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REVIEW

PCSK9 Manipulates Lipid Metabolism and the Immune Microenvironment in Cancer

Chaochu Cui[1,*], Aiwei Yan[1,*], Shengming Huang[1,2], Yifan Chen[1], Jinyu Zhao[1], Cixia Li[1,3], Xianwei Wang[1], Jianbo Yang[1,4]

[1]Henan Key Laboratory of Medical Tissue Regeneration, Xinxiang Medical University, Xinxiang, Henan, People's Republic of China; [2]Rudong County Hospital of Traditional Chinese Medicine, Nantong, Jiangsu, People's Republic of China; [3]School of Life Sciences and Technology, Xinxiang Medical University, Xinxiang, Henan, People's Republic of China; [4]School of Medical Technology, Xinxiang Medical University, Xinxiang, Henan, 453003, People's Republic of China

*These authors contributed equally to this work

Correspondence: Xianwei Wang; Jianbo Yang, Email Wangxianwei1116@126.com; Yangjianbo12@126.com

Abstract: Cancer remains the foremost cause of mortality on a global scale. Immunotherapy has yielded remarkable outcomes in the fight against cancer and is regarded as one of the most crucial and promising therapeutic modalities. PCSK9, a critical target for plasma lipids control, has been extensively and deeply studied in multiple diseases. Currently, the functions of PCSK9 in cancer, particularly its immunomodulatory role, have been progressively revealed. PCSK9 is capable of modulating a variety of immune response throughout tumor progression by orchestrating lipid metabolism. Moreover, PCSK9 governs the cell fate of diverse immune cells, such as inflammatory factor signals, MHC signals, and TCR signals. This review comprehensively summarizes the current state of knowledge regarding the role and underlying mechanisms of PCSK9 in tumorigenesis, progression, immune escape, and drug resistance.

Keywords: PCSK9, lipid metabolism, immunotherapy, cancer

Introduction

Cancer is still a leading cause of mortality worldwide, and immunotherapy has achieved notable success in cancer treatment by modulating the function of the human immune system.[1] Abnormal lipid metabolism plays critical roles in cancer cells and the immune response in the progression of malignant tumors.[2] Dysregulation of lipid metabolism enables tumor cells to obtain the energy necessary for proliferation, invasion and the formation of favorable tumor microenvironment (TME). Furthermore, lipid metabolism disorders may impede immune cell function, thereby impacting the efficacy of immunotherapy.[3–5]

Dysregulation of PCSK9 has been observed in a multitude of different cancers and affects the proliferation, invasion and drug resistance of tumor cells.[6] PCSK9 is essential for regulating lipid metabolism, apoptosis, immune cell signaling, etc.[7–10] As a soluble secreted serine protease that is synthesized primarily in the liver, PCSK9 functions through interactions with the low-density lipoprotein (LDL) receptor and CD36, thereby affecting cholesterol homeostasis, which may in turn be implicated in oncogenesis.[11]

In addition to affecting lipid metabolism, PCSK9 also regulates cuproptosis, which is essential in TME. Cuproptosis correlates with immunosuppressive tumor microenvironment based on pan-cancer multiomics and single-cell sequencing analysis, Evolocumab attenuates myocardial ischemia/reperfusion injury by blocking PCSK9/LIAS-mediated cuproptosis of cardiomyocyte.[12] Besides, PCSK9 manipulates TME immune cells through a range of pathways, including MHC and PD-1 signaling. PCSK9 binds to MHC-I and then recruits adaptor proteins, which facilitate the internalization of the MHC-I, impeding the ability of cytotoxic T cells to recognize and eliminate tumor cells. PCSK9 may suppress the production of cytokines by T cells, which are essential for the anti-tumor immune response.[13] This can influence

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processes such as monocyte differentiation, DC maturation, and T-cell and natural killer cell functions.[14] In the context of cancer, PCSK9 inhibitors can reverse the immunosuppressive effects of PCSK9 or displayed synergistic anti-tumor effects with immune checkpoint inhibitors, or even overcome therapy resistance in some cancers.[15–17] This review aims to comprehensively summarize the current research progress of PCSK9 in tumor immunotherapy, covering its molecular mechanisms in immune pathways and specific impacts on different cancer types.

Lipid Metabolism Regulates Immunity

Lipid metabolism is a primary energy supply of immune cells. It has been demonstrated that lipids regulate the proliferation and differentiation of immune cells. For example, following the activation of lymphocytes, there is a rapid increase in cholesterol and fatty acid synthesis to accommodate the demands of rapid proliferation and differentiation.[18,19] An increase in membrane cholesterol specifically promotes the differentiation of CD4+ T cells into the Th1 phenotype.[3] The inhibition of HMG-CoA reductase, an enzyme crucial for cholesterol synthesis, can suppress the proliferation of immune cells through mitogen activation.[20,21]

Moreover, lipids play vital roles in the structure and function of immune cell membranes, such as establishing immune synapses, which exerts a direct influence on TCR signal transduction that then affects immune cell activity.[22,23] In T cells, activation and effector functions are facilitated by specialized signal centers located in the cytoplasmic membrane, which are composed of cholesterol and sphingolipids. CD8+ T cells constitute one primary mechanism by which the immune system combats cancer cells, with their proliferation and effector functions closely associated with cholesterol levels.[23–26] Inhibition of ACAT1, the main enzyme involved in cholesterol esterification in CD8+ T cells, leads to an increase in the cholesterol content of CD8+ T-cell membranes and increased TCR clustering and signal transduction. This ultimately results in increased production of cytotoxic granules and cytokines by CD8+ T cells, along with increased cytotoxic capacity. Such enhancements facilitate the establishment of mature immune synapses and bolster the antitumor activity of CD8+ T cells.[27–29]

