Role of PCSK9 in hallmarks of cancer: From mechanisms to interventions (Review)

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Abstract. Although the role of proprotein convertase subtilisin/kexin type 9 (PCSK9) in regulating cholesterol homeostasis through low-density lipoprotein receptor (LDLR) is well established, accumulating evidence underscores its broader involvement in diverse biological processes such as angiogenesis and immunoregulation. These functions implicate PCSK9 in the pathogenesis of various human diseases, including cancer. Recent studies have revealed that PCSK9 mediates the lysosomal degradation of multiple substrates beyond LDLR, thereby expanding its potential importance in oncology. To the best of our knowledge, the present review summarized for the first time the identified repertoire of PCSK9 substrates, emphasising how these interactions enable PCSK9 to regulate novel biological pathways independently of cholesterol metabolism. Next, PCSK9 genetic variants were compiled, documented and discussed, focusing on how they influence disease susceptibility and progression by modulating PCSK9 activity or expression. Finally, the present review elaborated on the mechanisms by which PCSK9 contributes to several hallmarks of cancer, including sustained proliferative signaling, invasion and metastasis, metabolic reprogramming, angiogenesis and tumor immune evasion through the modulation of specific substrates. These insights highlight its relevance as a therapeutic target. The current review also provides an overview of ongoing clinical trials evaluating PCSK9 inhibitors, either as monotherapy or in combination with other anticancer strategies. Altogether, these advances lay a foundation for personalized and precision cancer therapy.

Contents

1. Introduction

Proprotein convertase subtilisin/kexin type 9 (PCSK9), together with other members of the PCSK family of proteases (including Furin, PC1/3, PC2, PC4, PACE4, PC5/6, PC7 and subtilisin/kexin-isozyme-1), use serine to hydrolyze peptide bonds (1,2). Unlike other PCSK members, PCSK9 recognizes the VFAQ amino acid motif in its internal sequence and becomes biochemically active. Notably, mature PCSK9 does not undergo additional proteolytic cleavage to release an active convertase. Instead, it primarily functions as a binding protein that regulates the degradation of its substrates/binding proteins via the lysosomal system (3). A previous study also found that the lysosomal system is critical for PCSK9 degradation, in which glucagon receptor signaling plays an important role (4). The most prominent event for the important role of PCSK9 in human disease was the identification of the PCSK9 variant (S127R) in familial hypercholesterolemia, which led to the identification of its first substrate, low-density lipoprotein receptor (LDLR) (5). Due to the critical function of LDLR

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in lipoprotein trafficking, PCSK9 has become an attractive therapeutic target for hypercholesterolemia and cardiovascular disease.

Beyond LDLR, emerging evidence suggests that PCSK9 also modulates other substrates. Given the important role of these substrates in the hallmarks of cancer, ranging from sustained proliferative signaling to tumor immune evasion, recent evidence supports that PCSK9 is closely associated with tumorigenesis. For example, Wang *et al* (6) reported that PCSK9 expression is significantly upregulated in colon cancer tissues compared to normal tissues. Furthermore, silencing PCSK9 expression markedly reduced the tumorigenic properties of colon cancer cells, supporting its functional role in cancer progression. These findings suggest that PCSK9 may represent a promising therapeutic target in oncology. In line with this, several clinical trials have been initiated to evaluate the efficacy of PCSK9 inhibition in patients with cancer. The present review highlights the emerging roles of PCSK9 in regulating key hallmarks of cancer and summarizes the latest advances in strategies to therapeutically interfere with PCSK9 activity, thereby underscoring its potential as a target for cancer treatment.

2. Biochemical features of PCSK9

The human PCSK9 gene spans 3,710 base pairs across 12 exons and encodes a protein with 692 amino acids. Unlike other PCSK family members like Furin and PC7, PCSK9 contains only four domains (Fig. 1), and each domain has a distinct function (7). The signal peptide, pro-domain and catalytic domain are conserved among all PCSK members. Specifically, the signal peptide (amino acid residues 1-30) is responsible for directing the protein into the endoplasmic reticulum (ER), while the pro-domain (residues 31-152) acts as a chaperone that enables proper folding of the catalytic domain. The catalytic domain (residues 153-452) contains the canonical serine proteinase catalytic triad composed of Asp^{186}, His^{226} and Ser^{386}, which mediates cleavage at the FAQ^{152} sequence within PCSK9 in the ER. Notably, this autocleavage event causes the loss of proteolytic activity, but it is necessary for its maturation and subsequent secretion (8). The Cys-His-rich domain (CHRD, residues 453-692) consists of three tandem repeats (M1: 453-529, M2: 530-603 and M3: 604-692) that interact with PCSK9 substrates to form a stable complex, thereby facilitating substrate trafficking from endosomes to lysosomes. Previous studies have indicated that partial deletion of the CHRD severely impairs PCSK9 secretion, possibly by interfering with the coat protein complex II component Sec24 (9), highlighting its critical role in PCSK9 maturation and secretion. In addition, other proteins such as cytosolic adenylyl cyclase-associated protein 1 can enhance the activity of PCSK9 by binding to the M1 and M3 repeats of the CHRD domain (10). A mutation within this domain mainly alters the activity of PCSK9 but not its maturation. Conversely, certain mutations in this domain may also promote the activity of PCSK9, thereby promoting substrate degradation (11). However, the precise molecular mechanism by which specific residues within the CHRD regulate PCSK9 maturation and activity remains largely elusive.

Similar to other PCSK family members, PCSK9 is enriched in the trans-Golgi network, where it can be sorted into different final destinations. PCSK9 is also localized to endosomes/lysosomes and the cell surface. Notably, substrate availability appears to regulate the subcellular distribution of PCSK9. For instance, Nassoury *et al* (12) reported that PCSK9 is also localized to the ER in cells lacking expression of LDLR, whereas in LDLR-expressing cells, PCSK9 was efficiently sorted to post-ER compartments. Further studies are still needed to elucidate the molecular mechanisms underlying this substrate-dependent trafficking.

Given the central role of LDLR in cholesterol and fatty acid metabolism, PCSK9 is most abundantly expressed in the liver, with lower expression in other tissues such as the intestine and kidney. According to the Human Protein Atlas (https://www.proteinatlas.org/) (13), PCSK9 is also highly expressed in the lung, colon and duodenum (Fig. 2). This widespread tissue distribution underscores its importance in the regulation of homeostasis. Emerging evidence further indicates that PCSK9 regulates additional biological processes, including adipogenesis, immune response and neurogenesis (14), thereby expanding its functional relevance in both physiological and pathological conditions.

3. Structural features of PCSK9

PCSK9 variants. PCSK9 was identified in 2003 alongside variants linked to autosomal dominant hypercholesterolemia, which highlights the important role of PCSK9 in abnormal cholesterol metabolism. Since then, numerous PCSK9 variants have been reported, including Y142X and Q152H (Table I). Notably, some of them are loss-of-function (LOF) variants, which are associated with decreased LDL cholesterol (LDLC) levels, while gain-of-function (GOF) variants decrease *LDLR* levels, thus causing hypercholesterolemia.

Subsequent studies have elucidated how individual PCSK9 variants impact its maturation and function. For instance, the S462P mutation in exon 9 of the PCSK9 gene clearly impairs the secretion of PCSK9, with the mutant protein being largely retained in the ER, indicating that this mutation results in a LOF phenotype (15). Structural analysis further revealed that residue Ser462 is located immediately after the first β-strand of the first tandem repeat of the CHRD domain. Notably, Ser462 is one of the few highly conserved non-cysteine residues in the CHRD domain across PCSK9 homologues, thus supporting its important role in the function of PCSK9. Consistent with this, the S462P mutation causes reduced *LDLR* degradation and can contribute to hypocholesterolemia (15).

Among the numerous PCSK9 variants identified to date, the most prevalent LOF variant is R46L, reported in >100,000 individuals across diverse ethnic groups, including British (16), Italian (17), Swedish (18), Canadian (19), Danish (20) and Spanish (21) populations. The R46L mutation is associated with plasma lipoproteins and reduced LDLC levels, which correlate with a decreased risk of cardiovascular diseases such as aortic valve stenosis and ischemic heart disease (22,23). However, a meta-analysis by Liu *et al* (24) reported that the PCSK9 R46L variant may also increase the risk of diabetes mellitus, likely as a consequence of chronically reduced LDLC levels. These contrasting effects highlight the need for

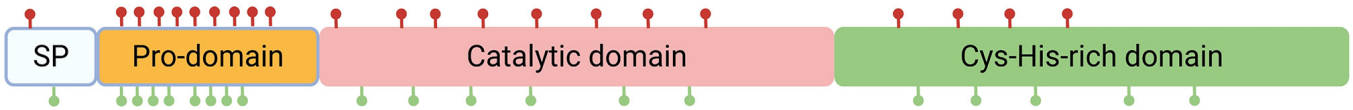

Figure 1. Schematic illustration of the structural domains of PCSK9. The coloured bar represents the distinct structural domains of PCSK9. The SP guides mRNA of PCSK9 into the endoplasmic reticulum. The pro-domain undergoes self-cleavage and then binds to the catalytic domain. Unlike other PCSK family members, the catalytic domain cannot perform an enzymatic function due to binding by the pro-domain. The Cys-His-rich domain is located at the C-terminus, which contains a three-fold tandem repeat (M1, M2 and M3). Mutations have been found in the four domains of PCSK9. Red dots mean gain of function, while green dots represent loss of function. The figure was created with BioRender (https://www.biorender.com/). PCSK9, proprotein convertase subtilisin/kexin type 9; SP, signal peptide.

