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PCSK9 and cancer: Rethinking the link

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ABSTRACT

Background: Cancer is emerging as a major problem globally, as it accounts for the second cause of death despite medical advances. According to epidemiological and basic studies, cholesterol is involved in cancer progression and there are abnormalities in cholesterol metabolism of cancer cells including prostate, breast, and colorectal carcinomas. However, the importance of cholesterol in carcinogenesis and thereby the role of cholesterol homeostasis as a therapeutic target is still a debated area in cancer therapy. Proprotein convertase subtilisin/kexin type-9 (PCSK9), a serine protease, modulates cholesterol metabolism by attachment to the LDL receptor (LDLR) and reducing its recycling by targeting the receptor for lysosomal destruction. Published research has shown that PCSK9 is also involved in degradation of other LDLR family members namely very-low-density-lipoprotein receptor (VLDLR), lipoprotein receptor-related protein 1 (LRP-1), and apolipoprotein E receptor 2 (ApoER2). As a result, this protein represents an interesting therapeutic target for the treatment of hypercholesterolemia. Interestingly, clinical trials on PCSK9-specific monoclonal antibodies have reported promising results with high efficacy in lowering LDL-C and in turn reducing cardiovascular complications. It is important to note that PCSK9 mediates several other pathways apart from its role in lipid homeostasis, including antiviral activity, hepatic regeneration, neuronal apoptosis, and modulation of various signaling pathways. Furthermore, recent literature has illustrated that PCSK9 is closely associated with incidence and progression of several cancers. In a number of studies, PCSK9 siRNA was shown to effectively suppress the proliferation and invasion of the several studied tumor cells. Hence, a novel application of PCSK9 inhibitors/silencers in cancer/metastasis could be considered. However, due to poor data on effectiveness and safety of PCSK9 inhibitors in cancer, the impact of PCSK9 inhibition in these pathological conditions is still unknown.

Search methods: A vast literature search was conducted to find intended studies from 1956 up to 2020, and inclusion criteria were original peer-reviewed publications.

Purpose of review: To date, PCSK9 has been scantly investigated in cancer. The question that needs to be discussed is "How does PCSK9 act in cancer pathophysiology and what are the risks or benefits associated to its inhibition?". We reviewed the available publications highlighting the contribution of this proprotein convertase in pathways related to cancer, with focus on the potential implications of its long-term pharmacological inhibition in cancer therapy.

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1. Introduction

Lipids are the main structural components of cell membrane which are involved in cell growth, division, signaling and energy supplies. Cholesterol is a constituent of cell membranes with a role in modulating the membrane fluidity, cell adhesion to the extracellular matrix, and signaling initiation [1]. Furthermore, it serves as a metabolic precursor for other important steroid molecules including the bile acids and steroid hormones, that can induce tumor cell proliferation, angiogenesis, and decrease the apoptotic level [2]. The main pathway for clearance of cholesterol from the blood is the low-density lipoprotein (LDL) receptor (LDLR) mediated uptake [3]. A large number of evidences support the association between cancer and hyperlipidemia. Accordingly, cancer cells meet their overwhelming demands for lipids by augmentation of dietary lipids uptake or lipogenesis [4]. Moreover, a role of LDL in tumor development has been documented, confirming that cholesterol has important functions in the development of many types of cancer [5]. These findings, supported by the evidence showing the induction of HMG-CoA reductase and LDL receptor in cancer setting, may explain at least in part the high cholesterol content and consumption in cancer cells [6,7]. Increase in LDLR and elevated plasma low-density lipoprotein cholesterol (LDL-C) have been reported as a feature of leukemia, glioblastoma, lungs and pancreatic tumors [8]. Cholesterol interaction with specific signaling pathways [9] and related proteins like kinase Akt [10] is a proposed mechanism. However, the link between serum cholesterol levels and cancer incidence has remained controversial. There are some reports indicating an opposite relationship between serum total cholesterol and cancer risk [11–15], while the other studies found a positive association [16,17].

Proprotein convertase subtilisin/kexin type 9 (PCSK9) originally discovered as neural apoptosis-regulated convertase 1 (NARC-1), was first characterized by Seidah et al. According to their report, this convertase was involved in the differentiation of cortical neurons [18]. PCSK9 is a critical actor in cholesterol metabolism via LDLR destruction [19]. As a result, PCSK9 inhibition can be used as a promising therapy for treatment of hypercholesterolemia [20]. However, there are concerns regarding possible adverse effects of such inhibition [21], since PCSK9 is overexpressed in both differentiating cells and various human cancer cell lines [22]. Thus, it is critical to conduct a comprehensive research on PCSK9 functions *in* various biological pathways for better assessment of benefit/safety of pharmaceutical inhibition of PCSK9 besides reducing serum LDL-C levels [23].

The goal of present manuscript was to review existing evidence of the relationship between PCSK9 and cancer. Specifically, we have attempted to address the effect of PCSK9 on apoptosis, cell-signaling pathways, and tumorigenesis, as well as the current therapeutic strategies targeting PCSK9, focusing on the long-term safety of PCSK9 inhibitors.

2. Methods of data collection

We discerned relevant publications by searching in PubMed, Scopus, Nature, ScienceDirect, and Cochrane Library using as key-words the different names of PCSK9 and cancer. In addition, we looked for and screened the papers listed in references of included studies.

3. Background

Metabolic reprogramming of lipid metabolism is considered as a key factor in tumorigenesis [24]. Abnormal lipoprotein profiles are a common finding in patients with cancer. Thus, a large number of studies have indicated the cholesterol accumulation in several different human cancers such as breast [25], prostate [26], HCC [27], colon [28], and others [29]. Besides, available evidences indicate the aberrant expression of enzymes involved in cholesterol metabolism in cancerous tissues [30,31]. As a matter of fact, cancer itself can affect blood cholesterol levels via various mechanisms like heightened cholesterol catabolism because of high expression of LDLR in malignant cells [32–34], as well as using excess cholesterol for new membrane synthesis, and the aggregation of esterified cholesterol in cancerous tissues [35].

3.1. Cholesterol and oncogenesis

Recent investigations have clarified the role of cholesterol synthesis pathway in cancer pathogenesis. The Cancer Genome Atlas (TCGA) project depicted all mutations in genes of this biosynthetic pathway and validated the role of overexpressed controlling genes in cancer [5,36]. Tumor-induced hyperlipidemia leads to a feed-forward mechanism and disruption of hepatic lipoprotein homeostasis, especially by LDL-C enrichment [8,37]. Mechanistically, cholesterol can switch on cancer-related signaling pathways, for instance, the hedgehog pathway, through its attachment directly to G-protein-coupled receptors; these receptors, like smoothened receptor [38,39] and adenosine A2A receptor [40], are involved in processes related to cell differentiation, proliferation, and cancer development [41]. Furthermore, cholesterol could directly drive other tumorigenic pathways via sticking to scaffold proteins like NHERF1/EBP50 [42], which modulate oncogenic signal networks through assembling cancer-related proteins [43].

