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Growth Factors, Signal Transduction Pathways, and Tumor Suppressor Genes in Esophageal Cancer

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1. Introduction

Esophageal cancer is the eighth common cancers in the world and the sixth most common cause of cancer-related death throughout the world [1, 2]. Histologically, esophageal cancer can be divided into adenocarcinoma and squamous cell carcinoma (SCCE). Esophageal cancer is among the most malignant type of cancers which rapidly invade into the surrounding tissues, metastases to the surrounding lymph nodes, and distant organs. Since clinical symptoms of esophagus cancer appear in the advanced stages of carcinogenesis, the majority of patients are diagnosed and receive medical attention only when the tumor has already gained substantial volume, spread into surrounding tissues, and cause obstruction when food is swallowed. Despite large improvements in the detection of cancers, surgical procedures and treatments, the prognosis of esophageal cancer remains poor and the 5-year survival rate is still low [3]. Therefore, early detection, seeking new strategies for treatment, comprehensive understanding of the molecular and genetic alterations of esophageal carcinogenesis are essential.

In addition to molecular alterations environmental and nutritional factors, as well as cultural habits are thought to be contributing factors in the development of esophageal cancer. The two major habitual risk factors are tobacco smoking and alcohol consumption. Chronic irritation and inflammation of the esophageal mucosa, which might be caused by substantial alcohol intake, achalasia, and frequent consumption of extremely hot beverages, increases the incidence rate of squamous cell carcinoma of the esophagus. In addition, a clear link between squamous cell carcinoma of esophagus and low socioeconomic status has also been established.

While the major risk factors for esophageal adenocarcinoma are the two altered physiological conditions: gastroesophageal reflux disease (GERD) and Barrett's esophagus [3], such association have not been proposed for squamous cell carcinoma of esophagus. In turn, a large number of molecular events were found to be involved in the development and progression of squamous cell carcinoma of esophagus. These events include genetic and epigenetic alterations in oncogenes, tumor suppressor genes, cell adhesion molecules, DNA repair genes, cell cycle regulatory genes, genetic instability as well as telomerase activation, and aberrant regulation of growth factors and their receptors. Recent studies have indicated that activation of cyclin D1, *erbB-2*, and *c-myc* oncogenes and inactivation of *p53*, *Rb*, *APC*, and *p16* tumor suppressor genes are frequently involved in esophageal cancers [3-6].

2. Growth factors

The significant role of growth factors and growth factor-mediated signaling pathways in the tumorigenesis of esophagus has been well established and similar to many other types of cancers as a preferred target for esophageal cancer therapy [4].

Growth factors regulate growth and development of cells. They might be supplied by distant glands and tissues, neighboring cells, or *in situ* by tumor cells themselves. Thus growth factors might be provided by endocrine, paracrine or autocrine mechanisms among which autocrine mechanism is thought to play a significant role in the growth of cancer cells [7, 8]. Most growth factors are polypeptides that regulate numerous cellular responses, notably cell proliferation. They exert their effects by binding to specific receptor on the cell surface; which most often is associated with an intrinsic tyrosine kinase activity, or by forming a complex with an intracellular tyrosine kinase [9]. Following to binding of growth factors to their corresponding receptors the tyrosine kinase activity is induced and phosphorylation of specific residue(s) in the intracellular domain of receptors occurs. Such phosphorylated cytoplasmic domains serve as docking sites for downstream signal transduction molecules and trigger signaling pathways that induce expression of cyclin D1, promoting cellular proliferation and survival (Fig 1, Fig 2) [10]. Aberrant regulation of growth factors and their corresponding receptors in addition to structural alterations in receptors play important role in tumorigenesis of esophageal cancer [4].

2.1 Epidermal Growth Factor Receptor (EGFR)

The epidermal growth factor receptor (EGFR) family and their ligands including epidermal growth factor (EGF) and transforming growth factor- α (TGF- α) are implicated in the development of esophageal cancer [7, 11-17]. The EGFR family composes of four members: EGFR (HER-1, *erbB-1*), HER2 (*erbB-2*, Neu), HER3 (*erbB-3*) and HER4 (*erbB-4*) [4, 18], all of which are tyrosine kinase receptors that are activated by ligand-induced homo or hetero dimerization. Overexpression of EGFRs is common in esophageal cancer and has been reported in several cell lines of SCCE, 29-92% of tumor samples of SCCE [19, 20] and 80% of patients with adeno and squamous cell carcinoma [21, 22]. EGFR upregulation correlates with poor prognosis, low survival rate and minimal response to chemotherapy [20, 23-25]. Amplification of EGFR gene has been found approximately in 8-30% of esophageal adenocarcinomas [21, 26]. Additionally, expression of EGF or TGF- α ligands along with overexpression of EGFR is correlated with esophageal cancer [7, 11, 12, 14-17]. EGF overexpression has also been detected in Barrett's-associated adenocarcinomas [13, 27, 28].

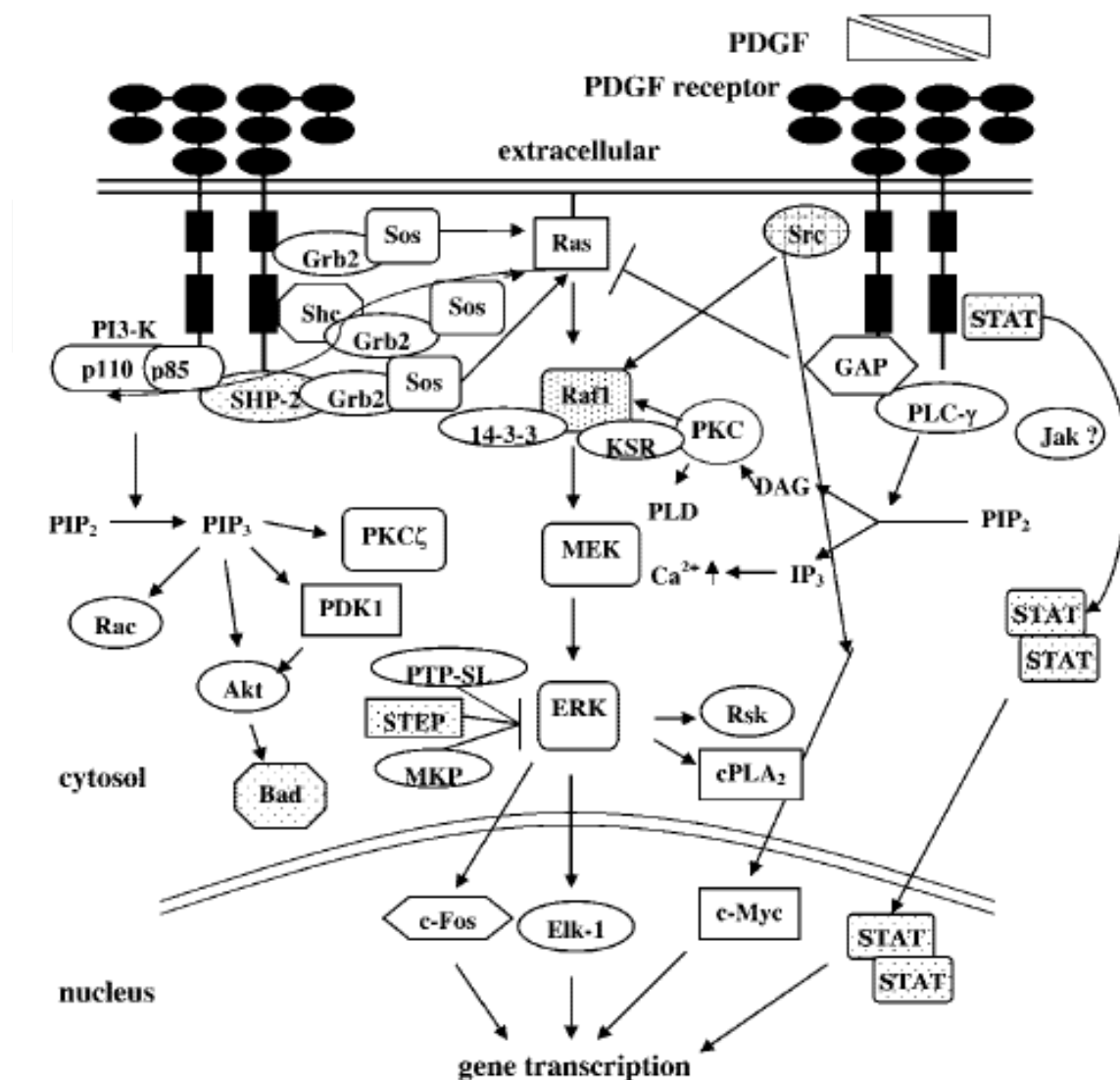


Fig. 1. Schematic presentation of growth factor-mediated signaling pathways. The picture illustrates signaling pathways downstream of PDGF receptors, activated by ligand-induced dimerization. Other tyrosine kinase receptors induce similar pathways. Arrows indicate activation; inhibitory interactions are indicated by blunted lines [4].

EGF may also serve growth inhibitory effect that shown to be mediated by STAT-1 (signal transducer and activator of transcription1) pathway and its mediation in the upregulation of p21 cyclin dependent kinase inhibitor [4, 29, 30].

EGFR activation is associated with metastasis as it modulates cell adhesion, angiogenesis, invasion and migration. Since EGFR activation increases expression of matrix metalloproteases (MMPs) it causes degradation of extracellular matrix and promotes invasion and metastasis in esophageal cancer [31, 32]. In addition, it has also been shown that EGF is implicated in relocalization of E-cadherin from the lateral adherent sides to cell surface, resulting in cell morphology change and increased invasiveness [33].

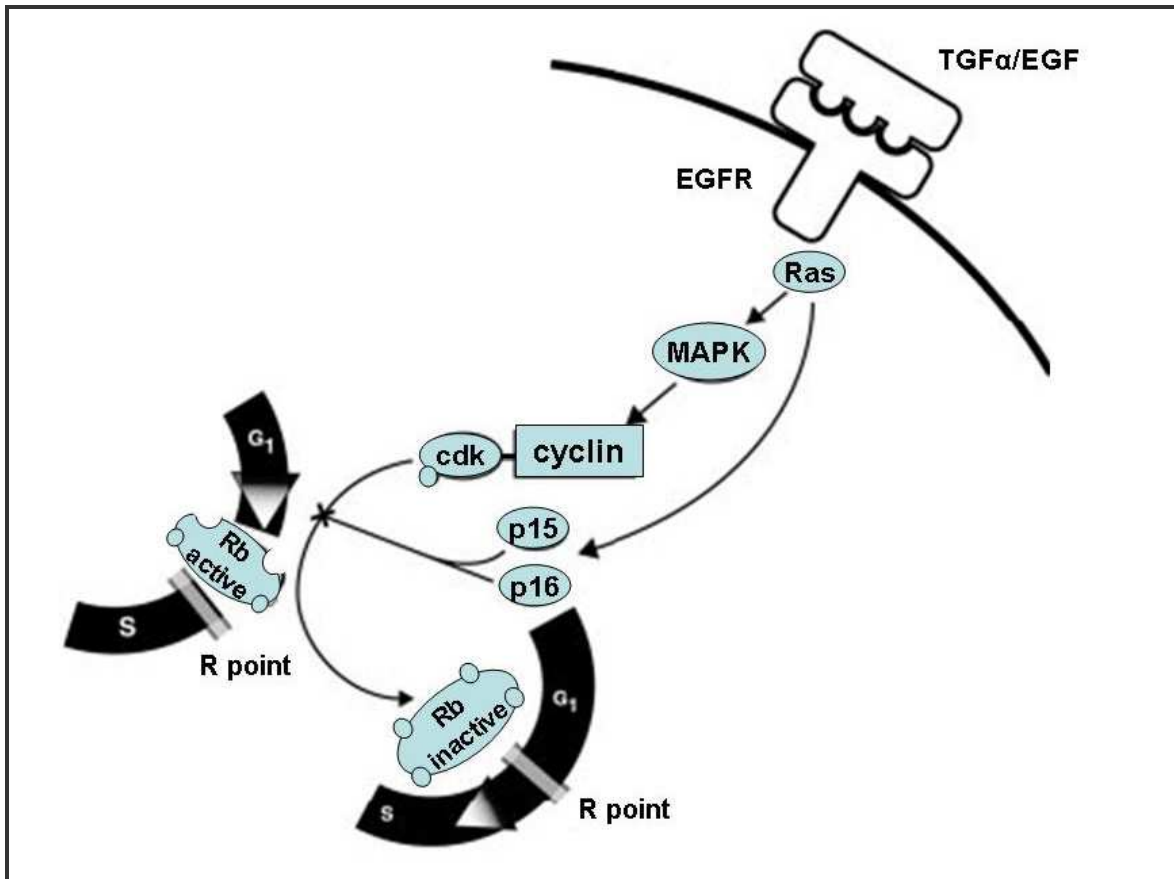


Fig. 2. Growth factors, Ras signaling and cell cycle regulation. Binding of growth factors TGF- α and EGF with EGFR (a tyrosine kinase receptor) promotes cell cycle progression by activating Ras and MAPK. MAPK signaling induces the expression of cyclins which bind CDKs and inactivate Rb. Activation of Ras also induces growth inhibitory effectors including p16 and p15. Similar to p53, p16 and p15 induce G1 arrest by inhibiting the function of cyclins and CDKs, thereby preventing cell cycle progression through the R-point [27]. By definition restriction point (R-point) is a point or event in G1 of a cell cycle at which cell becomes committed to progress cell cycle without requirement to extracellular proliferation stimulant.