Macrophages combat pathogens primarily through phagocytosis, a process involving the dynamic fusion and division of cellular membranes. Upon exposure to inflammatory stimuli, macrophages increase lipid synthesis through the activation of the mTOR pathway and increase sterol regulatory element-binding protein (SREBP) 1a activity, thereby increasing phagocytic ability. [30,31] Moreover, during atherogenesis, monocytes differentiate into macrophages in the subendothelial space and internalize oxidized LDL (oxLDL) through scavenger receptors such as SR-A and CD36. [32] Inhibiting cholesterol synthesis has been demonstrated to diminish macrophage-driven inflammation. [33–35] NFATc3 deficiency in macrophages potentiates SR-A- and CD36-mediated lipid uptake, both of which are targeted by PCSK9, thereby reducing the development of atherosclerotic plaques. [36]

Additionally, elevated cholesterol levels can activate NK cells, which can effectively eliminate liver cancer cells.[37] Following NK cell activation, there is an upregulation of intracellular SREBP and mTORC1, which enhances aerobic glycolysis and OXPHOS metabolic rates. However, excessive fatty acid uptake by cells can activate the PPAR-γ/PPARδ signaling pathway, which has been demonstrated to not only inhibit NK cell functions but also induce cellular toxicity.[38] Therefore, an appropriate lipid level is conducive to the killing function of NK cells.

PCSK9 Manipulates Lipid Metabolism

It is widely accepted that PCSK9 is critical for maintaining lipid metabolism homeostasis.[39] PCSK9 is synthesized primarily in hepatocytes, which are the major source of PCSK9 in circulating blood. While some PCSK9 can be synthesized in the kidney, intestine, macrophages, and endothelial cells, this type of PCSK9 is considered to be used primarily for autocrine or intracellular functions.[40] The structure of PCSK9 consists of a signal peptide, a precursor domain, a catalytic domain and a carboxyl terminal domain. The zymogen PCSK9 (approximately 74 kDa) undergoes self-catalyzed cleavage, resulting in the maturation of PCSK9 (approximately 60 kDa), which is then secreted into the extracellular space. PCSK9 has a variety of biological functions, such as regulating plasma lipid homeostasis, liver regeneration, insulin production, neurodevelopment, cardiovascular diseases and the tumor immune response.[41–46]

PCSK9 influences lipid metabolism primarily in diverse manners (Figure 1). PCSK9 can promote the endocytosis and degradation of LDL receptors (LDLRs), thereby inhibiting the clearance of LDLC from the blood.[47] PCSK9 also