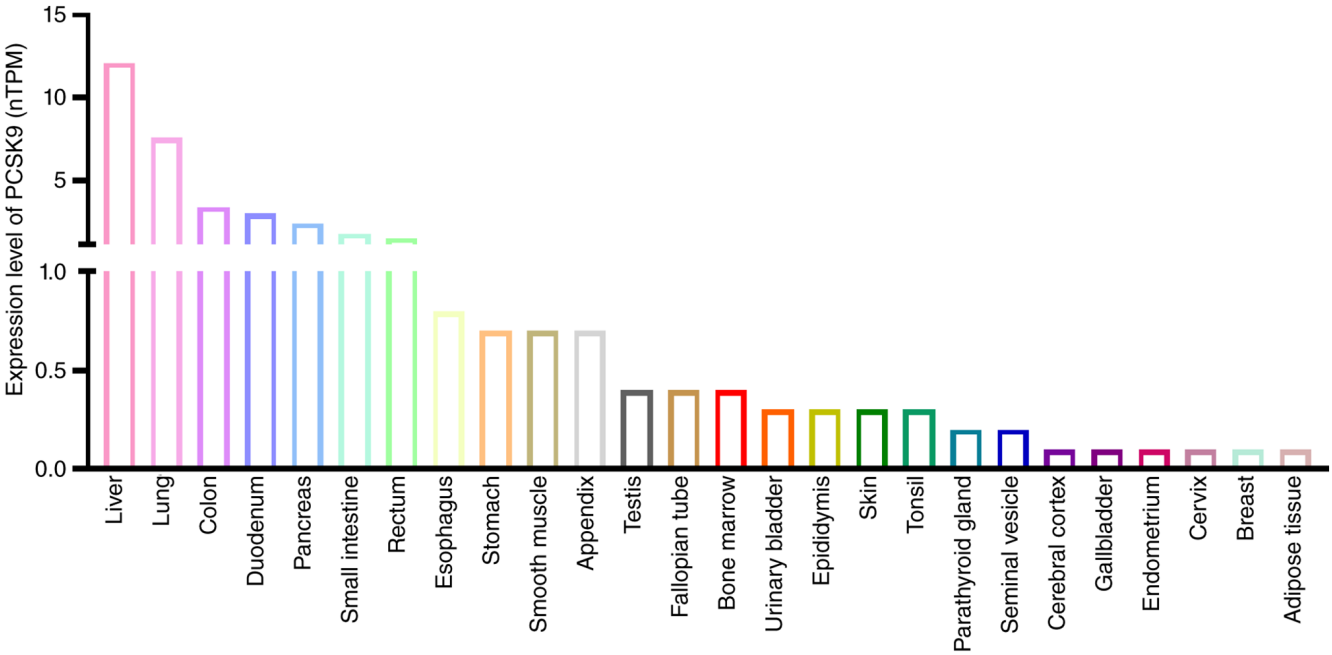

Figure 2. Expression levels of PCSK9 in the different tissues. Landscape of PCSK9 expression in different tissues based on proteomic data from the Human Protein Atlas. Color-coding is based on distinct tissue. The top tissues for high expression of PCSK9 include the liver, lung and colon, while PCSK9 expression is lower in cervix, breast and adipose tissue. The raw data were downloaded from The Human Protein Atlas (https://www.proteinatlas.org/) and the figure was created with GraphPad Prism9.0. PCSK9, proprotein convertase subtilisin/kexin type 9.

further studies to clarify the broader impact of this variant on human health, including its potential role in conditions beyond cardiometabolic diseases such as cancer.

On the other hand, several GOF variants of PCSK9 have been identified across different populations. One of the most studied is the D374Y variant, reported in Norwegian (23), British (25,26) and Turkish (27,28) cohorts. Unlike the R46L mutation, D374Y markedly increases circulating LDLC levels, likely through enhanced binding affinity to LDLR and subsequent acceleration of LDLR clearance (29). Furthermore, the D374H variant has been described in the Portuguese population (30). Similar to D374Y, D374H enhances PCSK9 function and adversely affects life expectancy and quality of life by promoting premature coronary heart disease in patients with familial hypercholesterolemia (FH) (30). Of note, the E32K variant appears to be unique to the Japanese population (31-33). This variant exacerbates the phenotype of FH by elevating PCSK9 function and plasma lipid levels. Additional GOF variants, including V4I and R496W, have also been identified in the Japanese population (32). Despite these insights, the precise molecular mechanisms by which different PCSK9 mutations confer GOF activity, as well as their broader implications for human diseases beyond lipid metabolism, remain incompletely understood and warrant investigation.

PCSK9 substrates. Despite PCSK9 being known for its role in regulating plasma LDLC by binding to LDLR, accumulating evidence suggests that it can interact with other substrates (Fig. 3), thereby promoting their degradation. For instance, very (V)LDLR and apolipoprotein E receptor 2 (ApoER2), which are the closest family members to LDLR, have been shown to bind PCSK9 (34,35). Notably, the D374Y mutation markedly enhances the degradation of both VLDLR and ApoER2 when co-expressed in 293T or HuH7 cells, supporting that this mutation promotes the function of PCSK9. Furthermore, the catalytic activity of PCSK9 is not required for the degradation of ApoER2, VLDLR or LDLR (35), indicating that the role of the catalytic domain of mature PCSK9 warrants further investigation.

Canuel *et al* (36) also demonstrated that LDLR-related protein 1 (LRP1), a protein highly homologous to LDLR, is regulated by PCSK9. Notably, PCSK9 was shown to act on LRP1 in CHO-A7 cells that lack LDLR expression, while re-introduction of LDLR decreases PCSK9-mediated

Table I. PCSK9 variants and their effects on the function of PCSK9.

Location	Amino acid changes and functional effects
Signal peptide	V4I (GOF) (143), L21dup/tri (LOF) (143)
Pro-domain	E32K (GOF) (143), D35Y (GOF) (144), R46L (LOF) (145), A53V (LOF) (146), A62D (LOF) (147), E85K (UNS) (143), R93C (GOF) (143), R96L (GOF) (148), R104C (LOF) (149), R105W (GOF) (148), R105Q (LOF) (146), G106R (LOF) (146), L108R (GOF) (144), S127R (GOF) (144), D129N (GOF) (143), D129G (GOF) (146), E132D (UNS) (143), Y142X (LOF) (150), Q152H (LOF) (151)
Subtilisin-like catalytic domain	P155L (UNS) (152), N157K (LOF) (146), R160Q (LOF) (153), A168E (UNS) (154), A168V (UNS) (143), R194A (LOF) (155), P209L (UNS) (156), R215H (GOF) (143), F216L (GOF) (149), R218S (GOF) (146), E228K (GOF) (149), R237W (LOF) (147), G263S (LOF) (143), T264I (UNS) (143), R357H (GOF) (146), D374N (UNS) (157), D374H (GOF) (146), D374Y (GOF) (146), F379A (LOF) (158), H417Q (GOF) (146), I424V (UNS) (143), A443T (LOF) (146)
Cys-His rich domain	V460 (UNS) (159), P467A (GOF) (147), R469W (GOF) (157), V474I (GOF) (146), A478T (UNS) (143), R496W (GOF) (143), R499C (UNS) (160), R499H(UNS)(161), G504W (UNS) (143), N513D (UNS) (162), G516V(GOF) (149), A598T(LOF) (163), G629D (UNS) (143), V644I (UNS) (143), A649T (UNS) (143), S668R (LOF) (143), E670G (LOF) (149), G670E (GOF) (164), C679X (LOF) (150), R682Q (UNS) (143)

GOF, gain-of-function; LOF, loss-of-function; UNS, uncertain significance; PCSK9, proprotein convertase subtilisin/kexin type 9.