2.2 Human Epidermal Growth Factor Receptor 2 (HER2)

Activation of certain tyrosine kinase receptors, such as EGF receptors and HER2 (erbB-2) results in phosphorylation of catenins and prevention of their binding to cadherins [34-36]. Regarding to this notion, overexpression of EGFR and HER2 (erbB-2) in esophageal cancer could possibly lead to sequestration of β -catenin, which result in the altered cell adhesion and increased tumor aggressiveness [27].

The role of HER-2 overexpression in esophageal cancer has been reported in 9%-60% of cases; depending on the stage of disease, tumor histology, or the applied methodology [4, 8, 11, 37-41]. There is no known ligand for HER-2, as it does its function by forming heterodimer with other tyrosine kinase receptors. In fact, *HER-2 (erbB-2)* is an oncogenic form of the normal receptor tyrosine kinase and overexpression of *erbB-2* by tumor cells is associated with hyperproliferation [4, 42]. Moreover, HER-2 expression may change during

tumor progression [4, 43-45]. Although some studies demonstrate that HER-2 overexpression correlates with invasion, lymph node metastasis, and chemoresistance in esophageal cancer [46-48], others have shown that its expression is associated with favorable response to chemo or radiotherapy in esophagus cancer [49].

2.3 Insulin-like Growth Factor-1 (IGF-1) and IGF-1 receptor (IGF-1R)

Insulin-like growth factor-1 (IGF-1) and its tyrosine kinase receptor: IGF-1R, contribute to esophageal cancer. Tumor growth upon overexpression of IGF-1R, prevention of apoptosis via IGF-1 autocrine loop, and mitogenic effects of IGF-1 and IGF-2 has been reported in esophageal cancer as well as Barrett's-associated neoplasia [7, 50-52]. In addition, IGF binding protein-3 (IGFBP3); the major regulator of IGF-1 or IGF-2, is frequently overexpressed in SCCE in parallel with EGFR overexpression [53]. IGFBP3 has been shown to promote transforming growth factor β 1-mediated epithelial to mesenchymal transition and motility in esophageal cancer [54]. Furthermore, the level of serum IGF-1 and IGFBP3 significantly increases in esophageal cancer patients, which correlates with tumor invasion, poor prognosis, and low survival rate of patients [55].

Platelet-derived growth factor (PDGF) comprise a family of dimeric isoforms including the related A, B, C, and D polypeptides chains which bind to α - and β -tyrosine kinase receptors [56]. The significance of PDGF and its receptors in esophageal cancer is unclear. In physiological condition, normally, there is no expression of PDGF receptors in epithelial cells, while a number of studies have indicated the expression of different PDGF isoforms in esophageal cancer. It was found that PDGF-BB isoform promotes the growth of human esophageal carcinoma cell line and prevents apoptosis of cancer cells [57]. Additionally, overexpression of PDGFR- β receptor has been shown in tumor tissues of esophageal cancer [23, 58].

2.4 Vascular Endothelial Growth Factor (VEGF) and other angiogenesis factors

Vascular endothelial growth factor (VEGF) is composed of a family of closely related members, including VEGF-A, VEGF-B, VEGF-C, and VEGF-D as well as placental growth factor, among which VEGF-A is usually known as VEGF which is the main growth factor of endothelial cells. VEGF contributes to the vascular permeability, proliferation, as well as prevention of endothelial cell apoptosis. VEGFs utilize tyrosine kinase receptors of VEGFR family, including VEGFR-1 and VEGFR-2, and VEGFR-3, in which VEGFR-1 and VEGFR-2 transmit growth signals for blood vascular endothelial cells while, VEGFR-3 is involved in the regulation of lymphatic endothelial cells [59-61].

Overexpression of VEGF has been found in 30-60% of esophagus cancer cases. It is significantly correlated with advanced stage of disease, extent of microvessel density, distant metastasis, and poor survival rate in patients [62-64]. Upregulation of VEGF along with fibroblast growth factor has been shown in Barrett's esophagus and adenocarcinomas of esophagus as well as gastroesophageal junction tumor [65]. Since VEGF overexpression is associated with malignant potential of esophageal carcinoma and a higher level of which could be observed in serum (S-VEGF) of esophageal cancer patients; it could be considered as a significant and independent prognostic factor and a useful clinical biomarker for evaluation of patient's prognosis [66].

The major role of VEGF is in the process of angiogenesis where it plays an essential role in growth and metastasis of esophageal carcinoma. Among VEGF family, VEGF-C has shown to be correlated with the process of lymphangiogenesis leading to lymph node micrometastasis (LMN). It is considered as one of the most important prognostic factors of esophagus squamous cell carcinoma [67-69]. The association between VEGF-C expression with angiolymphatic invasion, lymph node metastasis and lower survival rate has been shown in esophageal adenocarcinoma as well [70]. Moreover, bone marrow micrometastases in esophageal cancer correlates with an increased level of plasma VEGF [71]. It has been shown that VEGF-C, and VEGF-D are involved in the early stages of esophageal carcinogenesis since they are also expressed in dysplastic lesions of both types of esophageal carcinomas [72, 73].

In addition to VEGF, other factors such as heparin-binding growth factor (midkine), fibroblast growth factor, thymidine phosphorylase, and hepatocyte growth factor contribute to tumor angiogenesis as well [66].

Overexpression and release of fibroblast growth factor (FGF-2) by stromal fibroblasts correlates with tumor recurrence and short survival in esophageal cancer patients [66, 74]. Stromal fibroblasts are also involved in tumor progression through degradation of extracellular matrix, secretion of growth factors, and regulation of epithelial cell behavior. It has also been shown that FGF receptor 2-positive fibroblasts provide a suitable microenvironment for tumor development and progression through stimulation of cancer cell proliferation, induction of angiogenesis, cell mobility, inhibition of cell adhesion, and promotion of epithelial-mesenchymal transition [75].

While many studies indicate an anti angiogenesis role for TGF- β , one study by using 3D in vitro model, has shown the role of fibroblasts and TGF- β in VEGF-induced angiogenesis in esophageal cancer, in which the paracrine TGF- β secretion by SCCE cells leads to the activation of stromal fibroblasts, which undergo a myofibroblastic transdifferentiation and expression of VEGF. Secretion of VEGF from activated fibroblasts, known as carcinoma-associated fibroblasts (CAFs), subsequently stimulate endothelial cells migration and vascular network formation (Fig 3) [76].

Midkine (MK) is a heparin-binding growth factor which overexpresses in esophageal carcinoma and plays a role in tumor angiogenesis and invasion [77]. Serum MK (S-MK) is an independent prognostic factor and may be a useful tumor marker for esophageal carcinoma, since the level of S-MK is increased in patients with esophageal carcinoma. It is also associated with tumor size, immunoreactivity, and poor survival of patients [66, 78, 79].

Hepatocyte growth factor (HGF), also known as scatter factor, is another factor that derives from specialized cancer-associated fibroblasts (CAFs) in the extracellular matrix that acts in a paracrine way to promote SCCE invasion via activation of VEGF and IL8 expression [80, 81]. It has been found that HGF and its tyrosine kinase receptor, c-Met, play significant role in esophageal carcinogenesis. Increased levels of HGF in serum, correlates positively with VEGF of serum, and significantly associates with the advanced stage of metastasis and low survival; provide an independent prognostic factor as well [66, 80]. Moreover, increased expression of c-Met tyrosine kinase receptor is significantly correlated with the reduced survival rate, distant metastasis, and local recurrence of cancer in esophageal cancer patients [80, 82, 83]. Grugan *et al.* have shown activation of HGF/Met signaling in human SCCE

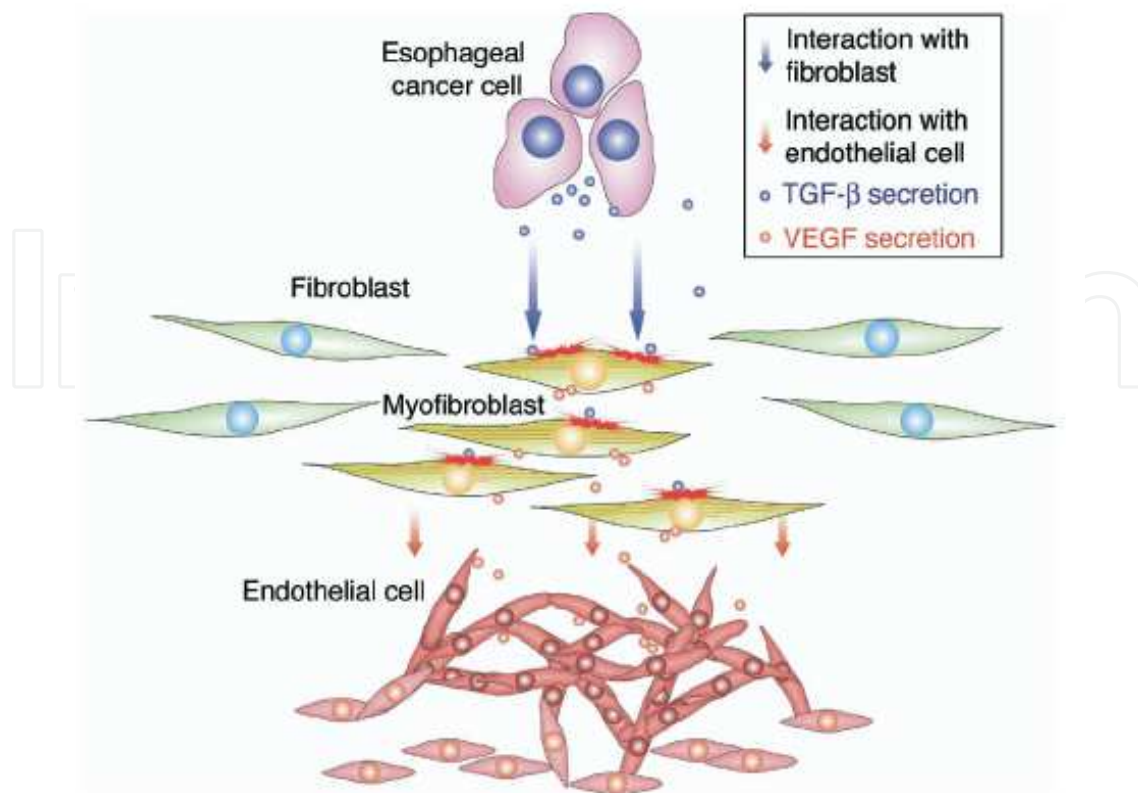


Fig. 3. Schematic illustration of SCCE cells and fibroblasts involvement in the vascular network formation. Esophageal cancer cells produce TGF- β to activate stromal normal fibroblasts. Tumor stromal fibroblasts become transdifferentiated into myofibroblasts that secrete VEGF, which in turn induce endothelial cell migration and the formation of a microcapillary network [76].

tissues and SCCE cell lines upon EGFR and p53 overexpression. Secretion of HGF by stromal fibroblasts induces the transformed esophageal epithelial cells to invade extracellular matrix; however, other unidentified factors may also cooperate with HGF in this process, which further highlight the significance of this pathway in esophageal carcinoma invasion and progression [84].