In addition to these data, the effect of fat-rich diet on enhancing tumor growth and metastasis has been supported by the experimental studies using human melanoma xenograft model [44,45]. Zhuang et al. [46] showed that in mice engrafted with prostate cancer cell lines, a high-cholesterol diet can promote tumor formation. According to their report, the elevated cholesterol content of lipid rafts results in higher survival in prostate cancer cell lines. Moreover, the dysregulated cholesterol biosynthesis pathway could have impact on cell proliferation process, as in proliferating cells, mevalonate derivatives might be rerouted away toward isoprenoid formation [47,48]. As a result, the cholesterol demand of cancer cells may increase to keep normal cellular cholesterol homeostasis.

Epidemiologic studies have proposed that cancer risk is either higher or lower for individuals with high serum LDL cholesterol levels [13]. Kitahara et al. [12] conducted a prospective cohort study on 1,189,719 Korean adults to explore the link between total cholesterol and cancer incidence. The participants were followed for 14 years, until they were diagnosed with cancer or died. They discovered that total cholesterol was linked to the risk of various cancers, though the relationships differed considerably depending on the location. In particular, this cohort study revealed that high total cholesterol level ($\geq$240 mg/dL) was positively correlated with prostate and colon cancer in men and breast cancer in women. Also, abnormalities in plasma lipid components [49–56], especially higher levels of LDL-C correlate with higher incidence [57,58] and risk [59,60] of colorectal carcinoma (CRC). Conversely, total cholesterol level was negatively related to lung cancer in men as well as liver and stomach cancer in both men and women [12]. Thus, the epidemiological association between plasma cholesterol levels and cancer risk remains controversial. Such a controversial association may be supported by the dual role of cholesterol and its derivatives on cancer cell survival.

Basically, tumor cells rely on cholesterol for membrane and lipid raft biosynthesis, signaling molecules, or other factors in order to meet the fast growth requirements [31]. Cancer cell's demand for cholesterol is supplied by both uptake from the blood or de novo synthesis (Fig. 1) [61]. Therefore, high plasma cholesterol may provide such a high cancer cell requirement. On the other hand, oxidized derivatives of cholesterol, namely oxysterols, show a significant apoptotic effect [62–64], thus opposing to cancer cell proliferation.

The main clearance pathway of LDL-C from the circulation is via hepatic LDLRs. Accordingly, regulating the expression of LDLR is critical in LDL-C hemostasis.

The LDLR family contains 14 single-transmembrane receptors with structural homology and common repeats, which distinctively recognize and internalize a broad range of extracellular ligands, followed by

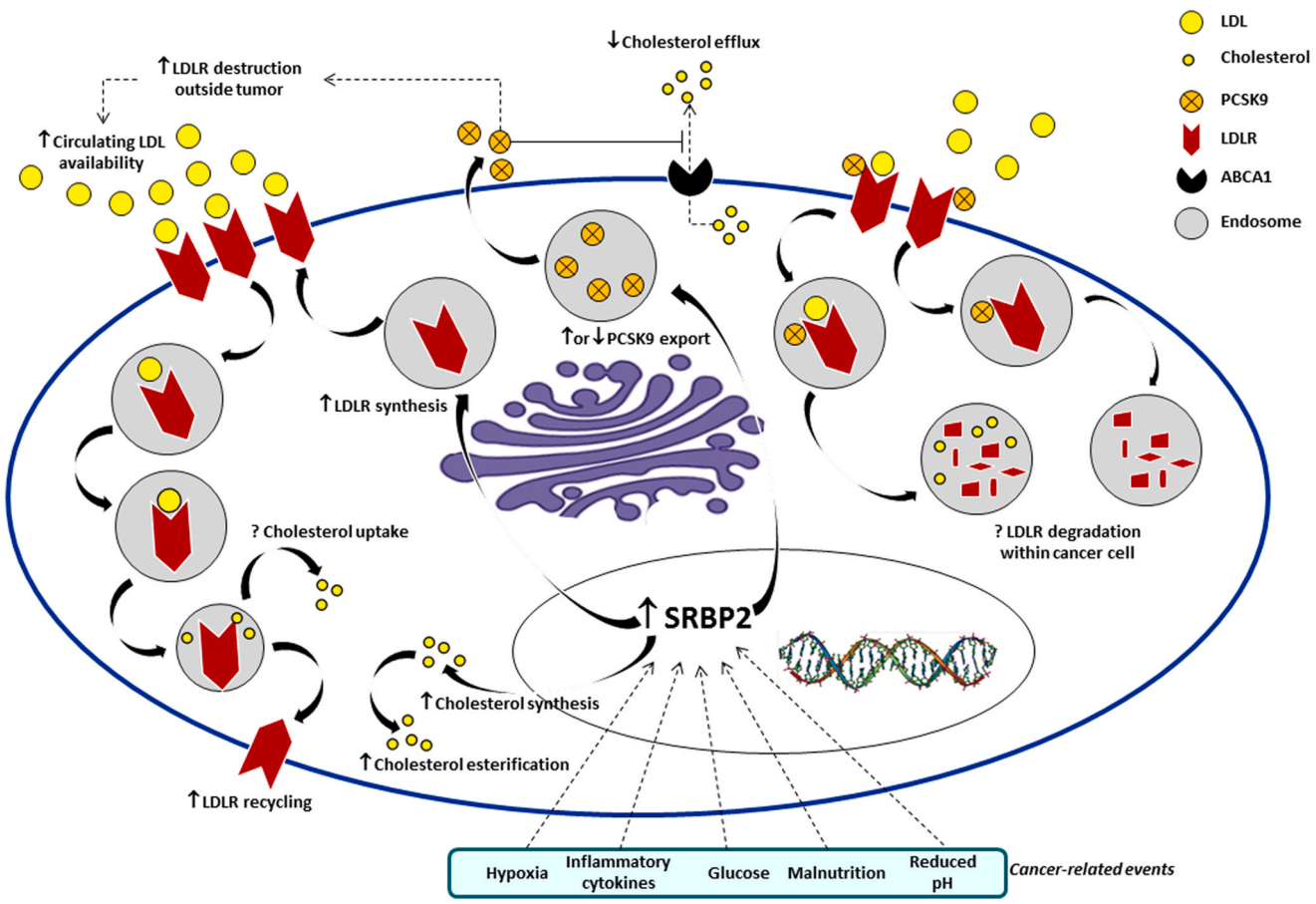

Fig. 1. Potential mechanisms contributing to increase cholesterol availability for cancer cells.

sorting for lysosomal destruction or cell-surface recovery. Initially, some members of the LDLR family were deemed as potential tumor suppressors owing to their role in clearance of extracellular matrix-degrading enzymes. In addition, LDLRs have several other functions, namely cell matrix adhesion turnover, chemoattraction, growth factor signaling, and matricellular proteins. Therefore, they can affect both tumor cells and their microenvironment [65].

