Bourguignon, K. Peyrollier, W. Xia, and E. Gilad, "Hyaluronan-CD44 interaction activates stem cell marker Nanog, Stat-3-mediated MDR1 gene expression, and ankyrin-regulated multidrug efflux in breast and ovarian tumor cells," *The Journal of Biological Chemistry*, vol. 283, no. 25, pp. 17635–17651, 2008.

[518] L. Y. W. Bourguignon, G. Wong, C. Earle, and L. Chen, "Hyaluronan-CD44v3 interaction with Oct4-Sox2-Nanog promotes miR-302 expression leading to self-renewal, clonal formation, and cisplatin resistance in cancer stem cells from head and neck squamous cell carcinoma," *The Journal of Biological Chemistry*, vol. 287, no. 39, pp. 32800–32824, 2012.

[519] W. K. Chu, P. M. Dai, H. L. Ki, C. C. Pao, and J. K. Chen, "Nanog expression is negatively regulated by protein kinase C activities in human cancer cell lines," *Oncogene*, vol. 34, no. 7, pp. 1497–1509, 2013.

[520] A. Singh, A. Singh, J. M. Sand, E. Heninger, B. B. Hafeez, and A. K. Verma, "Protein kinase Cε, which is linked to ultraviolet radiation-induced development of squamous cell carcinomas, stimulates rapid turnover of adult hair follicle stem cells," *Journal of Skin Cancer*, vol. 2013, Article ID 452425, 13 pages, 2013.

[521] H. Harrison, G. Farnie, S. J. Howell et al., "Regulation of breast cancer stem cell activity by signaling through the Notch4 receptor," *Cancer Research*, vol. 70, no. 2, pp. 709–718, 2010.

[522] J. Yun, A. Pannuti, I. Espinoza et al., "Crosstalk between PKCα and Notch-4 in endocrine-resistant breast cancer cells," *Oncogenesis*, vol. 2, article e60, 2013.

[523] W. L. Tam, H. Lu, J. Buikhuisen et al., "Protein kinase C α is a central signaling node and therapeutic target for breast cancer stem cells," *Cancer Cell*, vol. 24, no. 3, pp. 347–364, 2013.

[524] B. L. J. Webb, S. J. Hirst, and M. A. Giembycz, "Protein kinase C isoenzymes: a review of their structure, regulation and role in regulating airways smooth muscle tone and mitogenesis," *British Journal of Pharmacology*, vol. 130, no. 7, pp. 1433–1452, 2000.