Recently another growth factor: connective tissue growth factor (CTGF, CCN2), has been introduced by Li and colleagues to be involved in the development and progression of SCCE in addition to poor survival of SCCE patients. It is suggested to be an independent factor for SCCE patients' prognosis as well as diagnosis of the precancerous lesions; as a result early detection of SCCE [85].

3. Signal transduction pathways

3.1 Ras signaling

Activation of the Ras pathway takes place upon a wide range of stimuli that could initiate its signaling. Ras activation begins with a vast array of upstream activated receptors including receptor tyrosine kinases, serpentine receptors, heterotrimeric G-proteins, integrins and cytokine receptors [86]. Among these activators, the best described mean of Ras stimulation

is via receptor tyrosine kinases such as EGF receptor (Fig 4). Binding of growth factors to their cognate receptors promote cellular proliferation through signal transduction cascades, initiated by the activation of membrane associated Ras proteins. Ras/Raf/mitogen activated protein kinase (MAPK) is one of the key Ras dependent growth-stimulating signaling cascade activated when growth factors bind their tyrosine kinase receptors, which ultimately leads to the induction of cyclin D1 [87, 88].

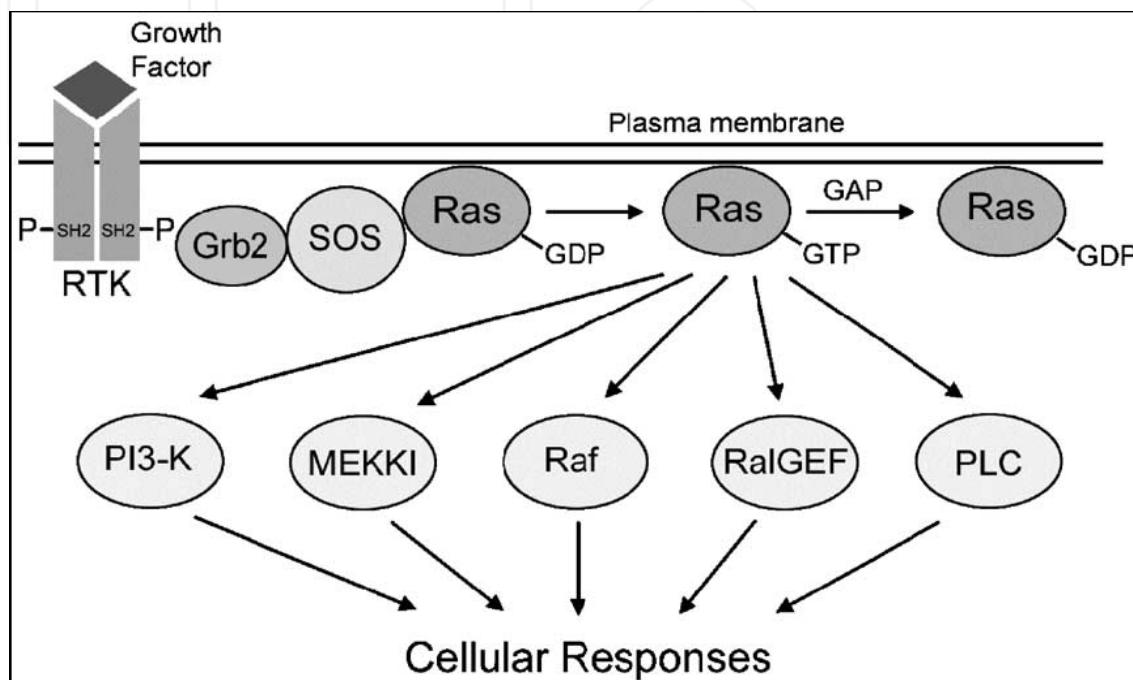


Fig. 4. A simplified overview of Ras activation and signaling cascade. Activation of a receptor tyrosine kinase (RTK) by an appropriate growth factor stimulates autophosphorylation of SH2 domains that recruit Grb2. Guanine nucleotide exchange factors (GEF) such as SOS are localized to the membrane by Grb2, which then stimulate Ras to exchange GDP for GTP. The activated Ras interacts with multiple signaling pathways, including phosphoinositide 3Vkinase (PI3-K), MEKKI, Raf kinase, RalGEFs and phospholipase C (PLC) to induce cellular responses. Ras signaling is terminated when GTPase activating proteins such as p120 and NF-1 stimulate Ras to hydrolyze GTP to GDP [86].

Ras pathway can also inhibit proliferation by inducing expression of p16 and p15 that are members of the INK4 family (Fig 2). These proteins block the Rb phosphorylation induced by cyclin D1/CDK complex, which results in cell cycle arrest in G1 [88]. Several lines of evidence have addressed the importance of Ras effector pathways in the carcinogenesis of esophagus cancer; most notably through contribution of growth factors and their tyrosine kinase receptors, and in particular EGF and EGFR which are commonly deregulated and/or found at high level of expression in esophageal cancer [4, 5, 21, and 89].

In addition, mitogen activated protein kinase (MAPK) signal transduction pathway including Ras-Raf-MEK-ERK, PI3K/Akt, and JNK were found to be hyperactivated in esophageal cancer. This pathway modulates cell proliferation, invasion and metastasis, and resistance to chemotherapeutic agents, and ionizing radiation in esophageal cancer cells [24,

91-93]; in which, inhibition of MAPK signaling could enhance sensitivity of esophageal cancer cells to chemotherapeutic agents [94-96].

Lawler *et al.* [97] have also shown that mobility and invasiveness of metastatic esophageal cancer cells are potentiated by shear stress through the Rho kinase (ROCK) and Ras-signaling pathways, suggesting a novel physiological role for Rock and Ras in metastatic behavior of cancer cells [97].

The contribution of Ras/ERK signaling has been demonstrated by Senmaru *et al.* They have shown a dominant negative H-ras mutant (N116Y) inhibits EGF-stimulated activation of Erk2 in esophageal cancer cells. Furthermore, using adenoviral vectors and increased expression of this mutant significantly reduces the growth of human squamous cell carcinoma of esophagus cells *in vitro* and *in vivo* [98].

Furthermore, the significance of Ras signaling and its downstream pathways has also been recently indicated in tumorigenesis of esophageal cancer. Since, it was found that activation of MEK/ERK and PI3K/Akt effector pathways play important role in downregulation of tropomyosin-1, which is a member of tropomyosin family and actin cytoskeleton-related proteins, in squamous cell carcinoma of esophagus [99].

Due to the importance of Ras dependent signaling drugs blocking these pathways were used in chemotherapy. Among such drugs are statins; a type of popular cholesterol-lowering agents including drugs such as Lipitor, were shown to inhibit tumor growth and proliferation of cancer cells as well as stimulation of apoptosis in esophageal cancer cell lines. These effects are achieved by inhibiting the Ras, ERK and protein kinase B (Akt) signaling pathways [90].

3.2 Wnt signaling

Wnt/ β -catenin pathway initiates a signaling cascade critical for the normal development. The aberrant activity of this signaling pathway is associated with several forms of human carcinomas [100, 101]. Wnt ligands begin intracellular signaling pathways by binding to the G-protein -coupled receptors frizzleds (Fzs) [102]. In the absence of Wnt signals, GSK-3 phosphorylates cytosolic β -catenin within a destruction complex comprised of adenomatous polyposis coli (APC), Axin-1, casein kinase-1 (CK-1), and other proteins, the end result of which is targeting β -catenin for ubiquitin-mediated degradation (Fig 5a).

Upon Wnt binding to the Frizzled receptor and low-density lipoprotein receptor-related protein (LRP) co-receptors, the cytoplasmic Dishevelled (Dsh) protein becomes activated which in turn antagonizes the effects of GSK-3 through prevention of destruction complex formation and thus β -catenin phosphorylation. This in turn leads to the stabilization and accumulation of cytoplasmic β -catenin. GSK-3 could also be inactivated through phosphorylation by PI3-K (Fig 5c). As a result, accumulated cytoplasmic β -catenin enters into the nucleus where it binds to the T cell factor/TCF/LEF (T-cell factor/lymphoid enhancer-binding factor 1) transcription factor family and stimulates transcription of target genes including *c-myc*, *cyclin D1*, *c-jun*, and *fra-1* (Fig 5b), which plays critical roles in cell growth, proliferation, and differentiation [101-104]. Aberrant expression and function of Wnt signaling components result in aberrant nuclear accumulation of β -catenin which in turn contributes to the tumorigenesis of esophageal cancer through increased expression of cyclin D1 [105].

In addition to its role in Wnt signaling, β -catenin is also involved in cell adhesion, providing a link between actin cytoskeleton and cadherin(s) cell adhesion molecules [106, 107]. E-cadherin and β -catenin are primarily found in the cell membrane of the normal squamous mucosa of esophagus and the nondysplastic, specialized intestinal metaplasia of Barrett's esophagus [108, 109]. Immunohistochemical studies of dysplastic Barrett's esophagus has shown that membrane E-cadherin and β -catenin are decreased, while their level is increased in cytoplasm and nucleus [110].

Loss of APC tumor suppressor gene plays important role in the development of esophageal cancer, since loss of heterozygosity (LOH) of 5q21, the APC locus, occurs commonly in adenocarcinomas of esophagus [111-113]. Mutations in β -catenin and/or APC gene also alter degradation of β -catenin, as a result, its aberrant accumulation leads to the increased transcription of target genes. However, it has been shown that mutations of APC and β -catenin genes, unlike in colorectal carcinoma, involve in only a small subset of esophageal and esophagogastric junction carcinomas [114], or somehow are rare in esophageal cancer [115]. However some studies have confirmed that mutations of APC gene occur in human esophageal cancer [116, 117].

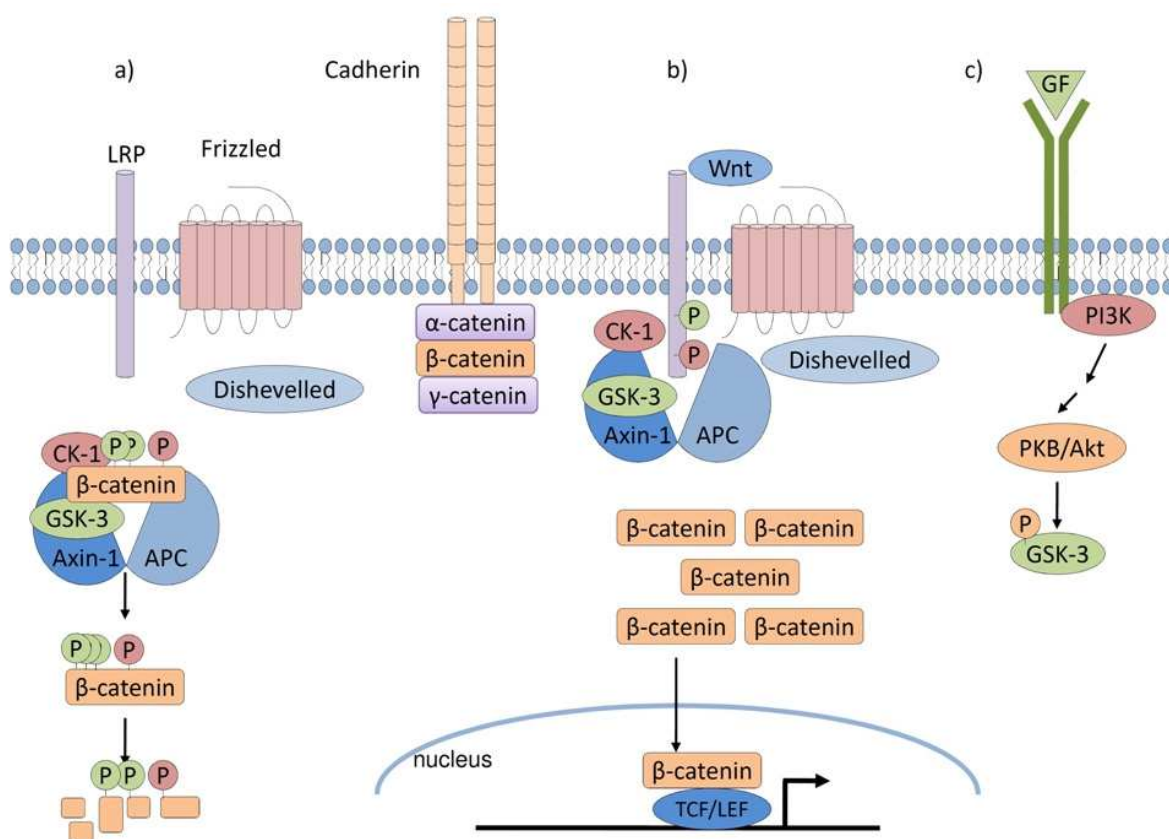


Fig. 5. The role of Wnt signaling in the activation of gene expression through mediation of β -catenin induced transcription. The non-phosphorylated form of β -catenin is active while the phosphorylated form of which is doomed to the inactivation and proteasomal degradation (a). Dishevelled antagonises β -catenin phosphorylation by GSK-3 (b) and PI3K does the same function by phosphorylating GSK-3 and thus inhibition GSK-3 mediated phosphorylation of β -catenin (c) [118].