Proprotein convertase subtilisin/kexin type 9 (PCSK9), a secreted glycoprotein, has been known as critical regulator of LDL metabolism by binding to the LDLR, promoting its degradation and reducing LDLR-mediated removal of LDLs from circulation. In consequence, the increased plasma LDL-C levels could cause hypercholesterolemia that could mediate tumor cell growth [66]. PCSK9 gene, as a member of proprotein convertases (PCs) family, is coding for a neural apoptosis-regulated convertase 1 (NARC-1) [67]. The two major biological functions of PCSK9 are modulation of plasma lipid homeostasis by regulation of LDLRs and neuronal apoptosis regulation [68–70]. More mechanistic information has been revealed on the regulation of LDLR levels in liver [71–73] and possibly in brain [74,75].

PCSK9 gene, as the 9th member of proprotein convertase family [18,76], is implicated in familial hypercholesterolemia along those genes encoding the LDLR and ApoB [77]. Biochemically, PCSK9 is synthesized as a precursor in a form of 692 residue zymogen with a 30 residue signal peptide [18]. More precisely, this zymogen consists of three domains including: prodomain (residues 31–152), catalytic domain (residues 153–454), and histidine (His)- and cysteine (Cys)-rich C-terminal domain (residues 455–692) [78,79]. The prodomain is spontaneously cleaved off from the 74 kDa pro-PCSK9 in endoplasmic reticulum (ER), which is a requisite step before it exits from this compartment and it is secreted [18]. However, after this step, prodomain remains connected to catalytic domain, keeping it in an inhibited state [18]. Consequently, the secreted form of PCSK9, whose plasma concentration can be measured by ELISA [80], is an enzymatic inactive protein. *PCSK9* is found to predominantly expressed in the liver, but also in several extrahepatic tissues, including the kidney, the pancreas, the intestine and the brain [18]. The catalytic subunit of PCSK9 binds to LDLR through the EGF-A domain [81]. Moreover, the C-terminal Cys-His-rich domain of PCSK9 is critical for targeting PCSK9–LDLR complex to lysosomes [82–84], leading to LDLR internalization and destruction via the endosomal-lysosomal system [82,85], independent of its enzymatic activity [86–88]. It is worth noting that PCSK9 enhances LDLR destruction via both intracellular and extracellular pathways [87]. In addition, PCSK9 can interact with other members of the LDLR-like family, especially very-low-density-lipoprotein receptor (VLDLR) and apoER2 [89].

PCSK9 gene is significantly polymorphic [90]. Gain-of-function (GOF) and loss-of-function (LOF) variants are clinically important, leading to contrasting phenotypes. GOF variants lead to reducing the amount of LDLR protein resulting in hypercholesterolemia, and in turn, increased risk of coronary heart disease (CHD). Hypercholesterolemia in autosomal dominant patients have severe phenotypic types [91]. Conversely, LOF mutations decrease LDLR destruction, accordingly reduce LDL-C levels, which can prevent CHD events [92].

PCSK9 has been proven as a unique drug target for therapeutic interventions against hypercholesterolemia. These treatment procedures targeting PCSK9 not only have the capability of reducing dramatically LDL-C, but also can decrease other pro-atherogenic apoB containing lipoprotein [93]. Recently, the efficacy of monoclonal antibodies trapping circulating PCSK9, i.e. alirocumab and evolocumab, was confirmed and approved for treatment purpose for management of hypercholesterolemia [94].

To date, PCSK9 has been broadly investigated in cardiovascular diseases [95], but far less is understood about its role in cancer. It is important to take into consideration that PCSK9 inhibitors are able to produce large LDL-C level reductions. This evidence is important because a relationship between low levels of LDL-C and incident cancer risk has emerged in some studies of lipid-lowering drugs [96]; there are, however, several other evidences suggesting that these drugs do not increase risk of cancer [97–100]. Another issue deserving attention is that PCSK9 is also engaged in multiple biological processes apart from its role in cholesterol metabolism, including cell cycle, inflammation, and apoptosis [73,101–107]. In addition, its expression in tissues other than liver [18] has raised questions regarding extrahepatic effects of PCSK9 and adverse effects of its pharmacological suppression.

Although PCSK9 inhibitors showed acceptable safety in patients with hypercholesterolemia, additional information regarding long-term safety in other pathological conditions such as cancer is awaited. Thus, it is clinically important to further clarify the correlation between PCSK9 and cancer.

4. PCSK9 in tumorigenesis

PCs were investigated in cancer and found to have important functions in tumor development and progression with different expression between normal and tumor cells [108,109]. However, there are limited number of experimental studies regarding the role of PCSK9 in cancer.

Folsom et al. [110], using a mendelian randomization design, analyzed the correlation between PCSK9 variations and occurrence of cancer over a period of 13 years in a prospective study (n = 13,250). In their research, the frequency of the PCSK9 variants was 0.8% higher in whites compared to blacks. Interestingly, their data could not prove that cholesterol lowering variants of PCSK9 increased the risk of total cancer, although in numerous previous cohorts, including mostly white participants, a low plasma cholesterol levels was associated with an increased cancer incidence [33,111]. A review of clinical trials which compared PCSK9 inhibitors to placebo reported no link with risk of any carcinoma [112]. Similarly, a non-significant protective correlation with cancer risk was documented in a phenome-wide association study of genetic variants in PCSK9 [113].

In a research by Zaid et al. [73] on the role of hepatic PCSK9, following partial hepatectomy, PCSK9 KO mice exhibited a lag in hepatocyte proliferation and raised apoptosis. All these manifestations were mitigated by feeding mice on a cholesterol rich diet.

Song et al. [114], found that the knockdown of annexin A11 expression leads to lower proliferation and ability of colony formation in ovarian cancer cells, highlighting that annexin A11 is directly implicated in cell proliferation and cisplatin resistance in ovarian cancer. After various in vitro assays, they identified a number of differentially expressed genes including PCSK9, related to annexin A11 expression in response to cisplatin therapy. According to their data, these genes are involved in cell cycling, proliferation, cell adhesion, migration, apoptosis, transcription regulation, and signal transduction. They suggested that targeting annexin A11 and its associated genes like PCSK9 could be considered as a novel treatment approach in ovarian cancers.

Lan et al. [101], treated HepG2 cells with recombinant wild type (WT) and D374Y GOF PCSK9 proteins for three time points (8, 24, and 48 h), followed by microarray analysis to detect genome-wide expression variations and pathways. They found novel pathways modulated by PCSK9 including protein ubiquitination, cell cycle, inflammation, xenobiotic metabolism, and stress response.

A similar microarray study reported that overexpression of PCSK9 with GOF mutation (D347Y), downregulates several pro-apoptotic genes in HepG2 cells [102]. The authors elucidated that genes involved in sterol metabolism, cholesterol and steroid biosynthesis were upregulated, while those in response to stress, unfolded protein, virus, and immune response were down-regulated. The implication of PCSK9 in these processes has been also confirmed by in vivo studies [73,103].