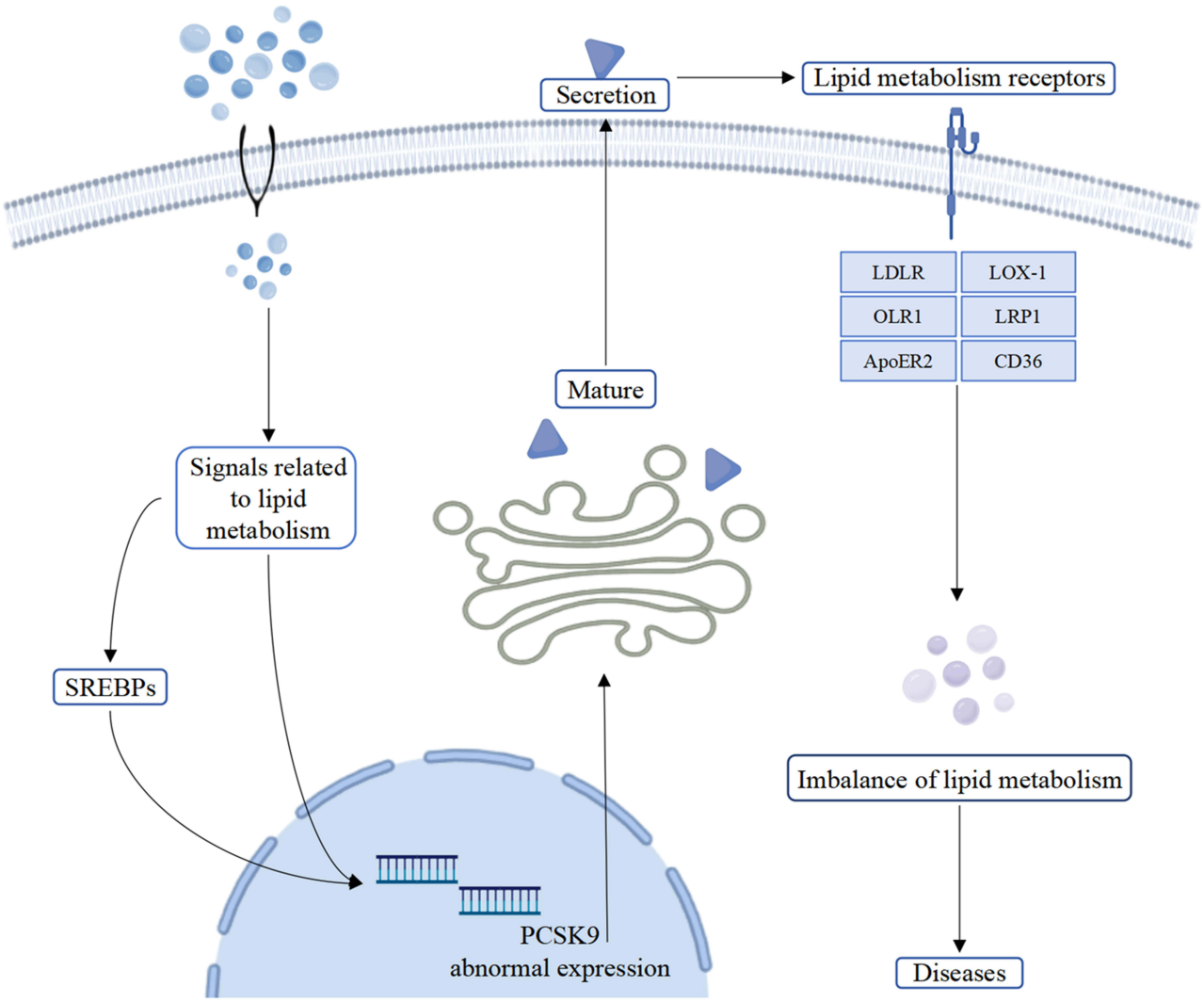

Figure 1 The mechanism by which PCSK9 regulates lipid metabolism. The level of PCSK9 on the cell surface is influenced by blood cholesterol levels. After undergoing maturation through Golgi modifications, PCSK9 becomes active on the cell membrane surface. It then binds to the low-density lipoprotein receptor (LDLR) and facilitates its degradation via lysosomal pathways. Additionally, PCSK9 plays a role in modulating the expression of SREBP-2, ApoER2, and HMG-CoA reductase, thereby impacting the accumulation of lipids within cells.

upregulates the expression of lectin-like oxidized low-density lipoprotein receptor 1 (LOX-1), promoting the uptake of oxidized low-density lipoprotein cholesterol (ox-LDLC) by macrophages.[48] Furthermore, SREBPs serve as crucial transcription factors that govern lipid metabolism. These proteins play pivotal roles by modulating PCSK9, which in turn impacts the synthesis of cholesterol and fatty acids. Consequently, the regulation of PCSK9 by SREBPs can lead to an increase in lipid levels.[49] Moreover, PCSK9 regulates the expression of apolipoprotein E receptor 2 (ApoER2), low-density lipoprotein receptor-associated protein 1 (LRP1), and oxidized low-density lipoprotein (lectin-like) receptor 1 (OLR1), which are proteins with central roles in lipid metabolism, thus mediating neuronal cell death. Therefore, PCSK9 is an important target for the treatment of LDL-mediated cell dysregulation.[50,51] Since the discovery that PCSK9 is related to lipid metabolism, PCSK9 has quickly become a research target for the treatment of diseases.[52–54]

PCSK9 Mediated-Immune Response

Interestingly, it was recently demonstrated that PCSK9 is also a promising target for cancer therapy.[13,55] Investigations have revealed diverse immunomodulatory capabilities of PCSK9 through modulation of the expression of cytokines or immune signal transduction proteins (Figure 2 and Table 1).

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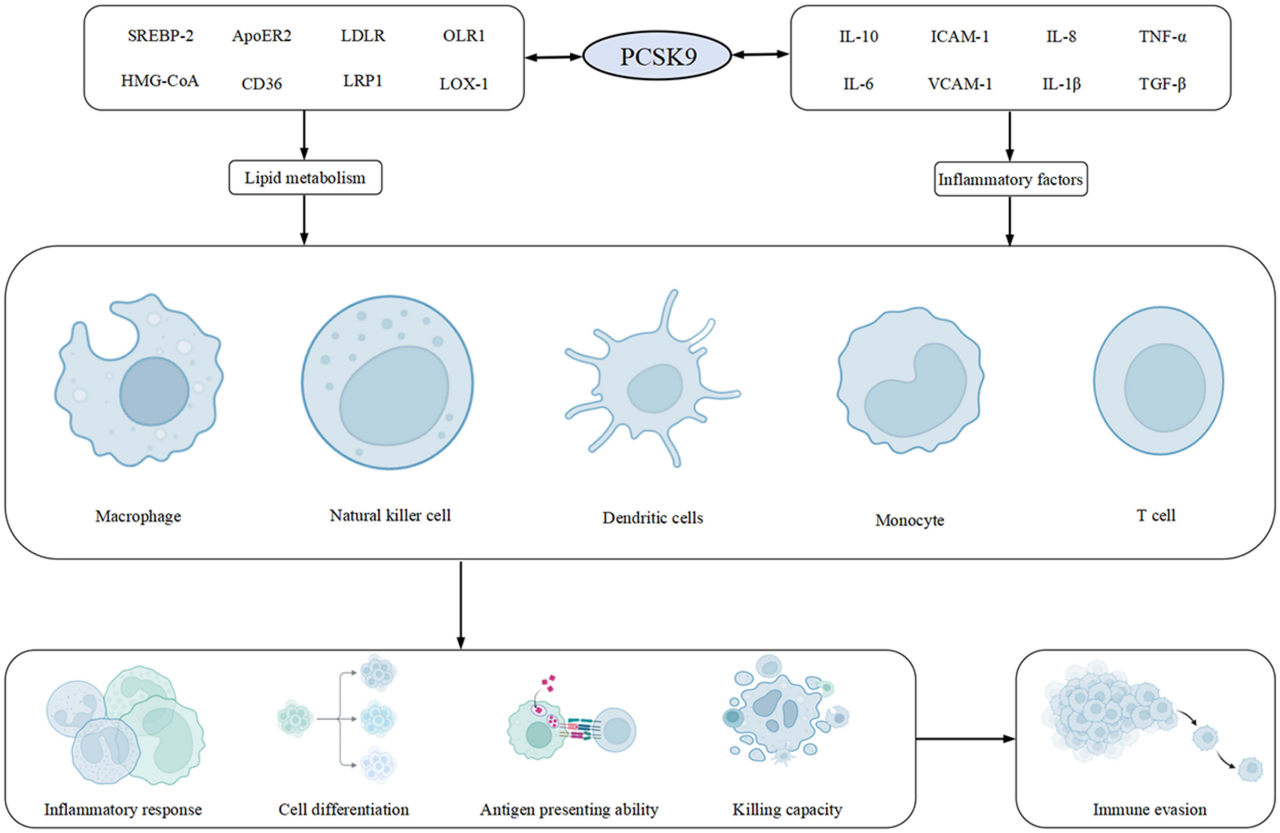