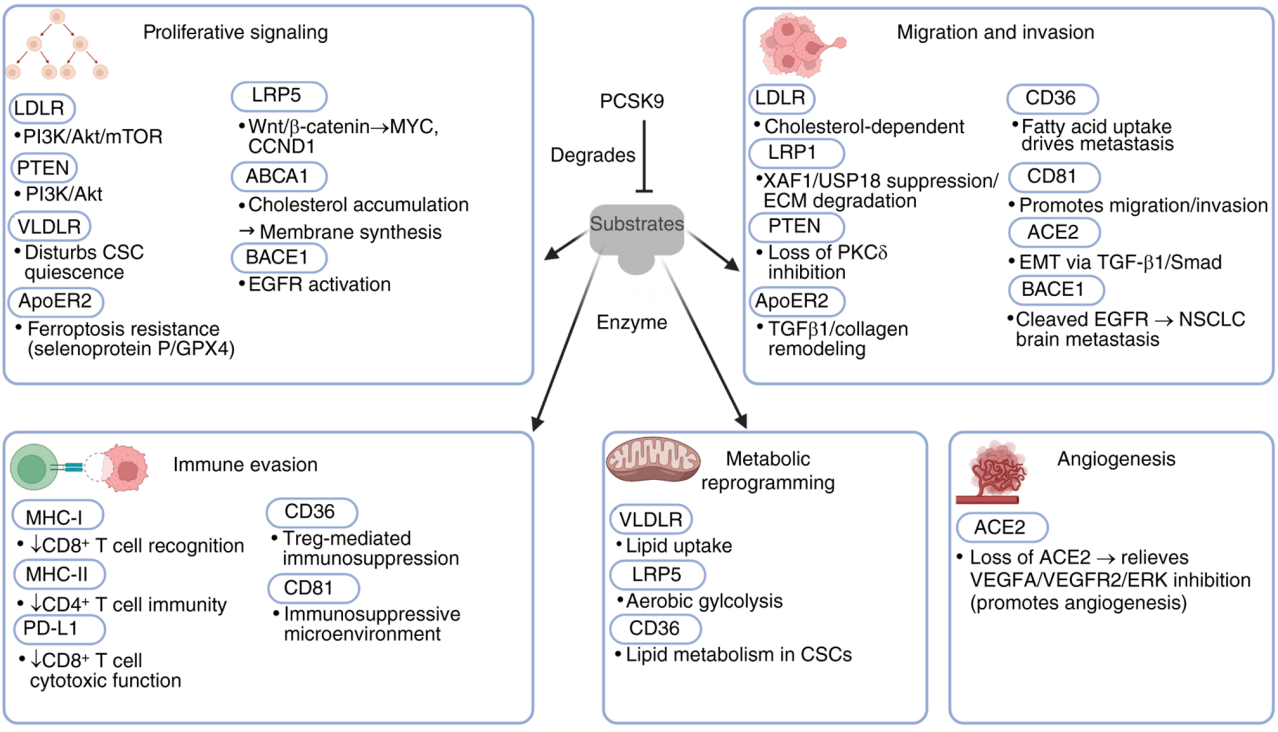

Figure 3. Role of PCSK9 in cancer hallmarks through modulation of key protein substrates. PCSK9 not only promotes the degradation of low-density lipoprotein receptor, but also regulates the expression of other proteins such as MHCI, MHCII and phosphatase and tensin homolog. Therefore, PCSK9 is involved in various cancerous features such as sustaining proliferative signaling, invasion/metastasis, metabolic reprogramming, angiogenesis and tumor immune evasion. The figure was created with BioRender (https://www.biorender.com/). PCSK9, proprotein convertase subtilisin/kexin type 9; LDLR, low-density lipoprotein receptor; LRPP5, low-density lipoprotein receptor related protein 5; PTEN, phosphatase and tensin homolog; ABCA1, ATP binding cassette subfamily a member 1; VLDLR, very low-density lipoprotein receptor; BACE1, β-secretase 1; ApoER2, apolipoprotein e receptor 2; MHC-I/II, major histocompatibility complex I/II; CD36/81, cluster of differentiation 36/81; PD-L1, programmed death-ligand 1; LRP1, low-density lipoprotein receptor-related protein 1; ACE1, angiotensin I converting enzyme 2.

degradation of LRP1, indicating that LDLR effectively competes with LRP1 for PCSK9 binding. Similarly, Badimon *et al* (37) reported that LRP5 can form a complex with PCSK9 in macrophages, thereby facilitating lipid uptake. However, whether PCSK9 directly promotes the degradation of LRP5 needs further investigation. The identification of

LDLR-related PCSK9 substrates highlights the important role of PCSK9 in regulating cholesterol homeostasis. Indeed, Canuel *et al* (36) showed that PCSK9 represses ATP-binding cassette transporter A1 (ABCA1)-mediated cholesterol efflux induced by liver x receptor/retinoid x receptor agonists in mouse peritoneal macrophages. The authors also found that PCSK9 downregulates both the mRNA and protein expression of ABCA1. Collectively, these findings suggest that PCSK9 may regulate a wider network of receptors and transporters involved in lipid metabolism, and further investigation is warranted to determine whether additional members of this superfamily act as PCSK9 substrates.

PCSK9 has been reported to regulate the degradation of other substrates. For instance, Demers *et al* (38) indicated that PCSK9 induces the degradation of CD36 through a proteasome-sensitive mechanism in the post-ER compartment. Consistently, knockout of PCSK9 does not alter the mRNA levels of CD36 in hepatocytes. Furthermore, proteasome and lysosome inhibitors block CD36 degradation, suggesting a key role for both the ubiquitin-proteasome and autophagy-lysosome systems in this process. In addition, PCSK9 deficiency reduces CD81 cell surface expression, supporting a role for PCSK9 in modulating CD81 degradation (39). Notably, the LOF mutants G236S and A239D of PCSK9 have no effect on CD81 expression, while the GOF mutant D374Y lowers CD81 expression (40). These findings suggest that the mutation site in PCSK9 may play an important role in determining the fate of CD81 expression.

Recently, PCSK9 was reported to enhance the cellular degradation of ACE2 by binding to the pro/catalytic domains of mature PCSK9 (41), which differs from the mechanism whereby the CHRD domain of PCSK9 is required for LDLR degradation. Sun *et al* (42) reported that PCSK9 can interact with phosphatase and tensin homolog (PTEN) and promote its lysosomal degradation, indicating an important role of PCSK9 in the phosphoinositide 3-kinase (PI3K)/Akt signaling pathway. Furthermore, secreted PCSK9 facilitates the disposal of β-site amyloid precursor protein-cleaving enzyme 1 (BACE1), a membrane-associated protein, in a post-ER compartment (43). As expected, mutations of the catalytic triad of PCSK9 do not impact BACE1 disposal by secreted PCSK9. Consistently, PCSK9 knockout mice showed increased levels of BACE1 in the brain (43). Liu *et al* (44) reported that histocompatibility 2, K1 (H2-K1) can interact with PCSK9 in tumor cells and deletion of the M2 domain of PCSK9 completely abrogates this interaction. Further analysis showed that overexpression of PCSK9 reduces the expression of H2-K1, while PCSK9 deficiency increases its expression, indicating that PCSK9 regulates the degradation of H2-K1 (44). The authors also found that PCSK9 reduces the expression of human leukocyte antigen A/B/C (HLA-ABC). Notably, bafilomycin, an inhibitor of lysosome function, increases the levels of HLA-ABC in wild-type (WT) cells but not in PCSK9-deficient cells, suggesting a key role for PCSK9 in regulating lysosome-mediated degradation of HLA-ABC. Similarly, Wang *et al* (45) reported that PCSK9 inhibition increases major histocompatibility complex (MHC)-II expression on the surface of tumor cells, indicating that MHC-II could be a potential binding protein of PCSK9. Whether PCSK9 regulates the expression of MHC-II via lysosome-mediated degradation needs further investigation. Additionally, future studies are needed to identify additional PCSK9 substrates.

4. PCSK9 and hallmarks of cancer

Cholesterol plays an important role in maintaining cellular homeostasis and abnormal cholesterol levels are closely associated with cancer because cancer cells require elevated cholesterol to sustain their high metabolic demands. Multiple prospective studies have demonstrated an association between cholesterol levels and risk of cancer (46,47). PCSK9, as a key regulator of cellular cholesterol homeostasis, has been implicated in the development and progression of various types of cancer. With the increasing identification of novel PCSK9 substrates, it has become evident that PCSK9 not only regulates cholesterol metabolism but also contributes to other biological processes such as immune responses (48). Therefore, PCSK9 is involved in carcinogenesis not only by modulating cholesterol metabolism but also by promoting aggressive features of cancer cells, including immune evasion. Indeed, analysis of The Cancer Genome Atlas database shows that PCSK9 is highly expressed in several types of cancer (49). The following subsections discuss how PCSK9 influences the hallmarks of cancer by modulating distinct cellular components.