Sun et al. [115], demonstrated that PCSK9 has an anti-apoptotic effect in mouse liver, and the absence of PCSK9 can be preservative against melanoma invasion in liver, as a result of lower circulating LDL-C. They injected B16F1 melanoma cells into both wild-type and PCSK9 KO mice to induce liver metastasis. They found a lower risk to develop liver metastases in PCSK9 KO mice, a result that was related to cholesterol levels. Thus, the authors proposed that PCSK9 inhibitors which lower LDL-C [20] could be advantageous to control hepatic metastasis. Indeed, these effects arise from lower cholesterol levels in PCSK9 deficiency and augmentation of tumor necrosis factor α-mediated apoptosis, resulting in a less desirable environment for tumor progression. They come into the conclusion that PCSK9 inhibitor, might be effective in melanoma and possibly other types of cancer. On the contrary, pro-apoptotic action of PCSK9 in primary cultures of cerebellar granular neurons has been described via its ability to promote the degradation of the apolipoprotein E receptor 2 [116].

To date, two human studies evaluated a possible connection between LDL-C-lowering polymorphisms of PCSK9 and risk of cancer [13,110]. Even though one of the studies illustrated a statistical link between low serum LDL-C and high risk of cancer [13], neither study could find association of heterozygote PCSK9 loss-of-function variants with a higher cancer occurrence.

Marimuthu et al. [117], applied a quantitative proteomic technique and designed differential proteomic analysis to distinguish differentially expressed secreted proteins in neoplastic versus non-neoplastic gastric epithelial cells. Stable isotope labeling by amino acids in cell culture (SILAC) is a pivotal tool for accurately quantifying protein expression [118]. They found that 263 proteins in the gastric cell cancer secretome were overexpressed at a rate higher than four-fold compared with non-neoplastic gastric epithelial cells. Moreover, they could validate three novel candidate markers including PCSK9 with 60% overexpression (13-fold) in gastric adenocarcinoma cases, while PCSK9 tended to be undetectable in gastric normal mucosa. Thus, this results validate PCSK9 as a potential biomarker for diagnosis and prognosis of gastric cancer in early stages.

Piao et al. [119] evaluated the effect of overexpression and silencing of PCSK9 on apoptosis in a neuroglioma cellular model. Surprisingly, PCSK9 small interfering (si)RNA was found to induce apoptosis by provoking caspase-3 and suppressing anti-apoptotic proteins, whereas PCSK9 overexpression inhibited apoptosis. Based on these results, PCSK9 has anti-apoptotic efficacy dependent on mitochondrial pathway in neuroglioma cells, which can represent a promising therapy for malignant glioma.

4.1. PCSK9 and HCC

Hepatocellular carcinoma (HCC) is the 3rd leading cause of cancer-related death [120], accounting for nearly 90% of all primary liver cancers in adults [121,122]. HCC occurs mainly in the context of fatty liver disorders, history of alcohol consumption, metabolic syndrome, chronic viral hepatitis, and cirrhosis [123]. Over the last years, management of hepatitis cases and therapeutic improvements, including molecular targeted therapy, local treatment, hepatectomy, liver transplantation, and radiation have provided great advantages for patients with HCC. At present, sorafenib, a multi-kinase inhibitor, is the main chemotherapeutic agent in HCC treatment [124]. Unfortunately, the development of drug resistance to sorafenib is emerging under various mechanisms [125]. The main features of poor prognosis in HCC are high aggressiveness, metastasis and recurrence. Therefore, there is an vital need to illustrate the molecular mechanisms of HCC progression in order to provide novel therapeutic strategies.

In a human study [126], 39 patients undergoing partial hepatectomy or liver transplantation were analyzed for HCC, and the tissue samples used for microarray followed by immunostaining for PCSK9. The data revealed a decreased expression of PCSK9 versus increased LDLR expression in HCC. This finding may suggest two main interpretations.

The first is that decreased PCSK9 is promoting HCC. In this regard, He et al. [127] discovered that by interacting with GSTP1 and blocking the JNK signaling pathway, PCSK9 inhibits HCC cell proliferation, cell cycle and apoptosis. On the other hand, an alternative interpretation is that tumor can manipulate the local microenvironment composition to secure a constant cholesterol supply. The data obtained from this research indicate that targeting PCSK9 with antibodies or targeted pharmaceuticals, could be effective against the metabolism of HCC and, accordingly, its growth potency.

Hyperlipoproteinemia (HL) is a common finding in HCC cases. According to current reports, its incidence is 10–25%, more rampant than other clinical manifestations of HCC like erythrocytosis, hypercalcemia, and hypoglycemia [128,129]. Importantly, the absence of negative feedback effect of cholesterol on 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase in malignant hepatocytes has been documented [130,131]. Moreover, the uptake of LDL-C and remnant lipoproteins are decreased in hepatoma cells due to reduced expression of LDL receptor [131].

Nagashima et al. [132] in a case report study, examined a sixty-nine year old Japanese man with type III hyperlipoproteinemia as a paraneoplastic symptom of hepatitis B virus–associated hepatocellular carcinoma. The results presented that the mRNA expression of sterol regulatory element–binding protein-2 (SREBP2) and PCSK9 in tumor tissue was increased compared with the non-tumor tissue. Further, they found that the non-tumor tissue had extremely low expression of LDLR and LRP1. Altogether these observations suggest that overexpression of SREBP2 in tumor may trigger the secretion of PCSK9, which in turn downregulates the lipoprotein receptors in the non-tumor tissue, ending at paraneoplastic hyperlipoproteinemia. It is noteworthy that PCSK9 modulates LRP1 expression in cancer cell lines and benign embryonic cells in vitro [133,134].

Another study investigated the correlation between inflammation and cholesterol assembly in HCC cells [135]. The authors stimulated HepG2 and Huh7 cell lines as Human HCC cells, with lipopolysaccharide (LPS) for 24 h. The results revealed that LPS substantially increased intracellular cholesterol content by augmenting the expression of SREBF2, HMGCR, and LDLR, coincident with downregulating the expression of PCSK9. Interestingly, these outcomes were dependent on NF-κB signaling pathway. These results indicate that LPS may enhance LDL cholesterol uptake via LDLR and stimulate cholesterol de novo synthesis via HMGCR.

Athavale et al. [136], used HepG2 tumor xenograft model to study the impact of glucose on PCSK9 expression and hypercholesterolemia. Mice were provided drinking water containing glucose. In mice with absence of HCC-xenograft, serum and hepatic PCSK9 was diminished, while it was upregulated in HepG2-tumor bearing mice. These data illustrate tumor-secreted PCSK9 is provoked by glucose availability that could lead to developing hypercholesterolemia in HCC.

In addition to the reported links between PCSK9, HCC and HCC-related dyslipidemia, it should be highlighted that a connection between PCSK9 and HCV (i.e., a recognized cause for HCC development) has been frequently observed [137]. Chronic HCV infection manipulates host lipid metabolism, contributing to hepatic steatosis, and increased risk of liver fibrosis [138,139]. According to epidemiological studies, patients with long-term chronic HCV infection have lower circulating lipid levels [140], suggesting that virus exploit or interfere with host lipid metabolism leading to disease progression [141]. Hepatocyte surface proteins including cluster of differentiation 81 (CD81), LDLR, VLDLR, and scavenger receptor class B type 1 (SR-B1) are associated to HCV entrance. Interestingly, PCSK9 downregulates these proteins and inhibits HCV replication [142–147]. Indeed, in response to infection the PCSK9's promoter activity is induced [148], suggesting a protective action of PCSK9 against HCV infection [145]. In animal studies, there was higher hepatic expression of CD81 in PCSK9 KO mice, compared to wild-type ones. Interestingly, incubation with PCSK9 blunted the infectious ability of HCV [145]. However, this raised concerns that pharmaceutical interfering with PCSK9 function may predispose individuals to HCV infection by increasing CD81 and LDLR. In this context, Ramanathan et al. [146] studied the effects of PCSK9 inhibition on CD81 levels and HCV entrance using alirocumab, a monoclonal antibody to PCSK9. Their data illustrated that blocking the action of PCSK9 mediated by alirocumab has no outcome on CD81 and HCV infection [146].