Figure 2 The role of PCSK9 in the immune response. The role of PCSK9 in the immune response influences the immune response in the tumor microenvironment and the differentiation, antigen presentation and killing ability of a variety of immune cells by interacting with many lipid metabolism-related molecules and inflammatory factors.

PCSK9 Regulates Inflammation

PCSK9 has been found to regulate nonspecific immune responses. During viral infections, PCSK9 levels increase, resulting in the induction of localized inflammatory reactions by modulating various inflammatory mediators.[8] In certain cell types and under specific physiological or pathological conditions, PCSK9 can promote inflammation. Elevated PCSK9 levels can increase the incidence of liver cancer in hepatitis patients.[9,56] Moreover, monoclonal antibodies (mAbs) targeting PCSK9 significantly alter the expression of the chemokine receptors CX3CR1, CXCR6, and CCR2 on certain leukocyte subsets. Concurrently, the plasma levels of the proinflammatory cytokine TNF-α are reduced, whereas those of the anti-inflammatory cytokine IL-10 are increased.[57]

Table 1 The Regulation of Immune Cells by PCSK9

Cell type	Disease Type	Signaling Pathway	Reference
Monocytes	Coronary Artery Disease	Inflammatory Cytokines Cholesterol Metabolism	[61]
	Atherosclerosis		[62]
	Hepatocellular Carcinoma		[63]
	Familial Hypercholesterolaemia		[64]
Macrophages	Hepatocellular Carcinoma	Cholesterol Metabolism	[71]
	Breast Cancer	CXCL12	[77]
	Skin Damage	IRF3	[78]

(*Continued*)

Table 1 (Continued).

Cell type	Disease Type	Signaling Pathway	Reference
Dendritic Cells	Hepatocellular Carcinoma	MHC-I	[79]
	Melanoma	TLR	[80]
	Atherosclerotic	Inflammatory Cytokines	[81]
	Subarachnoid Hemorrhage	SIRT6	[82]
	Systemic Lupus Erythematosus	CD86/HLA-DR	[83]
Natural Killer Cells	Neuroblastoma	Cholesterol Metabolism	[41]

Conversely, in other situations, PCSK9 can play a role in suppressing inflammation. In endothelial cells, PCSK9 may interact with specific membrane proteins and modulate the production of anti-inflammatory mediators. By inhibiting certain proinflammatory signaling cascades, such as the MAPK pathway under certain conditions, PCSK9 can reduce the expression of adhesion molecules and chemokines. This results in a decreased recruitment of immune cells to the site of potential inflammation, thereby dampening the overall inflammatory response.[58,59] PCSK9 intervention has also been demonstrated to be effective in mitigating the circulating levels of chemokines such as IL-8/CXCL8 and eosinophilic chemokine-2/CCL24. This has been shown to diminish the activation of neutrophils and eosinophils. Moreover, the inhibition of PCSK9 has been shown to reduce the expression of adhesion molecules such as ICAM-1 and VCAM-1, along with the chemokines CX3CL1 and CXCL16, thereby inhibiting interactions between leukocytes and endothelial cells. This results in a reduction in systemic inflammation and endothelial dysfunction.[57,60]

Inflammation exhibits a dual-edged sword effect in tumors. On one hand, chronic inflammation can create a microenvironment conducive to tumor initiation, growth, and metastasis by promoting cell proliferation, angiogenesis, and immune evasion. On the other hand, in some cases, an appropriate inflammatory response can also trigger anti-tumor immune reactions. This complex role of inflammation further complicates the function of PCSK9 in tumors.