Although mutations in *APC* or β -catenin are rare in esophageal cancer, alterations of upstream components, such as overexpression of Wnt2 ligand and Frizzled receptors or downregulation of Wnt antagonists and inactivation of secreted frizzled-related protein (SFRP) genes by promoter methylation have been reported to play a dominant role in the activation of the Wnt pathway during esophageal carcinogenesis [119, 120].

Nonetheless, inactivation of *APC* by promoter methylation is involved in esophageal cancer, where it occurs in 83-92% of Barrett's high grade dysplasia and esophageal adenocarcinoma as well as 40-50% of Barrett's metaplasia without dysplasia [121, 122]. Higher level of promoter methylation of *APC* was also found by Clement, *et al.* in 100% of Barrett's esophagus samples and in 95% of esophageal adenocarcinomas as well [119]. Several lines of evidence have also shown the role of *APC* promoter hypermethylation in squamous cell carcinoma of esophagus, as it was observed in about 50% of cases, to contribute in the progression of dysplasia to carcinoma in SCCE carcinogenesis along with low survival rate of patients [122-124]. Moreover, methylated *APC* DNA has been detected in the plasma of patients with esophageal adenocarcinoma and squamous cell carcinoma. Methylated *APC* promoter has shown to be associated with a significantly low patient survival [122], suggesting the capability of hypermethylated *APC* tumor suppressor gene to be a potential biomarker in esophageal cancer.

Wang *et al.* have recently shown a prominent role of Wnt signaling in SCCE carcinogenesis. They identified that Wnt2/ β -catenin signaling pathway is activated in SCCE cells, as sodium nitroprusside (SNP) and siRNA against β -catenin not only inhibit expression of β -catenin and its major downstream effectors including c-myc and cyclin D1, but also induce cell cycle arrest and apoptosis, suggesting that Wnt2/ β -catenin pathway may be a potential molecular target for SCCE therapy [125]. Inactivation of GSK3 β , observed by higher phosphorylation of Ser9 GSK3 β , has been found in most cancers with epithelial origin, including esophagus cancer [126, 127].

3.3 Dopamine and cyclic-AMP-regulated phosphoprotein

Recently, the role of t-DARPP (Dopamine and cyclic-AMP-regulated phosphoprotein) in the regulation of β -catenin has been investigated in esophageal cancer. DARPP-32 is a major regulator of dopaminergic neurotransmission in brain. It is the key factor for the functioning of the dopaminergic neurons [128]. DARPP-32 and t-DARPP, a truncated isoform of DARPP-32, are suggested as novel cancer-related genes [129].

Overexpression of t-DARPP has been reported in gastrointestinal malignancies as well as esophageal adenocarcinomas [130, 131], which leads to activation of Wnt signaling and increased cell proliferation through phosphorylation of GSK-3 β , nuclear accumulation of β -catenin, and upregulation of *cyclin D1* and *c-myc* target genes. It has also been shown that t-DARPP mediated GSK-3 β phosphorylation is AKT-dependent [132].

3.4 PI3K signaling

The involvement of phosphatidylinositol 3-kinase (PI3K)/AKT pathway in esophageal tumorigenesis was also subject of investigations. Phosphatidylinositol 3-kinases (PI3Ks) are a ubiquitous family of lipid kinases that catalyse the phosphorylation of phosphatidylinositol

(PI), PI(4)P and PI(4,5)P₂ that leads to formation of PI(3)P, PI(3,4)P₂ and PI(3,4,5)P₃, respectively [133]. These phosphorylated lipid products are then able to activate a variety of downstream targets, such as protein kinase B (PKB/AKT), that regulate a wide range of important cellular processes, including cell proliferation, survival, migration, apoptosis, oncogenic transformation and intracellular trafficking of proteins [134].

Constitutive activation of PI3K and AKT is common in cancers including esophageal cancer [135-137]. Amplification of the *PIK3CA*, the gene coding for the p110 α catalytic subunit of PI3K, has been reported in SCCE [136] and in a low percentage of adenocarcinoma [138]. In addition, mutation of *PIK3CA* has been found to be an important event in the etiology of esophageal cancer [139].

Recent studies have indicated that inhibition of PI3K reduces proliferation and enhances radiosensitivity of esophageal cancer cells [92, 140]. In addition, the level of p-AKT expression in SCCE increases during chemotherapy, and a high expression of p-AKT correlates with poor prognosis [141].

3.5 Hedgehog signaling

The Hh (Hedgehog) signaling is critical for embryonic development which initiates following to binding of Hh to patched (Ptch) receptor, which releases smoothed (Smo), a potential G protein-coupled receptor (GPCR), from Ptch mediated repression. Smo signal transduction eventually leads to increased expression and activation of Gli, a transcription factor that regulates corresponding target genes [142-144]. Deregulation of this pathway leads to abnormal proliferation and transformation of cells in different tumors, such as small cell lung cancer, pancreatic cancer, prostate cancer and digestive tract cancer, including esophageal cancer [145-149]. Hyperactive Hh signaling has been reported to be implicated in esophageal cancer [146, 147]. It has also been shown that PI3K/AKT pathway plays a critical role in epidermal growth factor (EGF), G $\beta\gamma$ and Shh-induced Hh signaling. Conversely, PI3K/AKT and MAPK signaling cooperate with the Shh pathway to promote esophageal cancer cell survival and proliferation [150].

3.6 Role of Id-1

Overexpression of Id-1, the inhibitor of differentiation or DNA binding, has also been shown in esophageal squamous cell carcinoma. Id-1 promotes proliferation [151], tumorigenicity and metastasis of human esophageal cancer cells through activation of PI3K/AKT signaling pathway [152-154]. Id-1 is a helix-loop-helix protein, which heterodimerizes with the basic helix-loop-helix transcription factors and inhibits them from DNA binding, therefore regulating gene transcription [155].

4. Tumor suppressor genes

4.1 P53

Tumor suppressor genes' inactivation occur by the genetic or epigenetic events such as mutations, allele deletions (LOH), promoter hypermethylation, abnormal splicing, and posttranscriptional silencing by microRNAs [156] in cancers. Alterations in multiple tumor

suppressor genes including *Rb*, *p53*, *APC*, *p16*, and *MCC* implicated in carcinogenesis of esophageal cancer. The majority of tumor suppressor genes are involved in the regulation of cell cycle. Cell cycle is controlled precisely through two major regulatory mechanisms, the *p53* (*p14-MDM2-p53-p21*) and *pRb* (*p16-cyclinD1-pRb*). Deregulation of both mechanisms play critical role in the development of most human cancers including esophageal cancer.

The *p53* tumor suppressor gene regulates cell cycle progression, apoptosis and DNA repair. It also inhibits vascular endothelial growth factor. *p53* is the most frequent mutated gene in all human malignancies. *P53* is normally expressed at low level but accumulates in the nucleus of the damaged cell and transactivates target genes including genes involved in G1 cell-cycle arrest (*p21/WAF1*) and apoptosis (*BAX*) [157-161]. In fact, it plays a role as a genomic policeman to prevent replication of damaged DNA; either by arresting cells in G1 and facilitating DNA repair or by apoptotic elimination of damaged cells [162]. *p53* mutations are common in esophageal cancer which occur in approximately 50-80% of esophageal cancers. More than 92% of these mutations occur in the four conserved domains of the *p53* gene; exon 5 to exon 8, with hot spots at Arg175, Cys176, Arg248, Arg273, and Arg282, 80% of which are point mutations including 46% transition and 36% transversion [5]. Several studies have indicated that alteration of *p53* gene in esophageal cancer occurs in the early stage of carcinogenesis and is associated with tumor progression; suggesting that loss of *p53* function is critical for the development of this type of cancer [5, 156].

Although the presence of mutant *p53* have shown to be correlated with the poor prognosis [163, 164], other studies have not found such correlation [165, 166]. It has also been shown that measurement of circulating anti *p53* antibody in serum of patients with SCCE is useful for detection of *p53* mutations, and as a tumor marker or prognostic marker [167-169].

4.2 p21/WAF1

The *p21/WAF1* gene is located on chromosome 6p21.2 and encodes a cyclin-dependent kinase inhibitor. Induced by wild-type *p53*, it mediates G1 arrest following to DNA damage [170]. Mutations and deletions of the *p21/WAF1* gene are less common in human cancers [171]. However, polymorphisms in exon 2 of the *p21/WAF1* gene has been documented to play important role in esophageal tumorigenesis [172]. Moreover, induction of *p21/WAF1* may occur via *p73* [173], a transcription factor that also regulates *p21/WAF1* expression [174] in esophageal cancer. The role of *p21/waf1/CIP1* expression in SCCE prognosis seems to be controversial. Several studies have indicated reduced expression of *p21* as an indicator of poor esophageal cancer prognosis [175, 176], while others have found no significant correlation [173, 177]. Conversely others have claimed that *p21* overexpression is correlated with a poorer prognosis [165, 178].

4.3 p16/INK4a and p15/INK4b

p16/INK4a, which is located on chromosome 9p21 is another member of cyclin dependent kinase inhibitors and is involved in *p53* independent G1 arrest through inhibition of D type cyclin dependent kinases (CDK4/CDK6) in the *Rb* phosphorylation [179, 180] and inactivation. Inactivation of *p16/INK4a* is a common event in esophageal cancer and occurs through homozygous deletion, point mutation and/or hypermethylation [181-184]. In

SCCE, homozygous deletion and promoter methylation are the major causes of *p16/INK4a* gene silencing, while somatic mutation is a rare event [185]. *p16/INK4a* methylation or loss of heterozygosity (LOH) occurs in the early stages of SCCE tumor progression [186, 187], while homozygous deletion of its locus is a late event [188]. The two common mechanisms of *p16/INK4a* inactivation in esophageal adenocarcinoma were found to be promoter hypermethylation, which occurs in the early stages of carcinogenesis and loss of heterozygosity [189, 190]; while homozygous deletion have not been documented to play significant role. In addition, loss of *p16/INK4a* expression together with overexpression of cyclin D1 may also be correlated with poor prognosis [191]. Detection of hypermethylated *p16/INK4a* could provide an appropriate biomarker for esophageal cancer screening as it could be observed in the early stages of carcinogenesis [192-194].

p15/INK4b, a homolog of INK4 family whose locus is close to INK4a locus could be subject of stimulation by TGF- β and activate G1 arrest [195]. Changes in *p15/INK4b* has been studied less often in esophageal cancer; however it has been found that inactivation of *p15/INK4b* occurs through homozygous deletion or abnormal methylation at the same time as *p16/INK4a*, which leads to the loss of Rb-regulated restriction point and plays an essential role in esophageal carcinogenesis [188].

4.4 Retinoblastoma (Rb)

The retinoblastoma protein (pRb or commonly known as Rb) is a nuclear phosphoprotein that plays essential role in the regulation of cell cycle. It negatively regulates transcription by forming complex with E2F transcription factor. Phosphorylation of Rb by the cyclin/CDK complex, results in E2Fs release, expression of target genes and cell division [196-198]. While deletions or mutations of *Rb* or inactivation by HPV infection are rare in SCCE, however several studies have indicated that alteration in *p16* and *p53* lead to the blockage of Rb function [199-201]. However, loss of heterozygosity of the retinoblastoma locus plays essential role in the inactivation of *Rb* gene and is associated with *p53* alterations in esophageal cancer. It is suggested that association of *Rb* with *p53* inactivation may be the major event in the development and progression of esophageal cancer [199, 202].

5. Other novel tumor suppressor genes

In addition to the well established role of well-known tumor suppressor genes such as *p53*, *Rb*, *APC*, *p21*, and *p16* in the carcinogenesis of esophagus cancer; there are other novel tumor suppressor genes which also play role in the development of esophageal cancer.