Hyrina et al. [149], investigated ninety-four HCV-infected cases, under combination treatment of pegylated interferon (PEG-IFN) and first-generation direct-acting antivirals. Based on their results, the content of serum PCSK9 soared in patients who attained sustained virologic response (SVR), suggesting that circulating PCSK9 may hamper viral infection.

Li et al. [142], observed that PCSK9 overexpression had negative effect on HCV replication, while PCSK9 knock down had the opposite outcome. Importantly, the gain-of-function (D374Y) or loss-of-function (Δaa. 31–52) PCSK9 mutants had neutral effect on HCV replication, confirming that PCSK9 inhibits HCV replication through a mechanism independent of LDLR degradation. In fact, only uncleaved ProPCSK9 was able to suppress HCV replication, highlighting that PCSK9 auto-cleavage has effect on HCV replication. Additionally, they found that PCSK9 interacts with NS5A, the non-structural protein of HCV, leading to suppression of NS5A dimerization or RNA binding which are fundamental steps in HCV replication.

A retrospective clinical research was conducted between the year 2011 and 2016, on 178 patients with HCC, cirrhosis, or chronic hepatitis, to clarify the impact of PCSK9 on HCV infection [150]. Data revealed that patients with HCV infection had higher levels of PCSK9, and there was a positive correlation between the HCV titer and serum PCSK9 concentration in such a way that the virus infection raised PCSK9 in all patients with or without HCC [150]. Furthermore, HCV genotype G2 was more effective in promoting PCSK9, compared to G3 phenotype [150]. In support of these findings, in vitro studies confirmed that PCSK9 promoter is activated in response to HCV infection [148]. Indeed, in HCV replicon cells, transcription factors SREBP1c and HNF1α had positive effect on PCSK9 promoter while SREBP1a, HNF1α, and FoxO3 inhibited this promoter [148].

All together, these findings highlight PCSK9 as a crucial but controversial actor in HCC pathophysiology.

4.2. PCSK9 and lung cancer

Lung carcinoma is a leading cause of cancer-related mortality, which mostly is diagnosed among aged individuals [151]. Notably, non-small cell lung cancer (NSCLC) is the most prevalent type of lung cancer with more than 80% of all cases. Monoclonal antibodies against programmed cell death protein-1 (PD-1) and its ligand are applied in NSCLC treatment [152]. In a pilot study conducted in Italy, Bonaventura et al. [153] aimed at assessing serum PCSK9 levels at different time points in patients with advanced NSCLC and under nivolumab (anti-PD1) therapy. Moreover, they evaluated whether PCSK9 might be as a predictive factor for overall survival (OS) in these cases. They observed that serum PCSK9 $>$ 95 ng/mL at second cycle of nivolumab therapy was an independent predictor of reduced OS in patients with advanced, pre-treated NSCLC. As a result, the assessment of serum PCSK9 might be a validated tool to monitor patients with advanced NSCLC. In line with this, findings from a study by Bonaventura et al. [154] revealed that raised PCSK9 serum levels could be a prognostic marker in patients with advanced NSCLC.

Recently, however, another role for PCSK9 has been identified in lung adenocarcinoma. Xu et al. [155] found that PCSK9 siRNA provides an anti-tumor effect via inducing mitochondrial pathway and ER-related cell death in A549 human lung adenocarcinoma cells. Mechanistically, PCSK9 siRNA profoundly provoked A549 cells apoptosis via both activation of caspase-3 and downregulation of survivin and X-linked inhibitor of apoptosis protein. Besides, PCSK9 siRNA also triggered ER stress by increasing 78 kDa and 94 kDa glucose-regulated proteins,

GRP78 and GRP94, phosphorylated eukaryotic initiation factor 2α, and phosphorylated protein kinase R-like ER kinase.

Another research by Demidyuk et al. [156] was conducted on samples of human lung cancer to investigate the expression profile of PCs genes. Expression analysis revealed dramatic differences between tumor and normal tissues. Among the other PCs, PCSK9 mRNA was found in 29 normal tissue samples versus only in 18 tumor ones. Thus, the variations in expression of PC genes may indicate different pathways involved in tumorigenesis.

4.3. PCSK9 and leukemia

Hypercholesterolemia arising from elevated LDL levels is a common manifestation among leukemia patients [157,158]. Importantly, the prolonged existence of LDL in blood raises its oxidation [159]. Interestingly, activation of scavenger receptor LOX1 by ox-LDL leads to induction of PCSK9 expression in non-hepatic tissues [160], highly suggesting the existence of a crosstalk between ox-LDL, LOX1 and PCSK9 [161]. It is important to mention that high levels of serum ox-LDL and upregulation of LOX1 can raise also the risk of prostate, lung, and colon cancer [162,163]. Zia et al. found that PCSK9 expression was significantly induced in leukemia cells [164]. In addition, since eugenol could block LDL oxidation and simultaneously reduce PCSK9 expression through the inactivation of LOX1 receptor, they suggested that PCSK9 could be a promising target in patients with leukemia [164].

4.4. PCSK9 and breast cancer

Pseurotin A (PS) is a unique spiroheterocyclic γ-lactam alkaloid isolated from the fungal culture of *Pseudeurotium ovalis* (strain S2269/F), as well as exists in soil, endophytic, and marine *Aspergillus* and Penicillium species [165,166]. Based on the literature, PS has shown anti-inflammatory [167], along with weak cytotoxic activity against various cancer cell lines [168].

Previous studies reported that PS attenuated PCSK9 secretion in hepatocellular carcinoma cells (HepG2) [169]. In view of data from docking studies, PS binds to the PCSK9 narrow interface pocket which is important in LDLR interaction [169]. Notably, breast cancer (BC) cells have high cholesterol content and overexpress PCSK9 [170]. Khaldoun et al. [169], provided the first evidence regarding the efficiency of targeting PCSK9-LDLR axis in blunting the progression and recurrence of hormone dependent breast cancer. In vitro results revealed that PS reduces PCSK9 in a dose-dependent manner, as well as enhances LDLR levels in hormone-dependent breast cancer cell lines. Their results proposed PS as a novel dual inhibitor of PSCK9 secretion and PCSK9-LDLR interaction against hormone dependent breast malignancies.