PCSK9 Regulates Monocytes

PCSK9 plays a pivotal role in the differentiation of monocytes into macrophages by modulating their surface receptors and signaling cascades. For example, the regulatory impact of PCSK9 on LDLRs influences the cholesterol metabolism of monocytes, thereby shaping their differentiation trajectories.[61] The overexpression of PCSK9 has been demonstrated to amplify the inflammatory response of monocytes, increasing the secretion of proinflammatory cytokines such as IL-1β, IL-6, and TNF-α, which can promote tumor progression and metastasis.[62]

PCSK9 has also been shown to enhance the immunosuppressive capabilities of monocytes, steering their differentiation toward immunosuppressive M2-type macrophages. These M2 macrophages secrete anti-inflammatory cytokines and facilitate cancer cell immune escape.[63] In the context of cardiovascular disease, circulating PCSK9 levels reflect the distribution of monocyte subsets in individuals with stable coronary artery disease. Moreover, monoclonal antibodies targeting PCSK9 have been demonstrated to mitigate the proinflammatory characteristics of monocytes, consequently reducing the expression of inflammatory markers.[61,64]

PCSK9 Regulates Macrophages

Elevated levels of PCSK9 are correlated with unfavorable outcomes in diverse cancers, potentially by modulating the function of immune cells, including tumor-associated macrophages (TAMs). [41] For example, in macrophages, PCSK9 can bind to cell-surface receptors, such as LRP1. This activates intracellular signaling pathways, like the nuclear factor-κB (NF-κB) mediated upregulation of pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6. These cytokines then initiate and amplify the inflammatory response, contributing to the development and progression of various inflammatory-related diseases, including those associated with tumor microenvironments. [73–75] Meanwhile, PCSK9 upregulates

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the expression of genes associated with M1 polarization, such as iNOS. iNOS produces nitric oxide (NO), a potent antimicrobial and pro-inflammatory molecule. In contrast, it may downregulate genes associated with M2 polarization.[76–78]

Supernatant from PCSK9-overexpressing MHCC97H cells inhibited THP-1 macrophage migration and M2-like TAMs polarization. In contrast, supernatant from PCSK9-silenced Huh7 cells enhanced these functions. In tumor bearing mice, PCSK9 overexpression promoted OX40L, suppressing M2-like TAM polarization.[63] Arenobufagin has been demonstrated to impede the progression of hepatocellular carcinoma by modulating PCSK9-mediated cholesterol metabolism, which in turn influences the polarization of TAMs. This process involves the suppression of PCSK9 expression, the regulation of cholesterol metabolism, the promotion of M1-type macrophage polarization, and the amplification of the antitumor immune response.[71]

Efferocytosis, mediated by macrophages, is a process to eliminate apoptotic cells. This is fundamental for maintaining homeostasis, preventing autoimmune diseases, and facilitating inflammation resolution. In cancer, efferocytosis often becomes dysregulated, while defects in efferocytosis can lead to the accumulation of apoptotic cells in TME. Cancer cells can actively interfere with efferocytosis to evade immune surveillance.[79–81] In vascular endothelial cells, recombinant PCSK9 protein has been shown to induce efferocytic defects and downregulate the expression of the efferocytosis receptor MerTK. During the aging process of endothelial cells (ECs), PCSK9 levels increase while MerTK levels decline, and knockout of the PCSK9 gene can partially restore the associated functions. It likely involves the induction of ROS production, which inhibits MerTK expression and causes its cleavage. Additionally, PCSK9 may activate the MAPK pathway and NF-κB signaling, thereby indirectly suppressing efferocytosis through an inflammatory response.[75,76]

High expression of CXCL12 in breast cancer tissues is linked to poor prognosis and is associated with the extent of infiltration by various immune cells, especially in high-risk patients, who have increased infiltration of M2-like macrophages. Through targeted gene screening, PCSK9 was identified as a key factor correlated with the infiltration of TAMs and regulatory T cells (Tregs), both of which typically exhibit immunosuppressive functions and can facilitate tumor immune evasion and growth.[77] PCSK9 also promotes the transport of double-stranded DNA fragments into macrophages, resulting in interferon regulatory factor 3 (IRF3) and STING activation.[78] Understanding the complex interactions between PCSK9 and macrophage is essential for developing targeted therapeutic strategies.

PCSK9 Regulates DCs

The regulatory effects of PCSK9 on DCs are manifested primarily through its ability to modulate their maturation process, as well as its influence on cytokine and miRNA expression. The combination of chemotherapy drugs with PCSK9 inhibitors has been shown to enhance the maturation of DCs within tumor sites. Furthermore, the expression level of PCSK9 is closely associated with the activation of DCs.[79,80]

In the context of other systemic diseases, the exposure of DCs to oxLDL has been shown to prompt the maturation process, leading to T-cell activation and potentially fostering a proinflammatory state.[81] By inhibiting DC maturation, PCSK9 inhibitors curtail the production of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 while simultaneously promoting the secretion of anti-inflammatory cytokines, including TGF-β and IL-10. This action helps prevent the polarization of Th1 and/or Th17 cells and instead encourages the emergence of T regulatory cells.[82,83]