ECRG4 (esophageal cancer related gene 4) is a novel candidate tumor suppressor gene for SCCE, which is downregulated through promoter hypermethylation. *ECRG4* is significantly associated with lymph node metastasis, tumor size, and tumor stage in SCCE, providing a candidate prognostic marker for SCCE [203].

ING (Inhibitor of growth gene) family, *ING1* to *ING5*, are new class of candidate tumor suppressor genes that are implicated in the cell cycle control, senescence, apoptosis, DNA repair, and chromatin remodeling. Downregulation of *ING1* was observed to be implicated in esophagus cancer [204].

The tetraspanin cell surface receptor uroplakin 1A (*UPK1A*) has been identified as another candidate tumor suppressor gene, which is downregulated by promoter hypermethylation in SCCE cells. *UPK1A* downregulation correlates with lymph node metastasis, tumor stage, and overall survival of patients, as well [205].

Expression of MAL (T-lymphocyte maturation associated protein), which is a component of protein machinery for apical transport in epithelial polarized cells, remarkably reduces in esophageal cancer. In addition, DNA methylation has shown to be associated with its downregulation [206].

DLC1 (deleted in lung cancer 1) is a putative tumor suppressor gene located on chromosome 3 (3p21.3) is supposed to act as a downstream gene in the serine/threonine kinase pathway. Its aberrant splicing was found in one third of esophageal, lung and renal cancers which plays a critical role in the carcinogenesis of these tissues [207].

The *WWOX* (WW domain containing oxidoreductase) gene located on chromosome 16 (16q23.3–24.1) is a candidate tumor suppressor gene for esophageal carcinoma. Both of *WWOX* alleles were seen to become inactivated in squamous carcinoma of the esophagus through combination of events among which mutations and LOH [208].

Annexin1, a member of annexin family which are calcium and phospholipid-binding proteins have also been shown to be lost or downregulated in esophageal cancer [209]. Additionally, its translocation from plasma membrane in normal cells to the nuclear membrane in malignant cells has proposed to be correlated with the tumorigenesis of esophageal cancer [210].

APC and *MCC* are the two tumor suppressor genes located on chromosome 5 (5q21) which are involved in the development of esophageal cancers through LOH of their corresponding genetic loci [111–113]. It has also been shown that mutations in *APC* and *MCC* genes take place in esophageal cancer as well as promoter hypermethylation [116, 122, and 124].

DCC (deleted in colorectal cancer) is a putative tumor suppressor gene whose loss has been implicated in colorectal tumorigenesis. Decreased or loss of *DCC* expression through promoter hypermethylation [211] as well as point mutations and LOH which are correlated with the degree of lymph node metastasis and differentiation [212], have been shown in esophageal cancer.

The involvement of tropomyosins (TMs) which are a family of cytoskeletal proteins and stabilizers of the actin microfilaments have been indicated in carcinogenesis of esophageal cancer; in which downregulation of β -TM (TM1), was described as a novel tumor suppressor gene [213]. The same role were also observed for TM2 and TM3 in esophageal squamous cell carcinoma [99, 214].

E-cadherin (*CDH1*), one of the most important molecules in cell to cell adhesion in epithelial tissues, localized on the surfaces of epithelial cells was reported to be lost in several cancers including esophageal tumors. Promoter hypermethylation was suggested to be involved in its inactivation as well. Loss of E-cadherin expression correlates with the high grade and advanced stages of disease along with poor prognosis [215, 216].

Downregulation of periplakin (a cell adhesion protein) [217] as well as loss of clusterin (a secreted glycoprotein) both in serum and tissue of esophageal squamous cell carcinoma [218] are among other events that have been correlated to the esophageal tumorigenesis.

6. References

- [1] Parkin, D.M., et al., Global cancer statistics, 2002. *CA Cancer J Clin* 2005; 55(2): 74–108.
- [2] Tomizawa, Y. and K.K. Wang, Screening, surveillance, and prevention for esophageal cancer. *Gastroenterol Clin North Am* 2009; 38(1): 59–73, viii.
- [3] Enzinger, P.C. and R.J. Mayer, Esophageal cancer. *N Engl J Med* 2003; 349(23): 2241–52.
- [4] Ekman, S., et al., Activation of growth factor receptors in esophageal cancer-implications for therapy. *Oncologist* 2007; 12(10): 1165–77.
- [5] Kuwano, H., et al., Genetic alterations in esophageal cancer. *Surg Today* 2005; 35(1): 7–18.
- [6] Karpinski, P., M.M. Sasiadek, and N. Blin, Aberrant epigenetic patterns in the etiology of gastrointestinal cancers. *J Appl Genet* 2008; 49(1): 1–10.
- [7] Chen, S.C., et al., Overexpression of epidermal growth factor and insulin-like growth factor-I receptors and autocrine stimulation in human esophageal carcinoma cells. *Cancer Res* 1991; 51: 1898–1903.
- [8] Yoshida, K., et al., EGF- and TGF- α , the ligands of hyperproduced EGFR in human esophageal carcinoma cells, act as autocrine growth factors. *Int J Cancer* 1990; 45: 131–135.
- [9] Heldin, C.H., Dimerization of cell surface receptors in signal transduction. *Cell* 1995; 80: 213–223.
- [10] Pawson, T., M. Raina, and P. Nash, Interaction domains: From simple binding events to complex cellular behavior. *FEBS Lett* 2002; 513: 2–10.
- [11] Friess, H., et al., Concomitant analysis of the epidermal growth factor receptor family in esophageal cancer: Overexpression of epidermal growth factor receptor mRNA but not of c-erbB-2 and cerbB-3. *World J Surg* 1999; 23: 1010–1018.
- [12] Hunts, J., et al., Hyperproduction and gene amplification of the epidermal growth factor receptor in squamous cell carcinomas. *Jpn J Cancer Res* 1985; 76: 663–666.
- [13] Jankowski, J., et al., Abnormal expression of growth regulatory factors in Barrett's oesophagus. *Clin Sci (Colch)* 1991; 81: 663–8.
- [14] Jones, G.J., et al., Amplification and expression of the TGF- α , EGF receptor and c-myc genes in four human oesophageal squamous cell carcinoma lines. *Biosci Rep* 1993; 13: 303–312.
- [15] Mukaida, H., et al., Expression of human epidermal growth factor and its receptor in esophageal cancer. *Jpn J Surg* 1990; 20: 275–282.
- [16] Ozawa, S., et al., High incidence of EGF receptor hyperproduction in esophageal squamous-cell carcinomas. *Int J Cancer* 1987; 39: 333–337.
- [17] Ozawa, S., et al., Epidermal growth factor receptors in cancer tissues of esophagus, lung, pancreas, colorectum, breast and stomach. *Jpn J Cancer Res* 1988; 79: 1201–1207.
- [18] Bazley, L.A. and W.J. Gullick, The epidermal growth factor receptor family. *Endocr Relat Cancer* 2005; 12(suppl 1): S17–S27.
- [19] Moghal, N. and P.W. Sternberg, Multiple positive and negative regulators of signaling by the EGF-receptor. *Curr Opin Cell Biol* 1999; 11: 190–6.

- [20] Ozawa, S., et al., Prognostic significance of epidermal growth factor receptor in esophageal squamous cell carcinomas. *Cancer Epidemiol Biomarkers Prev* 1989; 63: 2169–73.
- [21] Dragovich, T. and C. Campen, Anti-EGFR-Targeted Therapy for Esophageal and Gastric Cancers: An Evolving Concept. *J Oncol* 2009; 2009: ID 804108. doi:10.1155/2009/804108.
- [22] Takaoka, M., et al., Epidermal growth factor receptor regulates aberrant expression of insulin-like growth factor-binding protein 3. *Cancer Research* 2004; 64(21): 7711–7723.
- [23] Yoshida, K., et al. Expression of growth factors and their receptors in human esophageal carcinomas: Regulation of expression by epidermal growth factor and transforming growth factor alpha. *J Cancer Res Clin Oncol* 1993; 119: 401– 407.
- [24] Gibson, M.K., et al., Epidermal growth factor receptor, p53 mutation, and pathological response predict survival in patients with locally advanced esophageal cancer treated with preoperative chemoradiotherapy. *Clin Cancer Res* 2003; 9: 6461–6468.
- [25] Mukaida, H., et al., Clinical significance of the expression of epidermal growth factor and its receptor in esophageal cancer. *Cancer* 1991; 68: 142–148.
- [26] Rygiel, A.M., et al, Gains and amplifications of c-myc, EGFR, and 20.q13 loci in the no dysplasia-dysplasia-adenocarcinoma sequence of barrett's esophagus. *Cancer Epidemiology Biomarkers & Prevention* 2008; 17(6): 1380–1385.
- [27] Souza, R.F., C.P. Morales, and S.J. Spechler, a conceptual approach to understanding the molecular mechanisms of cancer development in Barrett's oesophagus. *Aliment Pharmacol Ther* 2001; 15: 1087–1100.
- [28] Vissers, K.J., et al., Involvement of cancer-activating genes on chromosomes 7 and 8 in esophageal (Barrett's) and gastric cardia adenocarcinoma. *Anticancer Res* 2001; 21: 3813–3820.
- [29] Watanabe, G., et al., Progression of esophageal carcinoma by loss of EGF-STAT1 pathway. *Cancer J* 2001; 7: 132–139.
- [30] Ichiba, M., et al., Epidermal growth factor inhibits the growth of TE8 esophageal cancer cells through the activation of STAT1. *J Gastroenterol* 2002; 37: 497–503.
- [31] Yoshida, K., et al. Growth factors in progression of human esophageal and gastric carcinomas. *Exp Pathol* 1990; 40: 291–300.
- [32] Xu, H., et al., Difference in responsiveness of human esophageal squamous cell carcinoma lines to epidermal growth factor for MMP-7 expression. *Int J Oncol* 2003; 23: 469–476.
- [33] Shiozaki, H., et al., Effect of epidermal growth factor on cadherin-mediated adhesion in a human oesophageal cancer cell line. *Br J Cancer* 1995; 71: 250–258.
- [34] Behrens, J., et al., Loss of epithelial differentiation and gain of invasiveness correlates with tyrosine phosphorylation of the E-cadherin/beta-catenin complex in cells transformed with a temperature-sensitive v-SRC gene. *J Cell Biol* 1993; 120:757–66.
- [35] Ochiai, A., et al., c-erbB-2 gene product associates with catenins in human cancer cells. *Biochem Biophys Res Commun* 1994; 205: 73–8.
- [36] Shibata, T., et al., Dominant negative inhibition of the association between beta-catenin and c-erbB-2 by N-terminally deleted beta-catenin suppresses the invasion and metastasis of cancer cells. *Oncogene* 1996; 13: 883–9.