4.5. PCSK9 and other tumors

Huang et al. [8] illustrated that in livers of tumor-bearing WT mice, PCSK9-mediated destruction of LDLR is amplified via activating hepatic PCSK9 and HNF1α, leading to hypercholesterolemia, which supplies tumors with essential exogenous lipids to secure proliferation [8].

He et. al. [171] found that Actinidia chinensis Planch root extract (acRoots), a traditional Chinese medicine with anti-tumor feature, enhances expression of PCSK9 with subsequent reduction of LDL receptor, resulting in lowering LDL uptake and proliferation rate in LM3 cells. In the light of these data, the anti-tumor efficacy of acRoots could be attributed to interfering with cholesterol metabolism in a way dependent on PCSK9 pathway.

In a study by Gan et. al. [172], PCSK9 siRNA treatment had protection effect on prostate cancer PCa cells against ionizing radiation (IR)-induced cell injury through apoptosis reduction and MMPs inhibition. In more details, PCSK9 siRNA hindered the increase of cytochrome C, caspase-3, and Bax expressions induced by IR, while up-regulated Bcl-2. Thus, PCSK9 modulates radiosensitivity through mitochondrial pathways, which highlights this protein as a therapeutic target in cases with prostate carcinoma [172].

Charbe et al. [173] developed a PCSK9 conjugated Paclitaxel-loaded Liposomes (PCSK9-PTX-liposomes) for targeting cancer cells. The authors assumed that the high expression of LDLR on cancer cells potentiates the tumor-specific delivery of drugs via PCSK9-Linked-Liposomes. In-vitro experiments proved that PCSK9-PTX-liposomes have acceptable cytotoxic activity versus to the PTX-liposomes without conjugation with PCSK9. Further, cells treated with PCSK9-PTX-liposomes had more agglomeration of PXT and in turn stronger cytotoxic effects.The degree of cytotoxicity was slight in non-cancerous cells, which could be explained by lower LDLR content compared to transformed cells. These observations suggest that PCSK9-PTX-liposomes might be a smart strategy as PTX delivery vehicle for targeted cancer therapy.

Bai et al. [174] studied 205 patients with pancreatic neuroendocrine neoplasms (p-NENs) retrospectively. The authors documented PCSK9 as a target of miR-224, which is involved in apoptosis, proliferation, cell cycle and invasion of several cancers [175–177]. They found that microRNA-224 agomir and PCSK9 siRNA could induce apoptosis as well as inhibit proliferation and invasion of BON-1 cells (Human p-NENs cell lines), while increase the level of glucocorticoid. In the light of these data, miR-224/ PCSK9/GC axis was associated with tumorigenesis and prognosis of p-NENs and could be considered as a treatment target for p-NENs.

Data analysis of prospective cohorts on patients with prostate cancer revealed that PCSK9 expression was not associated with progression to lethal disease [61].

In a mendelian randomization study by Yarmolinsky et al. [178], the effect of lipid-lowering drugs including ezetimibe, targeting Niemann-Pick C1-Like 1 (NPC1L1), and PCSK9 inhibitors on ovarian cancer was studied. The results pointed out no substantial association between inhibition of NPC1L1, PCSK9 or LDL cholesterol levels and epithelial ovarian cancer in general population or *BRCA1/2* mutation carriers.

5. Current therapeutic strategies targeting PCSK9

Currently, there are multiple therapeutic approaches targeting PCSK9 which have been evaluated, including monoclonal antibodies (mAbs) [179], peptidic inhibitor of PCSK9 [180–183], adnectins [184–187], antisense oligonucleotides (ASOs) [188–193], siRNA targeting PCSK9 [194,195], genome editing technique with CRISPR-CAS9 [196,197], PCSK9-vaccine [198], and small molecule inhibitors of PCSK9 [199].

Two PCSK9 inhibitory antibodies (Fig. 2) are currently used in clinical practice as lipid-lowering drugs, i.e. alirocumab and evolocumab, which can efficiently reduce LDL-C [200,201]. The bioavailability of alirocumab or evolocumab following subcutaneous administration is 85% and 72%, respectively [202].

The strategy of mAbs is very effective in reducing plasma LDL-C and cardiovascular risk [199]; however, they also hold some intrinsic negative features as drugs. In the first place, the high cost of development and synthesis of mAbs restricts their broad usage. Generally, they are proteins with high molecular mass (~150 kDa), more complex to generate, and with potential of immunogenicity and unsuitable for oral prescription. Moreover, they have limited access to intracellular targets, and have many targets in CNS.

A promising novel approach to reduce serum LDL-C levels is using small interfering RNAs (siRNAs) to inhibit hepatic PCSK9 synthesis, that could be more reasonable in terms of costs than mAbs. In this approach, translation of PCSK9 is suppressed as a result of siRNA association with RNA-induced silencing complex (RISC) leading to PCSK9 mRNA cleavage [202]. Inclisiran is a synthetic siRNA targeting PCSK9, which is subcutaneously delivered and is conjugated with triantennary N-acetylgalactosamine carbohydrates. Hepatic asialoglycoprotein receptors capture the carbohydrate group leading to uptake of inclisiran [203].