PCSK9 Regulates Natural Killer (NK) Cells

Following the genetic ablation of PCSK9, there is a notable increase in the number of NK cells in close proximity to the tumor. Furthermore, PCSK9 controls the antitumor efficacy of NK cells by affecting their cholesterol metabolism. Through the attenuation of PCSK9 activity, PCSK9 inhibitors increase the cholesterol content within NK cells, thereby reinforcing their antitumor capabilities.[6,41] Analyses of pancreatic adenocarcinoma (PAAD) patients and normal controls have revealed marked disparities in the infiltration of NK cells within tumor tissues compared to normal tissues. Notably, PCSK9 expression exhibits a correlation with the infiltration level of NK cells, with elevated PCSK9 expression inversely associated with the infiltration of activated NK cells. This inverse relationship suggests that PCSK9 may

impede the infiltration of NK cells, thereby potentially compromising the immune surveillance and anti-tumor cytotoxicity of NK cells against tumor cells. Subsequent experimental investigations further validated that modulating PCSK9 levels can effectively regulate NK cell function, ultimately influencing tumorigenesis and tumor progression. These findings highlight the crucial role of PCSK9 - NK cell interactions in the pathogenesis of PAAD and underscore the potential of targeting this axis for therapeutic intervention.[84,85]

Currently, the direct relationship between PCSK9 and NK cells across diverse cancers remains unclarified. However, within the framework of immune regulation, both PCSK9 and NK cells exert influence on disease development and treatment strategies.[85] They thus hold promise as potential therapeutic targets, warranting further investigation to fully understand their roles and exploit their therapeutic potential.

PCSK9 Regulates T Cells

In the complex microenvironments of the immune system and tumors, PCSK9 has emerged as a crucial regulator with far-reaching implications. Unraveling the precise mechanisms by which it exerts its differential effects on T cells and tumor cells has become a focal point of recent research endeavors (Figure 3).

When considering the interaction between PCSK9 and LDLR, it becomes evident that this binding event has profound consequences. LDLR, a key player in lipid uptake and homeostasis, normally undergoes a recycling process to return to the plasma membrane for continued function. However, when PCSK9 latches onto it, this recycling pathway is effectively blocked. This not only disrupts normal lipid metabolism but also directly affects the function of cytotoxic T cells. The TCR, which is integral for T-cell activation and antigen recognition, is also affected by this perturbed recycling, leading to impaired effector function. As a result, the ability of cytotoxic T cells to mount an effective immune response against tumor cells or pathogens is compromised.[55,83,86]

In the context of tumor cells, the physical association of PCSK9 with major histocompatibility complex class I (MHC I) initiates a series of intracellular events. MHC-I molecules are responsible for presenting antigenic peptides to cytotoxic T cells, thereby alerting the immune system to the presence of abnormal or tumorigenic cells. PCSK9, however, promotes the trafficking of MHC-I to lysosomes within tumor cells. Once inside lysosomes, MHC-I undergoes degradation, leading to a significant reduction in its surface expression. This devious tactic employed by tumor cells, facilitated by PCSK9, allows them to evade detection and destruction by the immune system, providing a survival advantage and promoting tumor progression.[13,87,88]

The impact of PCSK9 on intracellular cholesterol levels is yet another aspect that demands attention. By interfering with lipid metabolism pathways, PCSK9 causes a buildup of cholesterol within cells. Macrophages, which are highly sensitive to changes in their lipid environment, are particularly affected. Elevated cholesterol levels lead to lipid accumulation, altering the macrophage phenotype and function. These lipid-laden macrophages may exhibit impaired phagocytic activity or secrete factors that contribute to the tumor microenvironment, either directly or indirectly promoting tumor growth.[42,89]

The role of PCSK9 in modulating T-cell activation is multifaceted. Through the activation of MAPK, which subsequently phosphorylates and activates NFATc1, PCSK9 fine-tunes the activation state of cytotoxic T cells. This signaling cascade is a critical determinant of whether T cells become fully activated and carry out their effector functions.[71,90,91] On the other hand, the PI3K/Akt pathway represents a double-edged sword. Some therapeutic interventions have harnessed the power of this pathway to protect T cells from apoptosis, ensuring their survival and enhancing the immune response. In contrast, PCSK9 can act as an antagonist, inhibiting the PI3K/Akt pathway and tipping the balance toward apoptosis, potentially dampening immune defense mechanisms.[92,93]

With respect to Th cell differentiation, PCSK9 influences Th cell differentiation through activation of the NF-κB signaling pathway. This pathway is a master regulator of gene expression, dictating the fate of Th cells. By activating NF-κB, PCSK9 nudges Th cells toward a particular differentiation pathway, which can have implications for the type of immune response. For example, it may skew the response toward a more proinflammatory or anti-inflammatory phenotype, depending on the context.[94] Furthermore, the upregulation or activation of the TLR-4/NF-κB pathway by PCSK9 has far-reaching consequences. This not only fuels vascular inflammation, which can create a conducive environment for tumor growth and metastasis but also further drives Th cell differentiation. When engaged, the TLR-