PCSK9-related pathways and sustained proliferative signaling. Proliferation is a fundamental characteristic of all living cells and is essential for diverse cellular processes. Unlike normal cells, cancer cells sustain uncontrolled proliferative signaling by activating a series of signaling cascades. Cholesterol, as an essential component of cell membranes, is critical for maintaining cellular integrity and proliferation. Beyond its structural role, cholesterol also serves as a precursor for bile acids and steroid hormones such as glucocorticoids, estrogens, progesterone, androgens and aldosterone, thereby providing key signals for cell growth (50). Indeed, cholesterol levels are often significantly increased in the tumor microenvironment (TME).

Epidemiological studies have consistently suggested that high serum cholesterol levels are positively correlated with the risk of several cancer types, including prostate (51), colorectal (52) and ovarian (53) cancer, supporting a tumor-promoting role for cholesterol in carcinogenesis. Cholesterol exists primarily in two forms: LDLC and high-density lipoprotein cholesterol (HDLC). Similar to their opposing roles in cardiovascular health, increased LDLC levels are positively associated with cancer progression, while higher HDLC levels are inversely correlated with the risk of cancer (54). For instance, patients with colorectal cancer exhibiting high LDLC levels have a decreased likelihood of disease-free survival (DFS) (55), whereas high serum HDLC levels are associated with improved DFS (56). Furthermore, Rodrigues Dos Santos *et al* (57) demonstrated that LDLC enhances the phosphorylation of Akt and extracellular signal-regulated kinase by activating Erb-B2 receptor tyrosine kinase 2 (HER2), thereby promoting the proliferation of breast cancer cells. Collectively, these findings highlight the critical role of cholesterol in carcinogenesis by mediating proliferative signaling.

Since PCSK9 is critical for regulating LDLC levels, which are positively associated with cell proliferation, accumulating evidence suggests that PCSK9 acts as a key regulator of proliferative signaling. Lupo *et al* (58) reported that PCSK9 induces smooth muscle cell (SMC) proliferation in rats by activating the sterol regulatory element-binding protein pathway and upregulating its transcriptional targets [including 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase]. In mouse aortic vascular SMCs, silencing of PCSK9 represses cell proliferation by decreasing the expression of proliferating cell nuclear antigen (PCNA), Beclin1, p62 and light chain 3 via the PI3K/Akt/mTOR signaling pathway, suggesting that PCSK9 promotes vascular SMC proliferation independently of its lipid-regulating function (59). Similarly, Liu *et al* (60) reported that Pep2-8 trifluoroacetate salt, a PCSK9 inhibitor, represses the proliferation of vascular SMCs by regulating the small nucleolar RNA host gene 16/enhancer of zeste 2 polycomb repressive complex 2 subunit/TNF receptor-associated factor 5 axis, further supporting an important role for PCSK9 in mediating cell proliferation.

In human induced pluripotent stem cells (hiPSCs), PCSK9 overexpression stimulates hiPSC proliferation. Conversely, PCSK9 inhibition decreases cell proliferation by repressing the phosphorylation of SMAD2 (61). Further analysis demonstrated that PCSK9 modulates the Nodal growth differentiation factor (NODAL) growth differentiation factor pathway by regulating the expression of its endogenous inhibitor, dishevelled binding antagonist of β-catenin 2, which promotes the lysosomal degradation of TGF-β receptor 1. These findings support that PCSK9 is an important regulator of the cell cycle in hiPSCs. Consistent with these findings, PCSK9 knockout mice showed slower proliferation rates and decreased migratory capacity due to impaired G_1/S phase progression of the cell cycle (62). The authors also found that PCSK9 overexpression in PCSK9-deficient cells partially rescues the phenotype by downregulating the expression of α-smooth muscle actin, MHC-II and calponin (62). In these mice, partial hepatectomy leads to delayed expression of PCNA, an indicator of DNA replication (63). Furthermore, induction of cyclin E and cyclin-dependent kinase 2 is delayed in PCSK9 knockout mice following partial hepatectomy. Sun *et al* (64) reported that knockdown of PCSK9 significantly reduces cell proliferation in HepG2 cells, a liver cancer cell line. Notably, knockdown of PCSK9 has no effect on the proliferation of B16-F1 melanoma cells, which may be attributed to the undetectable expression of LDLR in these cells (64). In esophageal cancer cells, PCSK9 overexpression enhances cell proliferation, while PCSK9 knockdown inhibits tumor growth (65). Mechanistically, PCSK9 promotes the epithelial-mesenchymal transition (EMT) by increasing C-C motif ligand 25 secretion. However, the mechanism by which a PCSK9 substrate plays a role in this axis remains elusive.

Accumulating evidence suggests that the apoptotic pathway plays a critical role in mediating PCSK9-related effects on cell proliferation. For instance, in lung adenocarcinoma cells, PCSK9 deficiency leads to the activation of caspase-3 and repression of the anti-apoptotic protein survivin (66). Furthermore, PCSK9 deficiency induces ER stress by increasing the expression of glucose-regulated proteins and enhancing the activity of protein kinase R-like ER kinase (66). Similar mechanisms have also been observed in neuroglioma cells. Additionally, PCSK9 deficiency increases the ratio of Bcl-2-associated X protein to B-cell lymphoma 2 (Bax/Bcl-2), thereby promoting apoptosis by enhancing the release of cytochrome *c* from mitochondria to the cytoplasm (67). In neuroendocrine neoplasms, knockdown of PCSK9 also suppresses tumor growth by activating cleaved caspase-3 (68). In hepatocellular carcinoma (HCC), PCSK9 has been reported to promote the apoptosis of cancer cells by activating the fatty acid synthase/Bax/Bcl-2/caspase-9/caspase-3 pathway, leading to reduced proliferation of cancer cells *in vitro* and *in vivo* (69). Consistently, high expression of PCSK9 positively correlates with poor prognosis in patients with HCC. By contrast, in PCSK9-deficient mice, TNFα-mediated apoptosis predominates in regulating melanoma tumor cell growth in the liver, a phenomenon related to low cholesterol levels. Further analysis revealed that TNFα regulation is independent of LDLR, as its mRNA level is increased in mice lacking both PCSK9 and LDLR (64), indicating the involvement of other cholesterol-related mechanisms in regulating biological processes. In addition, PCSK9 has been reported to activate the mitogen-activated protein kinase (MAPK) signaling pathway by upregulating heat shock protein 70 (HSP70) expression in gastric cancer (GC) cells, thereby suppressing apoptosis. Notably, PCSK9 does not affect cell proliferation in GC cell lines (70). Given the central role of the MAPK signaling pathway in regulating cell proliferation, further studies are required to elucidate why PCSK9-driven alterations in this pathway do not impact the proliferation rate of GC cells.

Although the nanoliposomal anti-PCSK9 vaccine efficiently reduces the plasma levels and activity of PCSK9, it shows no significant effect on the growth of melanoma tumors in C57BL/6 mice (71). However, the same vaccine significantly suppresses tumor growth and prolongs the lifespan in BALB/c mice bearing breast (72) or colon (73) tumors. These discrepancies across cancer types suggest that both mouse strain and tumor context may influence the efficacy of the nanoliposomal anti-PCSK9 vaccine in regulating tumor growth, warranting further investigation. Consistently, PCSK9 expression is lower in tumor tissues compared with paired normal tissues, including in lung cancer and acute myeloid leukemia (49). In addition, previous genome-wide association studies have shown that genetically proxied inhibition of PCSK9 is not associated with epithelial ovarian cancer in either the Ovarian Cancer Association Consortium dataset or the Consortium of Investigators of Modifiers of BRCA1/2 dataset (74). In line with these findings, PCSK9 expression in ovarian tumors does not significantly differ from paired normal tissues (49). Taken together, these data suggest that PCSK9 plays diverse roles in regulating cancer cell growth.

PCSK9-related pathways and invasion/metastasis. Tumor invasion and metastasis refer to the process by which local tumor cells spread to neighboring or distant tissues via the circulation, representing one of the hallmarks of cancer. It has been reported that >90% of cancer-related mortalities are associated with tumor invasion/metastasis (75). Although the underlying mechanisms of tumor invasion/metastasis vary across tumor types, abnormal cholesterol metabolism plays an important role in this process. For instance, inhibition of

cholesterol biosynthesis markedly reduces the invasive and metastatic capacity of human, rat and mouse cancer cells (76). Cholesterol also facilitates metastasis by enhancing the resistance of metastatic cells to ferroptosis (77). Furthermore, elevated plasma LDLC levels positively correlate with the risk of lymphovascular invasion and metastasis in patients with breast cancer (78). These studies support the concept that dysregulated cholesterol metabolism is closely associated with cancer invasion and metastasis through multiple signaling pathways.