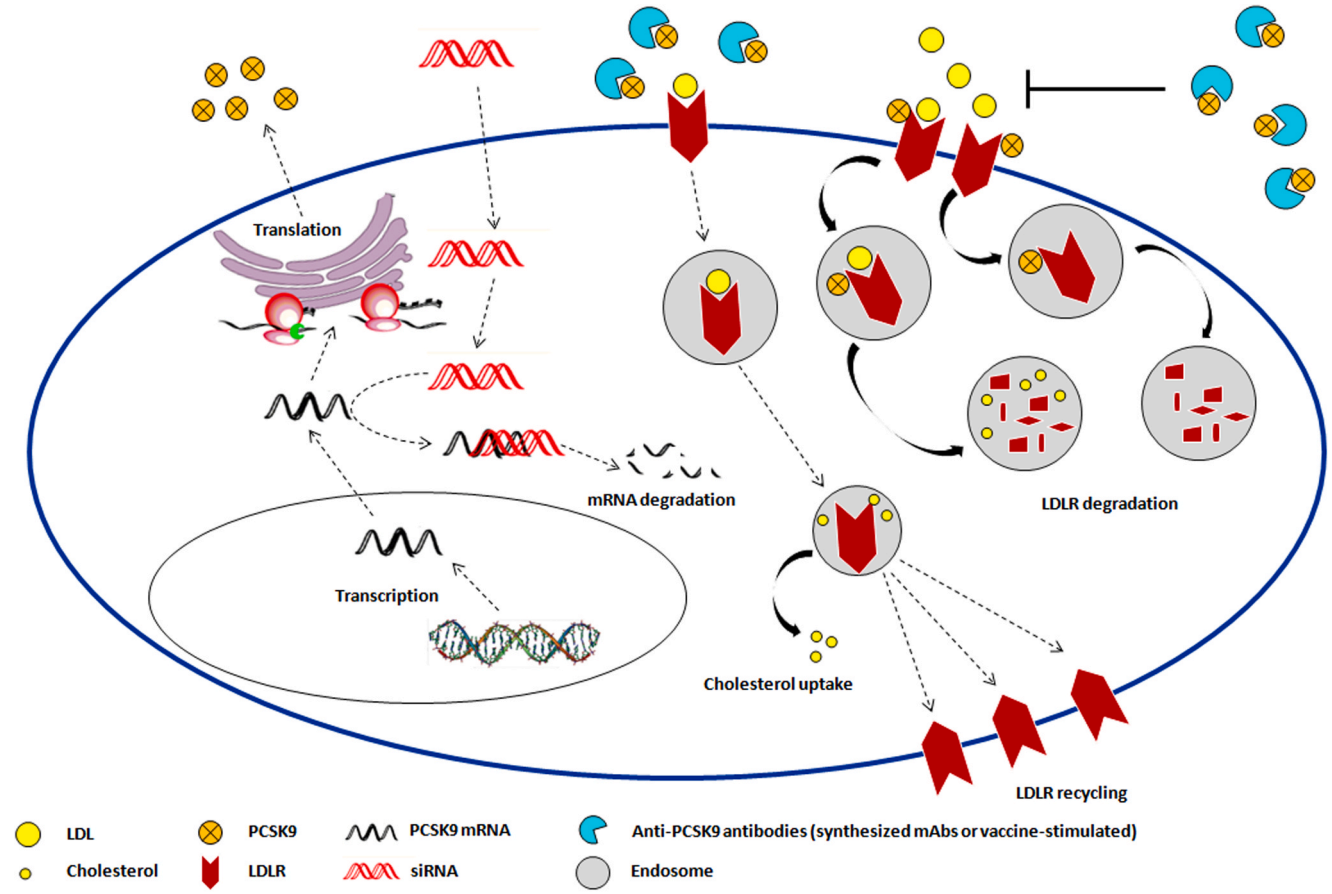

Fig. 2. Drugs for inhibiting PCSK9 pathway. Antibodies, either synthesized or produced by the host after specific vaccine immunization, interferes with LDLR degradation and promotes LDLR recycling. Silencing of PCSK9 mRNA interferes with PCSK9 protein synthesis.

Phase 3 clinical studies of inclisiran have already been conducted and promising effects regarding safety and LDL-C lowering efficacy have been recently published [204]; thus, European Commission recently granted authorization for inclisiran marketing.

As an additional approach, anti-PCSK9 vaccines, as new class of PCSK9 inhibitors, have been studied in terms of efficacy in lowering serum LDL-C in experimental models [198,205–207].

6. PCSK9 inhibitors in cancer

In view of the correlation between *LDLR* expression and cancer, modulating PCSK9 using monoclonal antibodies [199] could be an efficient way to increase cholesterol uptake by extra-tumoral tissues, mainly the liver, thus restricting cholesterol availability for tumor growth.

Recently, the role of cholesterol metabolism in cancer immunotherapy has attracted attention considering the fact that suppression of ACAT1—which is responsible for cholesterol esterification—can augment the anti-tumor cytotoxic T cells response [208]. Likewise, diminishing serum cholesterol levels could amplify the efficiency of cancer immunotherapy relying on adoptive T cells [209]. Moreover, cholesterol has important role in recycling of MHC I in cell membrane [210].

Liu et al. [211] indicated that inhibiting PCSK9 can intensify tumor response to immune checkpoint therapy, in a mechanism other than modulation of cholesterol. They also found that PCSK9 gene knockout in mouse cancer cells dramatically debilitates their growth in a cytotoxic dependent manner. Additionally, it augments the potency of immune therapy targeting the checkpoint protein PD-1. In fact, anti-PCSK9 antibodies have synergy with anti-PD-1 therapy in blocking tumor growth in mouse models. Blocking the function of PCSK9 elevates the expression of MHC I proteins on cancer cell, resulting in massive infiltration of cytotoxic T cells. From the mechanistic view, PCSK9 interrupts recycling of MHC I to the cell surface via binding to it, subsequently leading to its degradation in the lysosome. Their results illustrate that combination therapy of anti-PD-1 antibodies and evolocumab or alirocumab can boost the tumor suppressing efficacy [211].

In terms of safety of PCSK9 monoclonal antibodies, data exist from several large sample size trials showing that evolocumab and alirocumab did not influence cancer risk. The main limitation of these studies is lack of long-term follow-up (less than three years), and accordingly questions on long-term efficacy and safety have remained unanswered [212].

6.1. Anti-PCSK9 vaccine in cancer therapy

It has been shown that nanoliposomal anti-PCSK9 (L-IFPTA+) vaccine can efficiently disrupt the PCSK9 function via repression of PCSK9/LDLR association through provocation of anti-PCSK9 antibodies (Fig. 2) in vaccinated BALB/c mice [213]. This vaccine has also been shown to lower cholesterol and both prevent and treat atherosclerosis in mice [214,215].

In a previous experimental research on mouse model of colorectal cancer, L-IFPTA+ vaccine presented antitumor potency [216]. According to results, PCSK9 suppression had no detrimental effects, while it could relatively inhibit tumor growth, resulting in improved survival in mice bearing colon cancer.

Recent in vivo experiments illustrated higher frequency of proliferative breast tumors with frequent lung metastases in mice with hypercholesterolemia [217]. Consequently, ablation of cholesterol storage

machinery can diminish cell proliferation in breast cancer [218]. However, there are inconsistent correlations between circulating levels of lipids and risk of breast cancer based on observational studies reports [13,219–224]. In this context, another research carried out in our lab focused on evaluating the outcome of PCSK9 inhibition by nano-liposomal anti-PCSK9 vaccine on cancer in mice with breast tumor [225]. Similar to our previous study, the nanoliposomal anti-PCSK9 vaccine was effective in triggering antibodies targeting PCSK9 and improved breast cancer end points with no harmful effects.

In contrast, the L-IFPTA+ vaccine could not inhibit tumor growth, nor improved survival in melanoma-bearing mice [226].

Given that cholesterol can impose different effects depend on cancer type, hence, appraising the outcome of PCSK9 inhibition on various cancer types [227] is critical.

7. LDLR and cancers

There are many data regarding the role LDLR in cancers including liver, lung, breast, prostate, and colorectal carcinomas [8,228]. Normally, cancer cells require more LDLR- mediated cholesterol uptake than untransformed cells [229]. Moreover, LDLR has pro-tumorigenic effects through triggering signaling pathways involved in cell growth and transformation [230] and increasing migration of tumor cells [231, 232]. Guo et al. indicated that increased LDLR expression promotes the uptake of extracellular cholesterol in Glioblastoma (GBM) clinical samples, xenograft models, as well as cell lines [233]. Their results showed that Liver X receptor (LXR) strongly provokes tumor cell death in vivo. This outcome is associated to reduced LDLR expression and elevated ABCA1-mediated cholesterol efflux.

Moreover, lower LDL and LDLR expression were associated with longer survival in patients with SCLC [229].