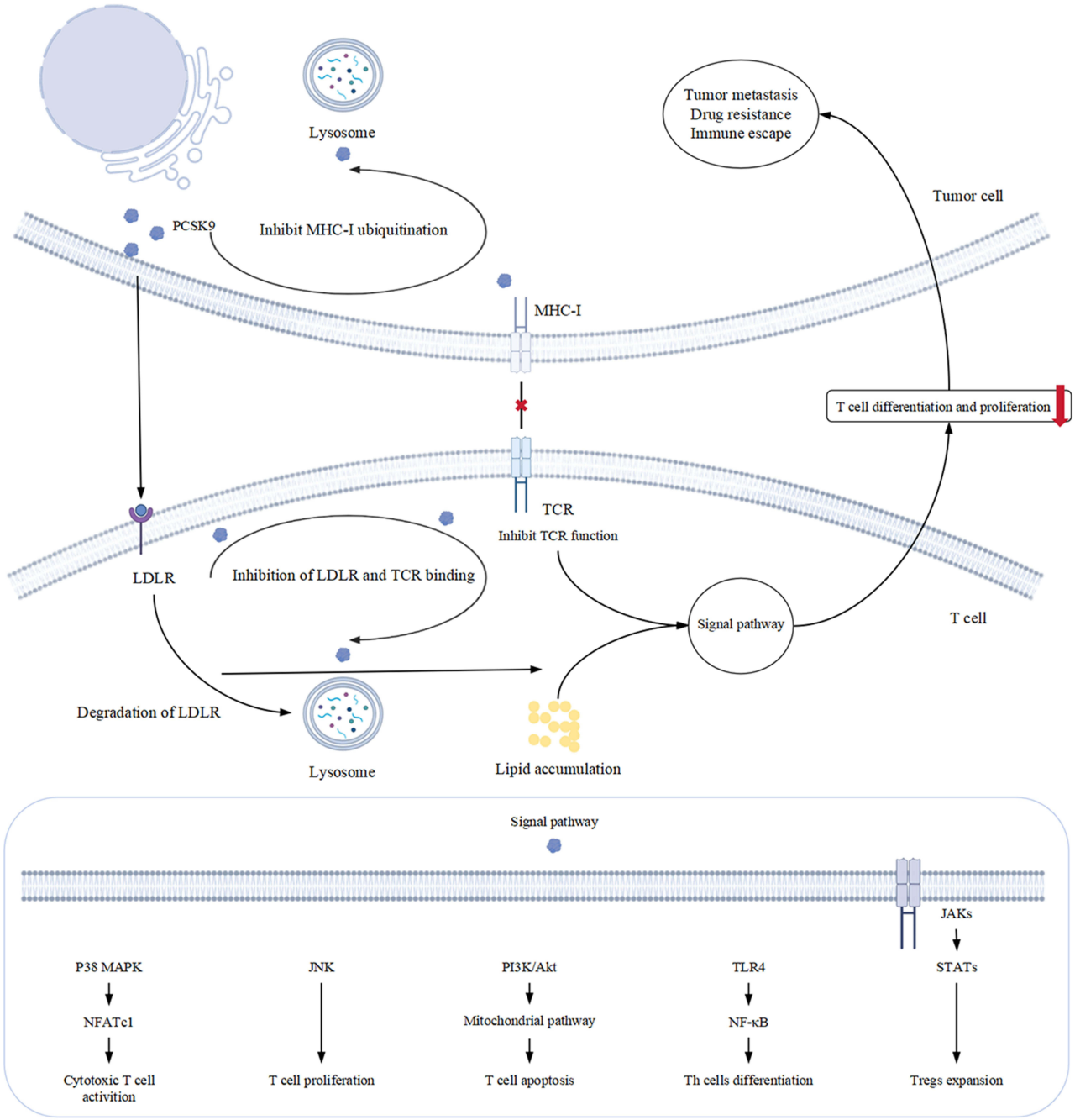

Figure 3 Mechanisms of the regulatory effects of PCSK9 in T cells and tumor cells. The binding of PCSK9 to LDLR impedes the recycling of LDLR and TCR back to the plasma membrane, consequently suppressing the effector function of cytotoxic T cells. By physically associating with MHC-I, PCSK9 instigates lysosomal degradation within tumor cells, which in turn diminishes the surface presentation of MHC-I, thereby facilitating tumor immune evasion. Moreover, PCSK9 triggers an increase in intracellular cholesterol levels, culminating in lipid accumulation within macrophages. PCSK9 modulates the activation of cytotoxic T cells via MAPK-mediated activation of NFATc1. Certain treatments can prevent T-cell apoptosis and promote T-cell survival through the PI3K/Akt pathway. Conversely, PCSK9 can promote apoptosis by inhibiting the PI3K/Akt pathway. PCSK9 drives Th cell differentiation by activating the NF-κB signaling pathway. Additionally, PCSK9 augments vascular inflammation and promotes Th cell differentiation by upregulating or activating the TLR-4/NF-κB pathway. Finally, PCSK9 facilitates the expansion of Tregs through the JAK/STAT pathway.

4 receptor initiates a signaling cascade that converges with the NF-κB pathway, leading to a complex interplay of gene activation and cell fate determination.[95,96]

PCSK9 promotes the amplification of Tregs through the JAK/STAT pathway, thus affecting immune balance. Tregs play a crucial role in maintaining immune homeostasis, preventing overactive immune responses that could lead to autoimmunity.[15,97–99] However, an overabundance of Tregs, potentially induced by PCSK9, could also suppress the

immune response against tumors, allowing them to thrive. Reducing the expression of PCSK9 in cancer cells leads to increased clonal expansion of CD8+ T cells, while the number of Tregs remains unchanged and the expression of PD-L1 does not change significantly, thus enhancing the immunotherapy response. Single-cell sequencing analysis revealed that PCSK9 may influence the functionality of circulating T cells via the PD-1/CTLA-4 pathway.[100] Overall, understanding these intricate mechanisms of PCSK9 is essential for devising novel therapeutic strategies that can either target PCSK9 directly or manipulate its downstream pathways to combat diseases such as cancer and autoimmune disorders.