Consistent with the role of cholesterol in tumor invasion and metastasis, PCSK9 knockout mice show reduced metastasis of melanoma cells to the liver, accompanied by decreased hepatic LDLC concentrations due to increased expression of LDLR. This phenotype can be reversed by a 2-week high-cholesterol diet (HCD) in PCSK9-deficient mice, suggesting that the PCSK9-LDLR axis promotes tumor cell metastasis (64). In agreement with this finding, the PCSK9-LDLR axis has also been identified as a main target of oleuropein-mediated suppression of castration-resistant prostate cancer metastasis (79). A previous study reported that mechanical stretch enhances melanoma cell invasiveness by upregulating PCSK9 and LDLR, which reduces the cholesterol concentration in tumor cells, further implicating the PCSK9-LDLR axis in this process (80). Similar effects have been observed in lung cancer cells, where alirocumab, a monoclonal anti-PCSK9 antibody, increases intracellular cholesterol while decreasing invasiveness *in vitro* and metastasis *in vivo* (80) Furthermore, increased PCSK9 expression in lung tumors is associated with metastasis and unfavorable patient survival (80). Suh *et al* (81) showed that PCSK9 is required for pulmonary metastasis of melanoma cells in Ahnak knockout mice, as pulmonary metastasis of B16F10 cells is clearly reduced in lung epithelial cell-specific tamoxifen-induced PCSK9 conditional knockout mice. However, the precise molecular mechanisms by which PCSK9 deficiency suppresses melanoma cell metastasis in these models require further investigation.

By contrast, in GC, PCSK9 has been shown to enhance invasive ability, while PCSK9 knockdown inhibits tumor metastasis *in vitro* and *in vivo* by downregulating the HSP70-MAPK pathway (70). Similarly, PCSK9 deficiency reduces the migration and invasion of colon cancer cells *in vitro* and represses metastasis *in vivo* (6). Mechanistic studies further indicate that PCSK9 can promote metastasis of colon cancer by inducing EMT and activating the PI3K/Akt signaling pathway. Accordingly, high expression of PCSK9 in GC tissues correlates with poor patient survival (70). In HCC, PCSK9 expression is positively associated with microvascular invasion, promoting vascular dissemination and metastasis of tumor cells and contributing to poor survival outcomes (69). However, the molecular basis of PCSK9-driven invasion and metastasis in HCC remains to be elucidated.

PCSK9 has been identified as a key determinant of organotropism in pancreatic ductal adenocarcinoma (PDAC) metastasis (82). Low PCSK9 expression in liver-avid PDAC cells enhances LDLC uptake, leading to lysosomal cholesterol release and subsequent mTORC1 activation. Furthermore, PCSK9-low PDAC cells convert free cholesterol into oxysterols such as 24-hydroxycholesterol, which induces hepatocytes to synthesize and secrete LDLC, thereby creating a tumor-supportive metabolic niche that promotes PDAC cell colonization in the liver (82). By contrast, PCSK9-high PDAC cells predominantly rely on *de novo* cholesterol biosynthesis through the mevalonate, Bloch and Kandutsch-Russell pathways. The expression levels of enzymes involved in cholesterol biosynthesis are positively correlated with PCSK9 expression in human PDAC samples. Notably, intermediates of cholesterol biosynthesis, including 7-dehydrocholesterol and 7-dehydrodesmosterol, protect cancer cells from ferroptosis due to their antioxidant function (83). This adaptation allows lung-avid PDAC cells to resist oxidative stress, supporting their ability to metastasize to the oxygen-rich lung microenvironment (82). Consistently, patients with pancreatic cancer who exhibit PCSK9 expression have a significantly shorter overall survival (OS) (84).

In a Swedish breast cancer cohort, homozygotes for the PCSK9 rs562556 (V474I) GOF variant, exhibited a 22% risk of distant metastatic relapse at 15 years, compared with only 2% in non-homozygotes (85). Similar associations have been confirmed in multiple independent breast cancer cohorts. Of note, PCSK9 knockout mice exhibit reduced breast cancer lung metastasis compared with WT littermates under both HCD and regular chow conditions, whereas HCD modestly promotes lung metastasis in WT mice. These results suggest that the metastasis-suppressive effect of PCSK9 deficiency is not solely mediated by LDLC reduction (85). Further experiments found that PCSK9 promotes metastatic initiation and proliferative competence in the lung by targeting tumor LRP1 receptors, thereby repressing the metastasis suppressors XIAP-associated factor 1 and ubiquitin specific peptidase 18 (85). As expected, evolocumab, a monoclonal antibody against PCSK9, suppresses breast cancer metastasis in several mouse models. Conversely, exogenous PCSK9 treatment enhances the metastatic capacity of breast cancer cells, while depletion of XAF1 and USP18 abolishes this pro-metastatic effect. Altogether, these findings highlight the role of PCSK9 in promoting cancer metastasis through diverse signaling pathways.

PCSK9-related pathways and metabolic reprogramming. To sustain uncontrolled proliferation in environments limited in oxygen and nutrients, tumor cells often alter their metabolic programs, a phenomenon known as metabolic reprogramming. Cholesterol is synthesized intracellularly from acetyl-CoA through the mevalonate pathway, which involves key enzymes such as HMG-CoA reductase. Excess cellular cholesterol is eliminated via ABCA1 (86). Dysregulation of this pathway can lead to abnormal cholesterol accumulation, which contributes to multiple oncogenic processes, including tumor initiation, migration and angiogenesis (87). PCSK9 plays a critical role in cholesterol homeostasis and metabolic reprogramming primarily by regulating cholesterol uptake. For instance, increased PCSK9 expression promotes colorectal carcinogenesis by repressing cholesterol uptake, which in turn enhances cholesterol biosynthesis and leads to the accumulation of its intermediate, geranylgeranyl diphosphate (88). Importantly, inhibition of PCSK9 can be combined with statins, which are HMG-CoA reductase inhibitors, to suppress adenomatous polyposis coli/*KRAS*-mutant colorectal cancer *in vitro* and *in vivo*, providing a potential

therapeutic strategy for KRAS-mutant tumors. In prostate cancer, PCSK9 deficiency protects cancer cells from ionizing radiation-induced cell death, likely by regulating cholesterol levels in the TME (89). Accumulating evidence suggests that excess cholesterol is a key regulator of radiation resistance in tumor cells, highlighting the importance of cholesterol metabolic reprogramming in determining therapy response (90,91). Furthermore, PCSK9 can switch cancer cell metabolism between cholesterol import (when PCSK9 is low) and biosynthesis (when PCSK9 is high), thus impacting the organ preference of pancreatic cancer cells during metastasis (82). In liver cancer, PCSK9 deficiency increases the oxygen consumption rate and mitochondrial respiratory capacity, which allows mitochondria to produce more ATP (92). In parallel, PCSK9 deficiency enhances lipogenesis by increasing both lipid uptake and endogenous synthesis. These lipid droplets can further interact with mitochondria, forming peri-droplet mitochondria, which supply ATP for triacylglycerol synthesis (93). Furthermore, increasing lipid/lipoprotein uptake can enrich polyunsaturated fatty acids, which provide the essential elements for ferroptosis by being esterified into membrane phospholipids (94). Meanwhile, PCSK9 deficiency can result in increased production of phosphatidylethanolamine, further enhancing ferroptosis in tumor cells (94). Previous research has revealed that excessive lipid peroxidation induces ferroptosis in liver cancer cells mainly by inhibiting the anti-oxidant p62/kelch-like ECH-associated protein 1/nuclear factor erythroid 2-related factor 2 pathway (94). Although the precise link between PCSK9-mediated lipid dysregulation and this pathway requires further clarification, these findings support that PCSK9 inhibition triggers ferroptosis in both lipid-dependent and -independent manners. Therefore, excessive lipid accumulation can promote cell death, suggesting that PCSK9 targeting may be a therapeutic strategy in liver cancer by regulating lipid metabolism.

A previous Mendelian randomization study revealed that PCSK9 LOF variants are associated not only with reduced circulating LDLC levels but also with elevated fasting glucose and an increased risk of type 2 diabetes, suggesting a role for PCSK9 in glucose metabolism (95). Consistently, PCSK9 deficiency in the pancreas impairs insulin secretion, which is attributed to increased pro-insulin content and a reduced number of insulin granules in the readily releasable pool (96). These findings collectively support the involvement of PCSK9 in regulating glucose metabolism. Given the established importance of glucose reprogramming in carcinogenesis, further investigation is warranted to determine whether PCSK9-related glucose metabolic reprogramming contributes to cancer development.