- [37] Mimura, K., et al., Frequencies of HER-2/neu expression and gene amplification in patients with oesophageal squamous cell carcinoma. *Br J Cancer* 2005; 92: 1253–1260.
- [38] Dahlberg, P.S., et al., ERBB2 amplifications in esophageal adenocarcinoma. *Ann Thorac Surg* 2004; 78: 1790 –1800.
- [39] Safran, H., et al., Trastuzumab, paclitaxel, cisplatin, and radiation for adenocarcinoma of the esophagus: A phase I study. *Cancer Invest* 2004; 22: 670–677.
- [40] Sunpaweravong, P., et al., Epidermal growth factor receptor and cyclin D1 are independently amplified and overexpressed in esophageal squamous cell carcinoma. *J Cancer Res Clin Oncol* 2005; 131: 111–119.
- [41] Dreilich, M., et al., HER-2 overexpression (3+) in patients with squamous cell esophageal carcinoma correlates with poorer survival. *Dis Esophagus* 2006; 19: 224–231.
- [42] Alroy, I., Y. Yarden, The ErbB signaling network in embryogenesis and oncogenesis: signal diversification through combinatorial ligand–receptor interactions. *FEBS Lett* 1997;410: 83–6.
- [43] Sauter, E.R., et al., HER-2/neu: A differentiation marker in adenocarcinoma of the esophagus. *Cancer Lett* 1993; 75: 41– 44.
- [44] Hardwick, R.H., et al., c-erbB-2 overexpression in the dysplasia/carcinoma sequence of Barrett's oesophagus. *J Clin Pathol* 1995; 48: 129 –132.
- [45] Walch, A., et al., Coamplification and coexpression of GRB7 and ERBB2 is found in high grade intraepithelial neoplasia and in invasive Barrett's carcinoma. *Int J Cancer* 2004; 112: 747–753.
- [46] Polkowski, W., et al., Prognostic value of Lauren classification and c-erbB-2 oncogene overexpression in adenocarcinoma of the esophagus and gastroesophageal junction. *Ann Surg Oncol* 1999; 6: 290 –297.
- [47] Brien, T.P., et al. HER-2/neu gene amplification by FISH predicts poor survival in Barrett's esophagus-associated adenocarcinoma. *Hum Pathol* 2000; 31: 35–39.
- [48] Akamatsu, M., et al., c-erbB-2 oncoprotein expression related to chemoradioresistance in esophageal squamous cell carcinoma. *Int J Radiat Oncol Biol Phys* 2003; 57: 1323–1327.
- [49] Duhaylongsod, F.G., et al., The significance of c-erb B-2 and p53 immunoreactivity in patients with adenocarcinoma of the esophagus. *Ann Surg* 1995; 221: 677– 683; discussion 683–684.
- [50] Cosaceanu, D., et al., Modulation of response to radiation of human lung cancer cells following insulin-like growth factor 1 receptor inactivation. *Cancer Lett* 2005; 222: 173–181.
- [51] Liu, Y.C., et al., Autocrine stimulation by insulin-like growth factor I is involved in the growth, tumorigenicity and chemoresistance of human esophageal carcinoma cells. *J Biomed Sci* 2002; 9: 665–674.
- [52] Irvani, S., et al., Modification of insulin-like growth factor 1 receptor, c-Src, and Bcl-XL protein expression during the progression of Barrett's neoplasia. *Hum Pathol* 2003; 34: 975–982.
- [53] Takaoka, M., et al., Epidermal growth factor receptor regulates aberrant expression of insulin-like growth factor-binding protein 3. *Cancer Res* 2004; 64: 7711–23.

- [54] Natsuizaka, M., et al., Insulin-like growth factor binding protein-3 promotes transforming growth factor- β 1-mediated epithelial-to-mesenchymal transition and motility in transformed human esophageal cells. *Carcinogenesis* 2010; 31(8): 1344–1353.
- [55] Sohda, M., et al., The role of insulin-like growth factor 1 and insulin-like growth factor binding protein 3 in human esophageal cancer. *Anticancer Res* 2004; 24: 3029–3034.
- [56] Heldin, C.H., A. Ostman, and L. Ronnstrand, Signal transduction via platelet-derived growth factor receptors. *Biochim Biophys Acta* 1998; 1378: F79–F113.
- [57] Liu, Y.C., et al., Platelet-derived growth factor is an autocrine stimulator for the growth and survival of human esophageal carcinoma cell lines. *Exp Cell Res* 1996; 228: 206–211.
- [58] Zhang, X., et al., [Expression and significance of C-kit and platelet-derived growth factor receptor-beta (PDGFRbeta) in esophageal carcinoma.] *Ai Zheng* 2006; 25(1): 92–95. Chinese.
- [59] Ferrara, N. Role of vascular endothelial growth factor in physiologic and pathologic angiogenesis: Therapeutic implications. *Semin Oncol* 2002; 29(suppl 16): 10–14.
- [60] Ferrara, N., VEGF as a therapeutic target in cancer. *Oncology* 2005; 69(suppl 3):11–16.
- [61] Sato, Y., et al., Properties of two VEGF receptors, Flt-1 and KDR, in signal transduction. *Ann N Y Acad Sci* 2000; 902: 201–205; discussion 205–207.
- [62] Shih, C.H., et al. Vascular endothelial growth factor expression predicts outcome and lymph node metastasis in squamous cell carcinoma of the esophagus. *Clin Cancer Res* 2000; 6: 1161–1168.
- [63] Kitadai, Y., et al., Significance of vessel count and vascular endothelial growth factor in human esophageal carcinomas. *Clin Cancer Res* 1998;4: 2195–2200.
- [64] Griffiths L, Stratford I J. Platelet-derived endothelial cell growth factor thymidine phosphorylase in tumor growth and response to therapy. *Br J Cancer* 1997; 76: 689–93.
- [65] Lord, R.V.N., et al., Vascular endothelial growth factor and basic fibroblast growth factor expression in esophageal adenocarcinoma and Barrett esophagus. *The Journal of Thoracic and Cardiovascular Surgery* 2003; 125: 246–53.
- [66] Oshima, Y., et al., Angiogenesis-Related Factors are Molecular Targets for Diagnosis and Treatment of Patients with Esophageal Carcinoma. *Ann Thorac Cardiovasc Surg* 2010; 16(6): 389–393.
- [67] Gu, Y., et al., The number of lymph nodes with metastasis predicts survival in patients with esophageal or esophagogastric junction adenocarcinoma who receive preoperative chemoradiation. *Cancer* 2006; 106: 1017–1025.
- [68] Stacker, S.A., et al., Lymphangiogenesis and cancer metastasis. *Nat Rev Cancer* 2002; 2: 573–583.
- [69] Matsumoto, M., et al., Overexpression of vascular endothelial growth factor-C correlates with lymph node micrometastasis in submucosal esophageal cancer. *J Gastrointest Surg* 2006; 10: 1016–1022.
- [70] Saad, R.S, Y. El-Gohary, et al., Endoglin (CD105) and vascular endothelial growth factor as prognostic markers in esophageal adenocarcinoma. *Hum Pathol* 2005; 36: 955–961.

- [71] Spence, G.M., A.N. Graham, et al., Bone marrow micrometastases and markers of angiogenesis in esophageal cancer. *Ann Thorac Surg* 2004; 78: 1944–1949; discussion 1950.
- [72] Kitadai, Y., S. Onogawa, et al., Angiogenic switch occurs during the precancerous stage of human esophageal squamous cell carcinoma. *Oncol Rep* 2004; 11: 315–319.
- [73] Auvinen, M.I., et al., Incipient angiogenesis in Barrett's epithelium and lymphangiogenesis in Barrett's adenocarcinoma. *J Clin Oncol* 2002; 20: 2971–2979.
- [74] Barclay, C., A.W. Li, et al., Basic fibroblast growth factor (FGF-2) overexpression is a risk factor for esophageal cancer recurrence and reduced survival, which is ameliorated by co-expression of the FGF-2 antisense gene. *Clin Cancer Res* 2005; 11: 7683–91.
- [75] Zhang, C., L. Fu, et al., Fibroblast growth factor receptor 2-positive fibroblasts provide a suitable microenvironment for tumor development and progression in esophageal carcinoma. *Clin Cancer Res* 2009; 15: 4017–27.
- [76] Noma, K., et al., The essential role of fibroblasts in esophageal squamous cell carcinoma-induced angiogenesis. *Gastroenterology* 2008; 134(7): 1981–93.
- [77] Ren, Y.J. and Q.Y. Zhang., Expression of midkine and its clinical significance in esophageal squamous cell carcinoma. *World J Gastroenterol* 2006; 12: 2006–10.
- [78] Shimada, H., Y. Nabeya, et al., Preoperative serum midkine concentration is a prognostic marker for esophageal squamous cell carcinoma. *Cancer Sci* 2003; 94: 628–32.
- [79] Shimada, H., Y. Nabeya, et al., Increased serum midkine concentration as a possible tumor marker in patients with superficial esophageal cancer. *Oncol Rep* 2003; 10: 411–4.
- [80] Ren, Y., B. Cao, et al., Hepatocyte growth factor promotes cancer cell migration and angiogenic factors expression: a prognostic marker of human esophageal squamous cell carcinomas. *Clin Cancer Res* 2005; 11: 6190–7.
- [81] Iwazawa, T., et al., Primary human fibroblasts induce diverse tumor invasiveness: Involvement of HGF as an important paracrine factor. *Jpn J Cancer Res* 1996; 87: 1134–1142.
- [82] Tuynman, J.B., S.M. Lagarde, et al., Met expression is an independent prognostic risk factor in patients with oesophageal adenocarcinoma. *Br J Cancer* 2008; 98: 1102–8.
- [83] Takada, N., et al., Expression of immunoreactive human hepatocyte growth factor in human esophageal squamous cell carcinomas. *Cancer Lett* 1995; 97:145–148.
- [84] Grugan, K.D., C.G. Miller, et al., Fibroblast-secreted hepatocyte growth factor plays a functional role in esophageal squamous cell carcinoma invasion. *Proc Natl Acad Sci USA* 2010; 107: 11026–31.
- [85] Li, L.Y., et al., Connective tissue growth factor expression in precancerous lesions of human esophageal epithelium and prognostic significance in esophageal squamous cell carcinoma. *Dis Esophagus* 2010; 24(5): 337–345
- [86] Friday, B.B. and A.A. Adjei, K-ras as a target for cancer therapy. *Biochim Biophys Acta* 2005; 1756(2): 127–44.
- [87] Liu, J.J., J.R. Chao, et al., Ras transformation results in an elevated level of cyclin D1 and acceleration of G1 progression in NIH 3T3 cells. *Mol Cell Biol* 1995; 15: 3654–63.

- [88] Malumbres, M., and A. Pellicer, RAS pathways to cell cycle control and cell transformation. *Front Biosci* 1998; 3: d887-d912.
- [89] Meloche, S. and J. Pouyssegur, The ERK1/2 mitogen-activated protein kinase pathway as a master regulator of the G1- to Sphase transition, *Oncogene* 2007; 26(22): 3227-3239.
- [90] Hawk, E.T. and J.L. Viner, Statins in esophageal cancer cell lines: promising lead? *Am J Gastroenterol* 2008; 103(4): 838-41.
- [91] Leu, C.M, C. Chang, and C. Hu, Epidermal growth factor (EGF) suppresses staurosporine-induced apoptosis by inducing mcl-1 via the mitogen-activated protein kinase pathway. *Oncogene* 2000; 19:1665-1675.
- [92] Akimoto, T., T. Nonaka, et al., Selective inhibition of survival signal transduction pathways enhanced radiosensitivity in human esophageal cancer cell lines in vitro. *Anticancer Res* 2004; 24: 811-819.
- [93] Chattopadhyay, I., et al., Gene expression profile of esophageal cancer in North East India by cDNA microarray analysis. *World J Gastroenterol* 2007; 13(9): 1438-1444.
- [94] Nguyen, D.M, D. Lorang, et al., Enhancement of paclitaxel-mediated cytotoxicity in lung cancer cells by 17- allylamino geldanamycin: In vitro and in vivo analysis. *Ann Thorac Surg* 2001; 72: 371-378.
- [95] Nguyen, D.M., G.A. Chen, et al., Potentiation of paclitaxel cytotoxicity in lung and esophageal cancer cells by pharmacologic inhibition of the phosphoinositide 3-kinase/protein kinase B (Akt)-mediated signaling pathway. *J Thorac Cardiovasc Surg* 2004; 127: 365-375.
- [96] Schrupp, D.S. and D.M. Nguyen, Novel molecular targeted therapy for esophageal cancer. *J Surg Oncol* 2005; 92(3):257-61.
- [97] Lawler, K., et al., Mobility and invasiveness of metastatic esophageal cancer are potentiated by shear stress in a ROCK- and Ras-dependent manner. *Am J Physiol Cell Physiol* 2006; 291(4): C668-77.
- [98] Senmaru, N., et al., Suppression of Erk activation and in vivo growth in esophageal cancer cells by the dominant negative Ras mutant, N116Y. *Int J Cancer* 1998; 78(3): 366-71.
- [99] Zare, M., et al., Downregulation of tropomyosin-1 in squamous cell carcinoma of esophagus, the role of Ras signaling and methylation. *Molecular Carcinogenesis* 2011; DOI: 10.1002/mc.20847,
- [100] Logan, C.Y. and R. Nusse., The Wnt signaling pathway in development and disease. *Annu. Rev. Cell Dev. Biol* 2004; 20: 781-810.
- [101] Moon, R.T, A.D. Kohn, et al., WNT and beta-catenin signalling: diseases and therapies. *Nat. Rev. Genet* 2004; 5: 691-701.
- [102] Liu, T., et al., G protein signaling from activated rat frizzled-1 to the beta-catenin-Lef-Tcf pathway. *Science* 2001; 292: 1718-1722.
- [103] Mann, B., M. Gelos, et al., Target genes of beta-catenin-T cell-factor/lymphoid-enhancer-factor signaling in human colorectal carcinomas. *Proc Natl Acad Sci USA* 1999, 96:1603-1608.
- [104] Behrens, J., et al., Functional interaction of beta-catenin with the transcription factor LEF-1. *Nature* 1996; 382: 638-642.