According to data from in vitro studies, human breast cancer cell lines (including triple-negative ones) express LDLR [234]. Actually, LDLR in human triple negative MDA-MB-231 cells is more expressed compared to estrogen receptor positive MCF7 or non-tumorigenic MCF-10A cell lines [234,235]. In view of data from clinical studies, tumors that are rich in esterified cholesterol content have more aggressive features, with more LDLR mRNA expression [25]. In addition, there is an inverse link between the amount of LDLR expression and survival in human breast cancers [236]. Reports from prospective studies indicated that women with increased total cholesterol levels have higher breast cancer recurrence [237], and higher serum LDL-C has a correlation with decreased survival [238]. In line with these data, cholesterol-lowering statins – which have pleiotropic actions [239–243] – could decrease recurrence and mortality of breast cancer [244].

A mendelian randomization study indicated that LDL-raising variants in PCSK9 were connected to elevated risk of total and ER-positive breast cancer, while declined LDL-cholesterol owing to variants in PCSK9 had protective effect against breast cancer risk [245]. Gallagher et al. [246] elucidated that increased LDL and high expression of LDLR in tumor cell stimulate breast cancer growth, while reducing LDLR expression promotes cell death and declines tumor growth. Studies have revealed that LDLR is downregulated by combined MEK and PKC inhibition in breast cancer cells [234]. Hence, LDLR downregulation through targeting specific pathways may amplify the efficacy of chemotherapy.

It is noteworthy that LDLR deficiency in brain was connected to lowered proliferation in hippocampus [247,248] and increased apoptosis in mice liver [249].

Importantly, LDL catabolism is increased in patients with metastatic prostate cancer with lower plasma cholesterol compared to non-metastatic patients and healthy men [250]. Considering high circulating cholesterol drives tumor growth in mice models of breast and prostate cancer [251], the low plasma LDL-C in cancer may be partially due to raised cholesterol uptake by tumors.

Recently Huang et al. [8], found a strong correlation between LDLR, Srebp1 mRNA and Srebp1-regulated lipogenic enzymes [252], suggesting that LDLR and other lipogenic enzymes have an important role in oncogenesis. In support of this finding, treatment of cells with VLDL and LDL neutralized the pro-apoptotic effect of lipoprotein-deficient serum, whereas, treating with cholesterol alone provoked cell proliferation. Biochemically, cholesterol has beneficial effects for tumor progression owing to its role in regulating plasma membrane's permeability and fluidity. Moreover, cholesterol is an important component of lipid rafts, which have a role in tumor signaling [251].

Cancer cells can take up exogenous cholesterol or synthesize it de novo, to meet their cholesterol requirement (Fig. 1). Prostate cancers rely for androgen biosynthesis on cholesterol as precursor of steroid hormones [253]. Various in vitro and in vivo investigations on prostate cancer have proved altered expression and activity of key elements in cholesterol homeostasis. Prostate cancer cells lack feedback regulation of LDLR in order to supply energy for their uncontrolled growth and proliferation [254]. Indeed, prostate cancer cells have lost ABCA1-mediated cholesterol efflux and simultaneously upregulated *LDLR*, *HMGCR*, *SCARB1* and *SOAT1* expression [26,255–260], resulting in disrupted cholesterol homeostasis [232,258,261].

On the contrary, data of a study by Stopsack et al. [61] on prostate cancer revealed downregulated *LDLR* without upregulation of *SCARB1* (the cholesterol uptake receptor) or downregulation of cholesterol efflux (*ABCA1* expression), which is in contrast to more aggressive cancer types [232,261]. They concluded that prostate tumors are mainly dependent on intracellular synthesis of cholesterol than its uptake from the blood. This is supported by the correlation between higher squalene monooxygenase (*SQLE)* expression, the second rate-limiting enzyme of cholesterol biosynthesis pathway, and higher risk of lethal outcome [61].

7.1. Safety of very low levels of LDL cholesterol and cancer risk

Despite several observations and guidelines support the conclusion that low LDL-C levels are safe, there are epidemiological and clinical trial data indicating an association of very low levels of LDL-C with increased cancer risk [14,33,111,262–266]. Rose et al. [264] found that men with colon carcinoma have lower plasma cholesterol levels. Since then, multiple prospective studies [14,33,111,265–267] acknowledged that low plasma cholesterol levels are linked to an increased risk of cancer.

In a prospective research on 22,000 men with 5-year follow-up, a substantially lower cholesterol level was observed in patients with cancer compared to controls [268]. In contrast, two meta-analyses in 1990s found no reverse connection between cholesterol levels and the overall cancer risk [33,269].

As a matter of fact, prospective studies on the role of lipids in cancer development have come into inconsistent results. The results derived from fifteen prospective cohort studies indicated the lack of an association between LDL-C levels and breast cancer in women [220]. Nevertheless, it has been documented that several hematologic malignancies have connection to low cholesterol levels [270]. Additionally, a study in Copenhagen observed cancer incidence was higher among individuals with LDL cholesterol levels less than 100 mg/dL [13]. However, a mendelian randomization analysis of these data [13] showed that cancer risk in a population with lowering LDL cholesterol polymorphisms in PCSK9, ABCG8, and ApoE was similar to healthy subjects. In agreement with these results, Folsom et al. published that PCSK9 variants have no correlation with increased risk of cancer [110].

The published reports suggest that plasma cholesterol level impacts differently on various types of cancer risk. One prospective Japanese cohort study was conducted on 33,368 Japanese men and women without cancer between 1990 and 1994 [16]. It was found that low cholesterol levels were associated with increased risk of liver cancer but did not raised total cancer risk [16]. Additionally, there was correlation between low cholesterol levels and decreased risk of prostate cancer.

However, no significant association was observed between total cholesterol levels and risk of colorectal cancer [16], while other cohort studies in United States [271–273] and Scotland [274] indicated a reverse correlation.

Several mechanisms have been proposed for decreased cholesterol occurring during malignancies including the impact of tumor necrosis factor on cholesterol metabolism [275] and the tendency of cancerous cells to increase LDLR activity resulting in high LDL-C uptake [32].

Considering pharmaceutical intervention to lower plasma LDL cholesterol, it is critical to ascertain whether low LDL-C may promote cancer risk. In analysis of individual statin trials, there was tendency towards higher cancer risk [276]. In another clinical trial in elderly individuals at risk of vascular disease [262], cancer incidence was substantially increased in patients on pravastatin compared to placebo. On the other hand, there are several meta-analyses of clinical trials and observational studies that reported statin therapy do not elevate cancer risk [100,224,277–281], and instead, might have a protective effect [279,282–284]. In line with these data, in a case-control study on prostate cancer, statin users showed a lower risk of advanced prostate cancer [285].

8. Conclusion

At this stage of research it is impossible to make firm conclusions on the role of PCSK9 in cancer risk. Considering lots of controversy and inconsistent reports, additional preclinical and clinical investigations should look at the potential role of PCSK9 in cancer. In addition, further preclinical, pathoepidemiologic and pharmacoepidemiologic studies are needed to evaluate various strategies of PCSK9 inhibition with longer follow-up durations to better understand the safety and efficacy of anti-PCSK9 therapy in cancer. As the other physiological roles of this protein have not been fully discovered yet, it is important to consider that modulating intracellular PCSK9 levels via approaches like siRNA, may not have the same effect as its systemic inhibition.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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