PCSK9-related pathways and angiogenesis. The formation of new blood vessels, known as tumor angiogenesis, supplies essential nutrients and oxygen to primary tumor cells, and facilitates their dissemination to both adjacent and distant organs. This process is mainly driven by various angiogenic factors, including vascular endothelial growth factor (VEGF) and platelet-derived growth factor, which are closely associated with tumor progression and metastasis (97). Accumulating evidence highlights that cholesterol metabolism also plays an important role in angiogenesis. For instance, statins, which inhibit cholesterol synthesis, suppress tumor angiogenesis by reducing VEGF levels, thereby inhibiting tumor growth (98).

The role of PCSK9 in angiogenesis is increasingly recognized. Overexpression of PCSK9 in human umbilical vein endothelial cells (HUVECs) inhibits angiogenic processes, as evidenced by impaired tubule formation and delayed wound healing in functional assays. Conversely, silencing PCSK9 restores angiogenic capacity (99). Bioinformatic analysis further suggests that PCSK9 regulates angiogenesis through six hub genes, namely matrix metallopeptidase 9, caspase-3, early growth response 1, nerve growth factor receptor, left-right determination factor 1 and NODAL. Consistently, PCSK9 overexpression represses the expression of these genes, while PCSK9 deficiency upregulates them. Furthermore, hiPSCs carrying the PCSK9-S127R GOF mutation show altered expression of multiple genes involved in vasculature development (99). In line with these findings, pharmacological inhibition of PCSK9 using evolocumab enhances HUVEC migration, and increases both tubule length and size (100). Treatment with evolocumab at 10 μg/ml also significantly increases VEGF release into the supernatant of HUVECs, further supporting an inhibitory role of PCSK9 in angiogenesis.

Similarly, in a colorectal cancer liver metastasis mouse model, treatment with evolocumab alone significantly attenuated the development of MC38 tumor cell metastasis *in vivo* and prolonged survival (101). While anti-angiogenic therapy targeting VEGF is largely ineffective in repressing metastasis in this model, its combination with evolocumab markedly suppresses the metastatic burden, underscoring the importance of PCSK9 in tumor angiogenesis. Further mechanistic studies revealed that evolocumab inhibits the expression of runt-related transcription factor 1 in metastatic niches, thereby delaying tumor growth (101). In HCC, increased PCSK9 activity induced by palmitoylation was shown to confer resistance to the anti-angiogenic drug sorafenib through activation of the PI3K/Akt signaling pathway (42). Together, these findings highlight PCSK9 as a critical regulator of tumor angiogenesis and a potential target for enhancing the efficacy of existing anti-angiogenic therapies.

PCSK9-related pathways and immune evasion. Immune evasion is a hallmark of cancer, which allows tumor cells to evade immune surveillance and destruction, thereby promoting tumor progression and metastasis (102). Accumulating evidence suggests that aberrant cholesterol metabolism contributes to tumor immune evasion. Indeed, elevated cholesterol levels are considered a critical causative factor of pro-inflammatory microenvironments, highlighting the important role of cholesterol in regulating immune cell function (103). Tumor cells often elevate cholesterol metabolism to generate an immunosuppressive microenvironment, characterized by an increase in regulatory T cells (Tregs) and M2-type macrophages. On the other hand, inhibition of cholesterol metabolism results in a higher abundance of $CD8^+$ cytotoxic T cells and M1-type macrophages (104). In addition, different types of immune cells release cholesterol to mediate tumor progression. For instance, tumor-associated macrophages (TAM) produce cholesterol to regulate tumor cell

metabolism and myeloid-derived suppressor cells (MDSCs) elevate cholesterol levels by consuming essential metabolites such as L-arginine, thereby suppressing T-cell proliferation and activation (105). Elevated cholesterol in the TME also impairs the migration and antigen-presenting capacity of dendritic cells (DCs). These findings collectively underscore the important role of cholesterol metabolism in tumor immune evasion and progression (Fig. 4).

Yuan *et al* (106) reported that inhibition of PCSK9 in tumor cells reshapes cholesterol metabolism within the TME, which promotes the priming and clonal expansion of $CD8^+$ T cells. This effect can be reversed by suppressing LDLR in $CD8^+$ T cells, indicating that these cells sense extracellular cholesterol levels through LDLR. It should be noted that the regulation of cytotoxic T-lymphocyte effector function by LDLR is not exclusively dependent on cholesterol availability, as the increase in plasma membrane cholesterol does not rescue the LDLR deficiency-induced reduction in cytotoxic factors such as IFN-γ, TNF-α and granzyme B (GzmB). Further mechanistic studies revealed that LDLR interacts with the T-cell receptor (TCR) complex to mediate TCR recycling and signaling, thus facilitating the effector function of cytotoxic T-lymphocytes. Therefore, PCSK9 inhibition in tumor cells reinforces the anti-tumoral activity of $CD8^+$ T cells via the LDLR/TCR axis (106).

Accumulating evidence has established the critical role of PCSK9 in immunological homeostasis. For instance, disruption of PCSK9 suppresses inflammation by upregulating histone deacetylase sirtuin 1 and inhibiting NF-κB inflammatory signaling (107). Macchi *et al* (108) reported that dysregulation of the JAK-STAT3 signaling pathway in a chronic inflammatory environment enhances PCSK9 expression. Another study reported that PCSK9 mediates the proliferation, differentiation and apoptosis of immune cells, including $CD4^+$/$CD8^+$ T cells, macrophages and Tregs (109). In Tohoku Hospital pediatrics-1-derived macrophages, stimulation with oxidized LDL increases PCSK9 expression in a dose-dependent manner, which subsequently induces the secretion of inflammatory cytokines such as IL-1α, IL-6 and TNF-α via activation of the NF-κB signaling pathway (110). Therefore, PCSK9 deficiency inhibits oxidized LDL-induced inflammation by reducing the degradation of IκB-α, the endogenous inhibitor of NF-κB. Consistently, when THP-1 macrophages are co-cultured with HepG2 cells overexpressing human PCSK9, macrophages exhibit elevated expression of TNF-α and IL-1β (111). Since LDLR deficiency impairs the PCSK9-driven inflammatory response in bone marrow-derived macrophages, it appears that PCSK9 promotes macrophage inflammation primarily through its classical substrate, LDLR (111). Wang *et al* (112) reported that PCSK9 regulates macrophage polarization via the Toll-like receptor (TLR4)/MyD88/NF-κB axis in an acute myocardial infarction mouse model, with PCSK9 knockout attenuating inflammatory cell infiltration compared with WT mice. In line with this, the TLR4-NF-κB axis is critical for the pro-inflammatory role of PCSK9 in human macrophages (113). However, increased expression of PCSK9 also elevates pro-inflammatory factors, such as IL-1β and TNFα, in peritoneal macrophages from $LDLR^{-/-}$ mice, indicating that PCSK9 can regulate macrophages via LDLR-independent mechanisms (114).

Beyond macrophages, Liu and Frostegård (115) reported that oxidized LDL induces PCSK9 expression in DCs, promoting their maturation, as indicated by increased expression of CD80, CD83 and HLA-DR. Although mature DCs typically stimulate naïve T cells, PCSK9 knockdown in DCs suppresses T helper (Th)1 and Th17 polarization, while increasing Treg differentiation. Furthermore, PCSK9 may directly regulate Th17-cell proliferation and differentiation, as elevated serum PCSK9 levels correlate positively with Th17 cells and IL-17 in patients with ankylosing spondylitis and rheumatoid arthritis (116).

During carcinogenesis, PCSK9 has been increasingly reported to play a role in immune regulation. For example, Liu *et al* (44) demonstrated that PCSK9 promotes the lysosome-mediated degradation of MHC-I in breast cancer, colorectal cancer and melanoma cells. Inhibition of PCSK9 enhances the infiltration of $CD8^+$ T, $CD4^+$ Th and natural killer cells, suppressing tumor progression by increasing the production of cytokines such as IFN-γ and GzmB. These findings indicate that PCSK9 inhibition substantially attenuates tumor growth by counteracting cytotoxic T cell-mediated immune evasion.