- [105] Kudo, J., et al., Aberrant nuclear localization of β -catenin without genetic alterations in β -catenin or Axin genes in esophageal cancer. *World Journal of Surgical Oncology* 2007; 5(21).
- [106] Aberle, H., H. Schwartz, and R. Kemler, Cadherin-catenin complex: protein interactions and their implications for cadherin function. *J Cell Biochem* 1996; 61: 514-23.
- [107] Barth, A.I., I.S. Nathke, and W.J. Nelson., Cadherins catenins and APC protein: interplay between cytoskeletal complexes and signaling pathways. *Curr Opin Cell Biol* 1997; 9: 683-90.
- [108] Swami, S., S. Kumble, and G. Triadafilopoulos., E-cadherin expression in gastroesophageal reflux disease, Barrett's esophagus, and esophageal adenocarcinoma: an immunohistochemical and immunoblot study. *Am J Gastroenterol* 1995; 90: 1808-13.
- [109] Washington, K., et al., Expression of beta-catenin, alpha-catenin, and E-cadherin in Barrett's esophagus and esophageal adenocarcinomas. *Mod Pathol* 1998; 11: 805-13.
- [110] Seery, J.P., et al., Abnormal expression of the E-cadherin-catenin complex in dysplastic Barrett's oesophagus. *Acta Oncol* 1999; 38: 945-8.
- [111] Dolan, K., J. Garde, et al., Allelotype analysis of oesophageal adenocarcinoma: loss of heterozygosity occurs at multiple sites. *Br J Cancer* 1998; 78: 950-7.
- [112] Boynton, R.F., et al. Loss of heterozygosity involving the APC and MCC genetic loci occurs in the majority of human esophageal cancers. *Proc Natl Acad Sci* 1992; 89:3385- 8.
- [113] Bektas, N., et al., Allelic loss involving the tumor suppressor genes APC and MCC and expression of the APC protein in the development of dysplasia and carcinoma in Barrett esophagus. *Am J Clin Pathol* 2000; 114(6): 890-5.
- [114] Choi, Y.W., et al., Mutations in beta-catenin and APC genes are uncommon in esophageal and esophagogastric junction adenocarcinomas. *Mod Pathol* 2000; 13(10): 1055-9.
- [115] Ogasawara, S., et al., Lack of mutations of the adenomatous polyposis coli gene in oesophageal and gastric carcinomas. *Virchows Arch* 1994; 424(6): 607-11.
- [116] Li, H. and S. Lu, [Mutation of tumor suppressor genes APC and MCC in human esophageal cancer]. *Zhonghua Zhong Liu Za Zhi* 1995; 17(1): 9-12.
- [117] Powell, S.M., et al., APC gene mutations in the mutation cluster region are rare in esophageal cancers. *Gastroenterology* 1994; 107(6): 1759-63.
- [118] Voskas, D., L.S. Ling, and J.R. Woodgett, Does GSK-3 provide a shortcut for PI3K activation of Wnt signalling? *F1000 Biol Reports* 2010; 2:82
- [119] Clement, G., et al., Alterations of the Wnt signaling pathway during the neoplastic progression of Barrett's esophagus. *Oncogene* 2006; 25(21): 3084-92.
- [120] Clément, G., D. Jablons, and J. Benhattar, Targeting the Wnt signaling pathway to treat Barrett's esophagus. *Expert Opin Ther Targets* 2007; 11(3):375-89.
- [121] Eads, C.A., et al., Fields of aberrant CpG island hypermethylation in Barrett's esophagus and associated adenocarcinoma. *Cancer Res* 2000; 60(18): 5021-6.
- [122] Kawakami, K., et al., Hypermethylated APC DNA in plasma and prognosis of patients with esophageal adenocarcinoma. *J Natl Cancer Inst* 2000; 92(22): 1805-11.

- [123] Ishii, T., et al., Oesophageal squamous cell carcinoma may develop within a background of accumulating DNA methylation in normal and dysplastic mucosa. *Gut* 2007; 56(1): 13-9.
- [124] Zare, M., et al., Qualitative analysis of Adenomatous Polyposis Coli promoter: hypermethylation, engagement and effects on survival of patients with esophageal cancer in a high risk region of the world, a potential molecular marker. *BMC Cancer* 2009; 9(24).
- [125] Wang, W., et al., Aberrant Changes of Wnt2/ β -Catenin Signaling Pathway Induced by Sodium Nitroprusside in Human Esophageal Squamous Cell Carcinoma Cell Lines. *Cancer Investigation* 2010; 28(3): 230-241
- [126] Ma, C., et al., The role of glycogen synthase kinase 3beta in the transformation of epidermal cells. *Cancer Res* 2007; 67:7756-7764.
- [127] Kang, T., Y. Wei, et al., GSK-3 beta targets Cdc25A for ubiquitin-mediated proteolysis, and GSK-3 beta inactivation correlates with Cdc25A overproduction in human cancers. *Cancer Cell* 2008;13: 36-47.
- [128] Greengard, P., The neurobiology of slow synaptic transmission. *Science*. 2001;294:1024-1030.
- [129] Varis, A., A. Zaika., et al., Coamplified and overexpressed genes at ERBB2 locus in gastric cancer. *Int J Cancer* 2004; 109: 548-553.
- [130] Beckler, A., C.A. Moskaluk, et al., Overexpression of the 32-kilodalton dopamine and cyclic adenosine 3',5'-monophosphate-regulated phosphoprotein in common adenocarcinomas. *Cancer* 2003; 98: 1547-1551.
- [131] Belkhiri, A., A. Zaika, et al., Darpp-32: a novel antiapoptotic gene in upper gastrointestinal carcinomas. *Cancer Res*. 2005; 65: 6583-6592.
- [132] Vangamudi, B., et al., Regulation of β -catenin by t-DARPP in upper gastrointestinal cancer cells. *Mol Cancer* 2011; 10: 32.
- [133] Vanhaesebroeck, B. and M.D. Waterfield, Signaling by distinct classes of phosphoinositide 3-kinases. *Exp Cell Res* 1999; 253: 239-54.
- [134] Cantley, L.C., The phosphoinositide 3-kinase pathway, *Science* 2002; 296:655-1657.
- [135] Brader, S., and S.A. Eccles, Phosphoinositide 3-kinase signalling pathways in tumor progression, invasion and angiogenesis. *Tumori* 2004; 90: 2-8.
- [136] Yen, C.C., et al., Genotypic analysis of esophageal squamous cell carcinoma by molecular cytogenetics and real-time quantitative polymerase chain reaction. *Int J Oncol* 2003; 23: 871-81.
- [137] Zhang, G., X. Zhou, et al., Accumulation of cytoplasmic beta-catenin correlates with reduced expression of E-cadherin, but not with phosphorylated Akt in esophageal squamous cell carcinoma: immunohistochemical study. *Pathol Int* 2005; 55: 310-7.
- [138] Miller, C.T., et al., Gene amplification in esophageal adenocarcinomas and Barrett's with high-grade dysplasia. *Clin Cancer Res* 2003; 9: 4819-25.
- [139] Phillips, W.A., et al., Mutation analysis of PIK3CA and PIK3CB in esophageal cancer and Barrett's esophagus. *Int. J. Cancer* 2006; 118: 2644-2646.
- [140] Mori, R., H. Ishiguro, et al., PIK3CA mutation status in Japanese esophageal squamous cell carcinoma. *J Surg Res* 2008; 145: 320-6.

- [141] Yoshioka, A., H. Miyata, et al., The activation of Akt during preoperative chemotherapy for esophageal cancer correlates with poor prognosis. *Oncol Rep* 2008;19:1099-107.
- [142] Ingham, P.W., Hedgehog signalling. *Curr Biol* 2008; 18: R238-41.
- [143] Hooper, J.E. and M.P. Scott, Communicating with hedgehogs. *Nat Rev Mol Cell Biol* 2005; 6: 306-17.
- [144] Philipp, M. and M.G. Caron, Hedgehog signaling: is Smo a G protein-coupled receptor? *Curr Biol* 2009;19:R125-7.
- [145] Karhadkar, S.S., G.S. Bova, et al., Hedgehog signalling in prostate regeneration, neoplasia and metastasis. *Nature* 2004; 431:707-12.
- [146] Ma, X., T. Sheng, et al., Hedgehog signaling is activated in subsets of esophageal cancers. *Int J Cancer* 2006; 118: 139-48.
- [147] Mori, Y., T. Okumura, et al., Gli-1 expression is associated with lymph node metastasis and tumor progression in esophageal squamous cell carcinoma. *Oncology* 2006; 70: 378-89.
- [148] Pasca di Magliano, M. et al., Hedgehog/Ras interactions regulate early stages of pancreatic cancer. *Genes Dev* 2006; 20: 3161-73.
- [149] Faried, A. L.S. Faried, et al., RhoA and RhoC proteins promote both cell proliferation and cell invasion of human oesophageal squamous cell carcinoma cell lines in vitro and in vivo. *Eur J Cancer* 2006; 42: 1455-65.
- [150] Wei, L. and Z. Xu, Cross-signaling among phosphoinositide-3 kinase, mitogenactivated protein kinase and sonic hedgehog pathways exists in esophageal cancer. *Int J Cancer* 2010; 129(2): 275-234.
- [151] Hui, C.M., P.Y. Cheung, et al., Id-1 promotes proliferation of p53-deficient esophageal cancer cells. *Int J Cancer* 2006; 119: 508-14.
- [152] Yuen, H.F., Y.P. Chan, et al., Id-1 and Id-2 are markers for metastasis and prognosis in oesophageal squamous cell carcinoma. *Br J Cancer* 2007; 97: 1409-15.
- [153] Li, B., et al., Id-1 activation of PI3K/Akt/NFkappaB signaling pathway and its significance in promoting survival of esophageal cancer cells. *Carcinogenesis* 2007;28: 2313-20.
- [154] Li, B., et al., Id-1 promotes tumorigenicity and metastasis of human esophageal cancer cells through activation of PI3K/AKT signaling pathway. *Int. J. Cancer* 2009; 125: 2576-2585
- [155] Benezra, R., R.L. Davis, et al., The protein Id: a negative regulator of helix-loop-helix DNA binding proteins. *Cell* 1990; 61:49-59.
- [156] McCabe, M.L. and Z. Dlamini, The molecular mechanisms of oesophageal cancer. *Int Immunopharmacol* 2005; 5(7-8): 1113-30.
- [157] Hollstein, M., et al., p53 mutations in human cancers. *Science* 1991; 253: 49-53.
- [158] Olivier, M. et al., The IARC TP53 database: new online mutation analysis and recommendations to users. *Hum Mutat* 2002;19:607-14.
- [159] el-Deiry, W.S., T. Tokino, et al., WAF1, a potential mediator of p53 tumor suppression. *Cell* 1993; 75:817-25.
- [160] Oltvai, Z.N., C.L. Milliman and S.J. Korsmeyer, Bcl-2 heterodimerizes in vivo with a conserved homolog, Bax, that accelerates programmed cell death. *Cell* 1993;74:609-19.