Other studies have reported that PCSK9 overexpression decreases the membrane abundance of programmed cell death ligand 1 (PD-L1), while PCSK9 deficiency leads to PD-L1 accumulation, indicating that PCSK9 regulates PD-L1 expression via lysosomal degradation (117). Accordingly, PCSK9 inhibition suppresses immune evasion in pancreatic cancer cells, thereby decreasing tumor growth and prolonging survival (117). Notably, PCSK9 deficiency increases PD-L1 expression more markedly than MHC-I expression in PDAC cell lines (117). PCSK9 expression has also been linked to limited efficacy of anti-programmed cell death 1 (PD-1) therapy in patients with advanced non-small cell lung cancer (NSCLC) (118). Patients with low PCSK9 expression showed significantly longer survival than those with high expression, underscoring the deleterious effect of PCSK9 on lung cancer progression. Consistent with this, combining a PCSK9 inhibitor with an anti-CD137 agent exerts stronger antitumor effects in a Lewis lung cancer mouse model than either inhibitor alone. Further analysis demonstrated an increase in cytotoxic $CD8^+$ T cells and a reduction in Tregs in the combination group, indicating that PCSK9 inhibition can enhance the efficacy of immunotherapy (118). Notably, Wang *et al* (119) reported that PD-1 blockade induces upregulation of PCSK9 in a colorectal cancer model. Therefore, PCSK9 inhibition during anti-PD-1 therapy produces a synergistic antitumor effect in colorectal cancer by promoting $CD8^+$ T-cell infiltration and excluding Tregs, highlighting its potential to improve the efficacy of anti-PD-1 immunotherapy. In melanoma, PCSK9 has been proposed as a biomarker to predict responses to immune checkpoint blockade (ICB), such as anti-PD-1 therapy (120), further supporting its crucial role in tumor immune evasion. In a syngeneic mouse model using the 4MOSC1 head and neck squamous cell carcinoma (HNSCC) line, PCSK9 inhibition increased $CD8^+$ T-cell infiltration and reduced MDSCs in the TME, thereby suppressing tumor growth (121). Furthermore, PCSK9 inhibition reinforces the antitumor effect of anti-PD-1 blockade in this mouse model. The authors also observed that higher PCSK9 expression predicts poorer prognosis in patients

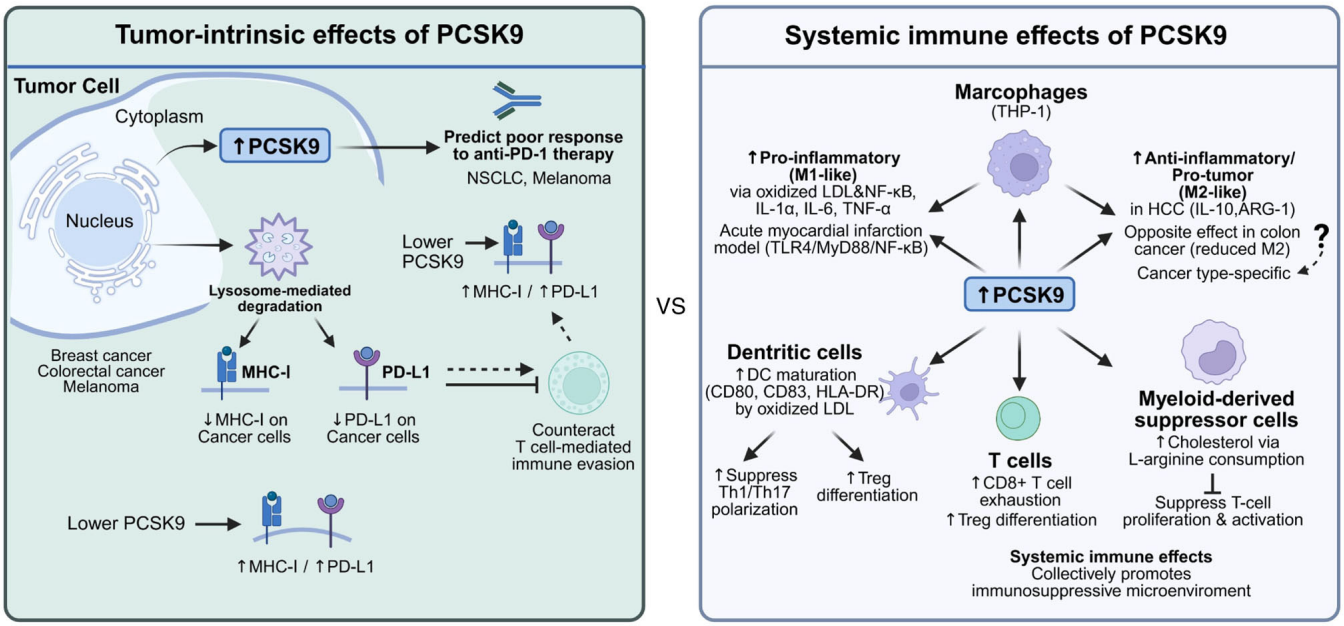

Figure 4. Detailed regulatory mechanisms of PCSK9 in the tumor immune microenvironment. PCSK9 exerts diverse regulatory effects within the tumor immune microenvironment. The tumor-intrinsic effects of PCSK9 are illustrated in the left panel, whereas the systemic immune effects of PCSK9 are presented in the right panel. The figure was created with BioRender (https://www.biorender.com/). Arrows indicate activating effects, while blunt-ended lines indicate inhibitory effects. PCSK9, proprotein convertase subtilisin/kexin type 9; MHC-I, major histocompatibility complex I; PD-L1, programmed death-ligand 1; NSCLC, non-small cell lung cancer; HCC, hepatocellular carcinoma.

with HNSCC. Consistently, PCSK9 inhibition decreased cholesterol levels in this model, indicating that PCSK9 regulates tumor immune evasion in an LDLR-dependent manner. These studies imply that PCSK9 mediates immune evasion in tumor cells via multiple protein targets.

On the other hand, a long-term high-fat diet induces the accumulation of hepatic free cholesterol and cholesterol crystals in PCSK9-knockout mice. This leads to enhanced formation of crown-like structures in CD68-positive macrophages by increasing the hepatic expression of inflammation-related genes such as TNF and NLR family pyrin domain containing 3 (122), thereby creating a pro-inflammatory microenvironment that promotes liver tumor growth. Despite this systemic effect, PCSK9 expression is reduced in tumor tissues compared with adjacent tissues in patients with HCC (123). When Huh7 cells with PCSK9 deficiency were co-cultured with THP-1 macrophages, the macrophages showed increased expression of M2 markers such as IL-10 and arginase 1. Conversely, overexpression of PCSK9 in MHCC97H cells suppressed THP-1 macrophage migration and M2-like TAM polarization, inhibiting the formation of a tumor-promoting immune microenvironment (123). By contrast, a different effect was observed in colon cancer models, as the co-culture of PCSK9-deficient HCT116 and HT29 human colon cancer cells with THP-1 macrophages reduced M2-like TAM polarization but promoted M1-like polarization by decreasing lactate levels, protein lactylation and macrophage migration inhibitory factor expression (6). Furthermore, Mei *et al* (85) demonstrated that depleting tissue-resident macrophages has no effect on breast cancer metastasis in PCSK9-knockout mice, indicating that PCSK9 does not influence TAM polarization or function in this context. The mechanisms underlying these discrepant findings require further investigation, but may indicate that the immunomodulatory effects of PCSK9 are cancer type-specific (Fig. 4).

5. Clinical application of PCSK9 inhibition in cancer

Clinical trials targeting PCSK9. Given the important role of PCSK9 in carcinogenesis, targeting PCSK9 is considered a promising therapeutic strategy for cancer. Several clinical trials have been initiated to explore this potential across different cancer types (Table II). For instance, plasma PCSK9 levels are associated with the severity of advanced breast cancer (124), indicating the potential of PCSK9 inhibitors to enhance antitumor immune responses. In NSCLC, low serum PCSK9 levels (<95 ng/ml) predict an improved response to anti-PD-1 therapy and are associated with improved OS in Italian patients, when compared with those with high PCSK9 levels (>120 ng/ml) (125). Similarly, Xie *et al* (126) reported that low baseline plasma PCSK9 levels predict a favorable prognosis in patients with advanced NSCLC treated with immune checkpoint inhibitors (ICI), including anti-PD-1 therapy. However, in a Chinese patient cohort, the optimal prognostic threshold for serum PCSK9 was identified as 232.2 ng/ml. This discrepancy may be associated with differences in ethnicity, age or sex, as serum PCSK9 levels are known to be influenced by these factors (127). Such variations in baseline PCSK9 levels likely affect the optimal threshold for predicting ICI efficacy, although the underlying causes remain to be elucidated. However, these findings support the potential of combining PCSK9 inhibition with anti-PD-1 therapy in NSCLC. In fact, several additional clinical trials are underway in NSCLC. For example, tafolecimab, a recombinant fully humanized monoclonal antibody against PCSK9, is currently being evaluated in

Table II. Clinical trials of PCSK9-related therapies in cancer.

Interventions	Cancer type	Phase	Country	Status	NCT ID
PCSK9 inhibitor	Colorectal cancer with pMMR/MSS	II	China	Not yet recruiting	06391905
PCSK9 inhibitor + PD-1 inhibitor + chemoradiotherapy	Rectal cancer with pMMR/MSS	II	China	Active, not recruiting	06933251
CRT + PD-1 inhibitor + Tafolecimab	pMMR/MSS locally advanced middle and low rectal cancer	II	China	Not yet recruiting	06304987
Alirocumab + PD-1 inhibitor	NSCLC	II	USA	Active, not recruiting	05553834
Recaticimab + PD-1 inhibitor	Metastatic biliary tract carcinoma	II	China	Not yet recruiting	07062328
HMG-CoA inhibitor + NPC1L1 inhibitor + Evolocumab	Advanced or metastatic pancreatic adenocarcinoma	I	Canada	Active, not recruiting	04862260
VEGF inhibitor + Tafolecimab	IIIB-IIIC/IV NSCLC	III	China	Not yet recruiting	07014215
Tafolecimab + PD-1 inhibitor + chemotherapy	ES-SCLC	II	China	Not yet recruiting	07061535
Evolocumab + statin therapy	Pan-cancer	IV	China	Not yet recruiting	05976893
PD-1 inhibitor + JS002	Pan-cancer	I	China	Terminated	05128539

Tafolecimab, Alirocumab, Recaticimab, Evolocumab and JS002: Anti-PCSK9 monoclonal antibodies. PCSK9, proprotein convertase subtilisin/kexin type 9; PD-1, programmed cell death 1; pMMR, proficient mismatch repair; MSS, microsatellite stable; CRT, chemoradiotherapy; NSCLC, non-small cell lung cancer; HMG-CoA, β-hydroxy-β-methylglutaryl-coenzyme A; NPC1L1, Niemann-pick c1-like 1; VEGF, vascular endothelial growth factor; ES-SCLC, extensive-stage small cell lung cancer.

combination with ICBs in various lung cancer types, including NSCLC (NCT06385262, NCT07014215 and NCT05553834) and SCLC (NCT07061535 and NCT07014215). The preliminary results of these trials have not yet been published.

Furthermore, several clinical trials are investigating whether combining PCSK9 inhibitors with standard treatments can improve therapeutic outcomes in patients with advanced mismatch repair-proficient or microsatellite stable colorectal cancer (NCT06391905, NCT06304987 and NCT06933251). In addition, an anti-PCSK9 antibody is being evaluated in combination with standard chemotherapy for metastatic PDAC to assess the feasibility and acceptability of this strategy (NCT04862260). For patients at a markedly high risk of both atherosclerotic cardiovascular disease and cancer, another trial aims to determine whether PCSK9 inhibition can reduce the risk of cardiovascular mortality, recurrent unstable angina, myocardial infarction, stroke or coronary revascularization (NCT05976893). Although these trials are still ongoing, a retrospective study supports that PCSK9 inhibitors can clearly reduce both cardiovascular disease and cancer mortality, thereby prolonging OS among patients with cancer (128). However, a Mendelian randomization study by Wang *et al* (129) reported that PCSK9 inhibitors could cause divergent effects among patients with cancer. In breast and lung cancer, PCSK9 inhibition is beneficial for patients. By contrast, PCSK9 inhibition exacerbates clinical outcomes among patients with gastric, hepatic and oropharyngeal cancer. Although these ongoing clinical trials support PCSK9 as a promising therapeutic target in cancer treatment, optimizing the benefit of this strategy for patients with cancer will require further clinical studies.

PCSK9 functions as a biomarker for cancer diagnosis, prognosis and treatment response. Since altered expression of PCSK9 has been observed in various malignancies, elevated circulating PCSK9 can distinguish malignant from benign lesions. In pancreatic cancer, high serum PCSK9 levels reflect worse OS compared with low serum PCSK9 levels, indicating the diagnostic potential of serum PCSK9 for patients with early-stage pancreatic cancer (84). When combined with CA19-9, the diagnostic performance of serum PCSK9 is further improved. Similarly, the diagnostic potential of serum PCSK9 levels was observed in women with stage III breast cancer (130). Serum PCSK9 levels positively correlated with breast disease severity, supporting the important role of serum PCSK9 in diagnosing breast cancer. Similarly, PCSK9 expression positively correlated with pathohistological grading and hormone receptor status in patients with HER2-positive breast cancer.

Beyond its diagnostic value, higher PCSK9 expression was associated with a worse response to neoadjuvant therapy in these patients, indicating the prognostic potential of PCSK9 in patients with cancer (131). Sun *et al* (132) further demonstrated the prognostic value of PCSK9 in pan-cancer, as evidenced by its positive correlation with immune infiltrates in the TME. Notably, serum anti-PCSK9 antibody levels reflected improved OS prognosis after surgery in patients with esophageal cancer (133). These findings support that PCSK9 could be a biomarker for cancer diagnosis and prognosis. Besides, in patients with NSCLC treated with PD-1 immunotherapy, Wood *et al* (134) found that patients with higher PCSK9 levels had worse progression-free survival compared with those with

low PCSK9 levels, a finding that could result from increased $CD8^+$ and $GzmB^+$ $CD8^+$ T cells and reduced Tregs (118), supporting that serum PCSK9 levels could be a biomarker for PD-1 immunotherapy response among patients with NSCLC. Consistently, the combination of PCSK9 inhibitors with PD-1 inhibitors resulted in stronger antitumor activity compared with PD-1 inhibitors alone in pancreatic cancer (117). A previous study also reported that PCSK9 deficiency caused downregulation of Nrf2, which was associated with conferring cellular resistance to chemotherapeutic drugs such as sorafenib in liver cancer (94), suggesting an indirect connection between PCSK9 expression and sorafenib resistance. Sun *et al* (42) further reported that PCSK9 palmitoylation enhances the interaction between PCSK9 and PTEN, which induces PTEN to enter lysosomes for degradation and Akt activation, decreasing the antitumor effects of sorafenib in HCC. Therefore, PCSK9 is a potential biomarker for sorafenib treatment response. However, whether PCSK9 can be a biomarker for other cancer treatments such as chemotherapy and radiotherapy still needs to be further evaluated.

6. Discussion and future perspectives

PCSK9, the most recently identified member of the PCSK family, is currently the only family member with a clinically approved therapeutic application, namely in the treatment of hypercholesterolemia. This is based on its canonical role in mediating the lysosomal degradation of LDLR. However, accumulating evidence suggests that PCSK9 also targets other substrates, including MHC-I and LRP1, thereby implicating it in diverse pathological processes such as sepsis (135) and Alzheimer's disease (136). Whether PCSK9 exhibits substrate-binding preferences that dictate its functional roles in different disease contexts remains elusive, but represents a critical question for understanding its broader physiological importance. For instance, while PCSK9 deficiency has been reported to suppress tumor growth by preventing MHC-I degradation (44), it remains unclear why PCSK9 does not concurrently regulate LDLR degradation in the same tumor cells. Therefore, systematic identification of new PCSK9 substrates across the human proteome will be essential to fully elucidate its mechanistic contributions to both physiological and pathological processes, which would advance the current understanding of its role in cancer.

Carcinogenesis is a multistep process driven by several abnormal physiological features, known as the hallmarks of cancer, which provide ideal targets for therapy. The present review highlighted the role of PCSK9 in five key hallmarks of cancer, including sustaining proliferative signaling, invasion/metastasis, metabolic reprogramming, angiogenesis and immune evasion. However, cancer cells exhibit additional hallmarks, such as non-mutational epigenetic reprogramming and polymorphic microbiomes (137), and whether PCSK9 contributes to these features remains to be determined. Although PCSK9 may not directly regulate every hallmark, it influences the degradation of >10 proteins, some of which are critically involved in these processes. PTEN serves as a prime example, as its deletion not only promotes epigenetic reprogramming in prostate cancer (138) but also disrupts gut microbiome homeostasis (139). Determining whether PCSK9 regulates these carcinogenic properties through such substrates will be essential for a comprehensive understanding of its role in tumor biology. It should also be noted that a single PCSK9 substrate can influence multiple hallmarks. For instance, LDLR, through cholesterol modulation, not only promotes cell proliferation but also regulates angiogenesis (87,140). Thus, dissecting the specific contributions of PCSK9 substrates to different hallmarks of cancer will be crucial to unravel the multifaceted role of PCSK9 in carcinogenesis.

Since multiple PCSK9 substrates have been identified *in vivo*, PCSK9 inhibition could cause various unexpected side effects. Thus far, several clinical trials have reported PCSK9 inhibitor-related adverse effects, including neurocognitive impairment, diabetes-related complications and statin-associated muscle symptoms (141). For example, the ODYSSEY trial, an open-label extension that continued to evaluate the long-term safety and efficacy of a PCSK9 inhibitor in patients with heterozygous familial hypercholesterolemia, showed that 1.7% of the enrolled patients reported neurocognitive adverse events, of which 0.5% were serious adverse events, including moderate dementia (142). Therefore, reducing these side effects would likely contribute to improving clinical outcomes for patients with cancer.

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Authors' contributions

LT conceived the study and wrote the manuscript with contributions from ZH, SY and YZ. The figures of the manuscript were conceived and designed by ZH. BRM and YX contributed to designing the study, writing/revising the manuscript, acquiring the funding and supervision. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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