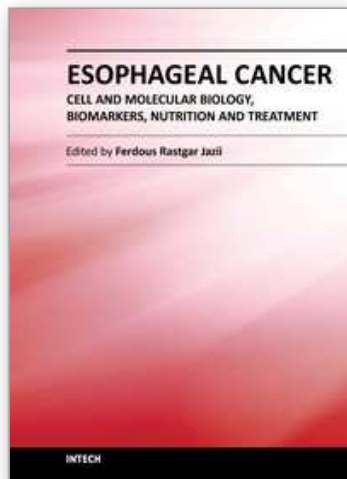
- [161] Miyashita, T., et al., Tumor suppressor p53 is a regulator of bcl-2 and bax gene expression in vitro and in vivo. *Oncogene* 1994; 9: 1799–805.
- [162] Lane, D.P. Cancer. p53, guardian of the genome. *Nature* 1992; 358: 15–6.
- [163] Ikeguchi, M., H. Saito, et al., Clinicopathologic significance of the expression of mutated p53 protein and the proliferative activity of cancer cells in patients with esophageal squamous cell carcinoma. *J Am Coll Surg* 1997; 185: 398–403.
- [164] Ikeda, G., S. Isaji, et al., Prognostic significance of biologic factors in squamous cell carcinoma of the esophagus. *Cancer* 1999; 86: 1396–405.
- [165] Lam, K.Y., et al., The clinicopathological significance of p21 and p53 expression in esophageal squamous cell carcinoma: an analysis of 153 patients. *Am J Gastroenterol* 1999; 94: 2060–8.
- [166] Kato, H., M. Yoshikawa, et al., An immunohistochemical study of p16, pRb, p21 and p53 proteins in human esophageal cancers. *Anticancer Res* 2000; 20: 345–9.
- [167] von Brevern, M.C., M.C. Hollstein, et al. Circulating anti-p53 antibodies in esophageal cancer patients are found predominantly in individuals with p53 core domain mutations in their tumors *Cancer Res* 1996; 56: 4917–21.
- [168] Shimada, H., Nabeya, Y., et al. Prognostic significance of serum p53 antibody in patients with esophageal squamous cell carcinoma. *Surgery* 2002; 132: 41–7.
- [169] Shimada, H., K. Nakajima, et al., Detection of serum p53 antibodies in patients with esophageal squamous cell carcinoma: correlation with clinicopathologic features and tumor markers. *Oncol Rep* 1998; 5: 871–4.
- [170] Slebos, R.J., M.H. Lee, et al., p53-dependent G1 arrest involves pRB-related proteins and is disrupted by the human papillomavirus 16 E7 oncoprotein. *Proc Natl Acad Sci USA* 1994; 91: 5320–4.
- [171] Shiohara, M., W.S. el-Deiry, et al., Absence of WAF1 mutations in a variety of human malignancies. *Blood* 1994; 84: 3781–4.
- [172] Bahl, R., S. Arora, et al., Novel polymorphism in p21 (waf1/cip1) cyclin dependent kinase inhibitor gene: association with human esophageal cancer. *Oncogene* 2000; 19: 323–8.
- [173] Masuda, N., H. Kato, et al., Synergistic decline in expressions of p73 and p21 with invasion in esophageal cancers. *Cancer Sci* 2003; 94: 612–7.
- [174] Jost, C.A., M.C. Marin, and W.G., Kaelin, p73 is a human p53-related protein that can induce apoptosis. *Nature* 1997; 389: 191–4.
- [175] Nita, M.E., H. Nagawa, et al., p21Waf1/Cip1 expression is a prognostic marker in curatively resected esophageal squamous cell carcinoma, but not p27Kip1, p53, or Rb. *Ann Surg Oncol* 1999;6:481–8.
- [176] Natsugoe, S., S. Nakashima. et al., Expression of p21WAF1/Cip1 in the p53-dependent pathway is related to prognosis in patients with advanced esophageal carcinoma. *Clin Cancer Res* 1999;5: 2445–9.
- [177] Shimada, Y., M. Imamura, et al., Prognostic factors of oesophageal squamous cell carcinoma from the perspective of molecular biology *Br J Cancer* 1999; 80: 1281–8.
- [178] Sarbia, M., et al., Expression of p21WAF1 predicts outcome of esophageal cancer patients treated by surgery alone or by combined therapy modalities. *Clin Cancer Res* 1998; 4: 2615–23.

- [179] Serrano, M., G.J. Hannon, and D. Beach, A new regulatory motif in cell-cycle control causing specific inhibition of cyclin D/CDK4. *Nature* 1993; 366: 704 –7.
- [180] Lukas, J., D. Parry., et al., Retinoblastoma protein-dependent cell cycle inhibition by the tumor suppressor p16. *Nature* 1995; 375: 503–6.
- [181] Igaki, H, H. Sasaki, et al., Highly frequent homozygous deletion of the p16 gene in esophageal cancer cell lines. *Biochem Biophys Res Commun* 1994;203:1090–5.
- [182] Liu, Q., Y.X. Yan., et al., MTS-1 (CDKN2) tumor suppressor gene deletions are a frequent event in esophagus squamous cancer and pancreatic adenocarcinoma cell lines. *Oncogene* 1995; 10: 619–22.
- [183] Tanaka, H., et al., Multiple types of aberrations in the p16(INK4a) and the p15(INK4b) genes in 30 esophageal squamous-cell-carcinoma cell lines. *Int J Cancer* 1997; 70: 437–42.
- [184] Mohammad Ganji, S., et al., Associations of risk factors obesity and occupational airborne exposures with CDKN2A/p16 aberrant DNA methylation in esophageal cancer patients. *Dis Esophagus*, 2010. 23(7): p. 597–602.
- [185] Maesawa, C., G. Tamura, et al., Inactivation of the CDKN2 gene by homozygous deletion and de novo methylation is associated with advanced stage esophageal squamous cell carcinoma. *Cancer Res* 1996; 56: 3875–8.
- [186] Fong, L.Y., Nguyen VT, Farber JL, Huebner K, Magee PN. Early deregulation of the p16ink4a-cyclin D1/cyclin-dependent kinase4-retinoblastoma pathway in cell proliferation-driven esophageal tumorigenesis in zinc-deficient rats. *Cancer Res* 2000; 60: 4589–95.
- [187] Tokugawa, T., H. Sugihara, T. Tani, T. Hattori, Modes of silencing of p16 in development of esophageal squamous cell carcinoma. *Cancer Res* 2002; 62: 4938–44.
- [188] Xing, E.P., Y. Nie, et al., Aberrant methylation of p16INK4a and deletion of p15INK4b are frequent events in human esophageal cancer in Linxian, China. *Carcinogenesis* 1999; 20: 77–84.
- [189] Wong, D.J., et al., p16INK4a promoter is hypermethylated at a high frequency in esophageal adenocarcinomas. *Cancer Res* 1997; 57: 2619–22.
- [190] Eads, C.A., et al., Epigenetic patterns in the progression of esophageal adenocarcinoma. *Cancer Res* 2001; 61(8): 3410–8.
- [191] Takeuchi, H., S. Ozawa, et al., Altered p16/MTS1/CDKN2 and cyclin D1/PRAD-1 gene expression is associated with the prognosis of squamous cell carcinoma of the esophagus. *Clin Cancer Res* 1997; 3: 2229– 36.
- [192] Nie, Y., J. Liao, et al., Detection of multiple gene hypermethylation in the development of esophageal squamous cell carcinoma. *Carcinogenesis* 2002; 23: 1713–20.
- [193] Hibi, K., M. Taguchi, et al., Molecular detection of p16 promoter methylation in the serum of patients with esophageal squamous cell carcinoma. *Clin Cancer Res* 2001; 7: 3135–8.
- [194] Abbaszadegan, M.R., H. R. Raziee, et al., Aberrant p16 methylation, a possible epigenetic risk factor in familial esophageal squamous cell carcinoma. *Int J Gastrointest Cancer* 2005; 36: 47–54.
- [195] Hannon, G.J., and D. Beach, p15INK4b is a potential effector of TGF β -induced cell cycle arrest. *Nature* 1994; 371: 257–61.

- [196] Weinberg, R.A., The retinoblastoma protein and cell cycle control. *Cell* 1995; 81: 323–30.
- [197] Taya, Y., RB kinases and RB-binding proteins: new points of view. *Trends Biochem Sci* 1997; 22: 14–17.
- [198] Ezhevsky, S.A., H. Nagahara, et al., Hypo-phosphorylation of the retinoblastoma protein (pRb) by cyclin D : Cdk4/6 complexes results in active pRb. *Proc Natl Acad Sci USA* 1997; 94: 10699–704.
- [199] Boynton, R.F., Y. Huang, et al. Frequent loss of heterozygosity at the retinoblastoma locus in human esophageal cancers. *Cancer Res* 1991; 51: 5766–9.
- [200] Huang, Y., S J. Meltzer, et al., Altered messenger RNA and unique mutational profiles of p53 and Rb in human esophageal carcinomas. *Cancer Res* 1993; 53: 1889–94.
- [201] Coppola, D., R.H. Schreiber, et al., Significance of Fas and retinoblastoma protein expression during the progression of Barrett’s metaplasia to adenocarcinoma. *Ann Surg Oncol* 1999; 6: 298–304.
- [202] Xing, E.P., G.Y. Yang, et al., Loss of heterozygosity of the Rb gene correlates with pRb protein expression and associates with p53 alteration in human esophageal cancer. *Clin Cancer Res* 1999; 5: 1231–40.
- [203] Li, L.W., et al., Expression of esophageal cancer related gene 4 (ECRG4), a novel tumor suppressor gene, in esophageal cancer and its inhibitory effect on the tumor growth in vitro and in vivo. *Int J Cancer* 2009; 125(7): 1505–1513.
- [204] Chen, L., N. Matsubara, et al., Genetic alterations of candidate tumor suppressor ING1 in human esophageal squamous cell cancer. *Cancer Res* 2001; 61(11): 4345–4349.
- [205] Kong, K.L., et al., Characterization of a Candidate Tumor Suppressor Gene Uroplakin 1A in Esophageal Squamous Cell Carcinoma. *Cancer Res* 2010; 70(21): 8832–8841.
- [206] Mimori, K., et al., MAL gene expression in esophageal cancer suppresses motility, invasion and tumorigenicity and enhances apoptosis through the Fas pathway. *Oncogene* 2003; 22: 3463–3471.
- [207] Daigo, Y., et al. Molecular cloning of a candidate tumour suppressor gene, DLC1, from chromosome 3p21.3. *Cancer Res* 1999; 59: 1966– 72.
- [208] Kuroki, T., et al., Genetic alterations of the tumor suppressor gene WWOX in esophageal squamous cell carcinoma. *Cancer Res* 2002. 62: 2258– 60.
- [209] Xia, S.H., et al., Three isoforms of annexin I are preferentially expressed in normal esophageal epithelia but down-regulated in esophageal squamous cell carcinomas. *Oncogene* 2002; 21(43): 6641–8.
- [210] Liu, Y., et al., Translocation of annexin I from cellular membrane to the nuclear membrane in human esophageal squamous cell carcinoma. *World J Gastroenterol* 2003; 9(4): 645–649.
- [211] Park, H.L., et al., DCC promoter hypermethylation in esophageal squamous cell carcinoma. *Int J Cancer* 2008; 122(11): 2498–502.
- [212] Miyake, S., et al., Point mutations and allelic deletion of tumor suppressor gene DCC in human esophageal squamous cell carcinomas and their relation to metastasis. *Cancer Res* 1994; 54(11): 3007–10.

- [213] O'Neill, G.M., J. Stehn, and P.W. Gunning, Tropomyosins as interpreters of the signaling environment to regulate the local cytoskeleton. *Semin Cancer Biol* 2008; 18(1): 35-44.
- [214] Jazii, F.R., et al., Identification of squamous cell carcinoma associated proteins by proteomics and loss of beta tropomyosin expression in esophageal cancer. *World J Gastroenterol* 2006; 12(44): 7104-12.
- [215] Lee, E.J., et al., CpG island hypermethylation of E-cadherin (CDH1) and integrin 4 is associated with recurrence of early stage esophageal squamous cell carcinoma. *International Journal of Cancer* 2008; 123 (9): 2073-2079.
- [216] Pećina-Šlaus, N., Tumor suppressor gene E-cadherin and its role in normal and malignant cells. *Cancer Cell International* 2003; 3:17.
- [217] Nishimori, T., et al., Proteomic analysis of primary esophageal squamous cell carcinoma reveals downregulation of a cell adhesion protein, periplakin. *Proteomics* 2006; 6: 1011-1018.
- [218] Zhang, L.Y., et al., Loss of clusterin both in serum and tissue correlates with the tumorigenesis of esophageal squamous cell carcinoma via proteomics approaches. *World J Gastroenterol* 2003; 9(4): 650-654.

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Esophageal Cancer illustrates recent achievements and investigations in the esophageal tumorigenesis from different perspectives. Readers find mechanisms involved in esophageal tumorigenesis, cellular, molecular, genetic, epigenetics, and proteomics, their relevance as the novel biomarkers and application in esophageal cancer diagnosis and therapy. The book covers detailed effect of nutritional factors in addition to ethanol metabolic pathway in the inhibition of retinoic acid metabolism and supply. Diagnosis, classification, and treatment of esophageal cancer, application of both surgical and non surgical methods as well as follow up of the disease are described in detail. Moreover readers are endowed with especial features of esophageal cancer such as multiple early stage malignant melanoma and pulmonary edema induced by esophagectomy, the two features that received less attention elsewhere in literature.

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