In addition to its direct regulatory relationship, PCSK9 can also indirectly regulate T cells. Inhibition of PCSK9 can promote DCs infiltration and the expression of MHC-II, improving the activation of CD8+ T cells within the TME.[43] In the TME, PCSK9 downregulates the expression of LDLR and TCR signaling in CD8+ T cells, which ultimately blunts the functions of cytotoxic T lymphocyte effectors. The elimination of PCSK9 or administration of PCSK9 inhibitors has the potential to alleviate this inhibitory effect on CD8+ T cells, thereby increasing their antitumor activity and curtailing tumor progression. Combining PCSK9 inhibitors with OVA-II tumor vaccines can enhance the therapeutic efficacy of monotherapy.[43,101]

The intracellular cholesterol content of γδ T lymphocytes is positively associated with the activation of the TCR signaling pathway, cell activation, and proliferation. PCSK9 influences the antitumor activity of CD8+ T cells through the LDLR/TCR axis, thereby affecting tumor progression. The combination of PCSK9 inhibitors and PD-1-related drugs has synergistic antitumor effects.[44,55]

Elevated levels of PCSK9 can attenuate the efficacy of anti-PD-1 immunotherapy in patients diagnosed with advanced non-small cell lung cancer (NSCLC). Moreover, the concurrent administration of PCSK9 inhibitors and anti-CD137 agonists has been shown to increase the recruitment of CD8+ and GzmB+ CD8+ T cells, thereby extending the lifespan of lung cancer model mice.[102] In the context of colorectal cancer, the inhibition of PCSK9 expression in conjunction with the PD-1/PD-L1 pathway can restrain tumor growth by encouraging the infiltration of cytotoxic T cells and the expression of IFN-γ.[16] Furthermore, the combination of evolocumab and DOX increased the proportions of mature DCs, tumor-infiltrating CD8+ T cells, and NK cells, thereby enhancing the efficacy of immunotherapy in hepatocellular carcinoma.[79]

Furthermore, cholesterol metabolism regulates the activation, clonal expansion, and effector functions of CD8+ T cells, particularly with respect to their antitumor efficacy.[27,103] Within the TME, PCSK9 has been identified as an inhibitory factor of cholesterol metabolism in CD8+ T cells. This results in a reduction in the antitumor capabilities of these T cells due to a decrease in their cholesterol levels. Notably, two monoclonal antibodies targeting PCSK9, namely, evolocumab and alirocumab, which have been granted approval for clinical use in lowering cholesterol levels, enhances the response to tumor immunotherapy.[104,105] PCSK9 knockout tumors exhibit a marked increase in the number of CD8+ cytotoxic T cells (CTLs), CD4+ T-helper (TH) cells, and γδ T cells within the tumor.[98,106] These findings suggest that PCSK9 deficiency may hinder tumor growth by enhancing the antitumor activity of T cells.

Mechanisms of PCSK9 and the Application of PCSK9 Inhibitors in Tumor Therapy

Breast Cancer

The levels of PCSK9 exhibit progressively increase as breast cancer advances. Remarkably, following tumor regression, PCSK9 levels decrease to levels similar to those of the control group.[107] The overexpression of PCSK9 is correlated with increased breast cancer cell proliferation and invasion and avoidance of apoptosis, and a reduction in PCSK9 is correlated with a decreased risk of breast cancer.[108,109]

Pseurotin A has been demonstrated to effectively inhibit the secretion and interaction of PCSK9 with LDLR. This action inhibits the uptake of LDL-C, thereby limiting the growth and metastatic potential of breast cancer.[110] These findings strongly imply that PCSK9 has considerable potential as a diagnostic and prognostic biomarker in the context of breast cancer, heralding new avenues for enhanced disease management and patient outcomes.

Melanoma

Either genetic ablation of the PCSK9 gene or the administration of a PCSK9 inhibitor will delay melanoma progression.[111] This compelling evidence implies that curbing PCSK9 activity could exert a direct inhibitory effect on melanoma growth. PCSK9 plays a pivotal role in modulating cholesterol homeostasis within the TME. Cholesterol accumulation has been implicated in furnishing the requisite lipid substrates that fuel rapid tumor cell proliferation. By impeding PCSK9 function, alterations in the lipid metabolic circuitry impede the growth and expansion of melanoma cells.[6,112] In parallel, PCSK9 knockout mice engrafted with B16F1 mouse melanoma cells has also been examined. Intriguingly, in this model, cancer cells were found to have metastasized to the liver, accompanied by a pronounced increase in hepatic interstitial and tumor cell apoptosis. This phenomenon is plausibly attributed to the activation of the TNF-α pathway.[113,114]

Prostate Cancer

Elevated PCSK9 expression in prostate cancer (PC) is correlated with a reduced disease-specific survival time. This finding implies that the expression level of PCSK9 could serve as a predictive biomarker for the prognosis of PC patients.[115] Suppressing PCSK9 in prostate cancer cells can confer protection against ionizing radiation (IR)-induced damage. This is achieved through promoting cell viability and concomitantly inhibiting apoptosis and the activity of matrix metalloproteinases (MMPs). Upon IR exposure, characteristic changes, such as increases in CytC, caspase-3, and Bax levels, along with decreases in Bcl-2 levels, are observed. Notably, siRNAs targeting PCSK9 lead to increased radioresistance. These results suggest that PCSK9 might modulate the radiosensitivity of prostate cancer cells by orchestrating mitochondrial signaling pathways.[116]

Furthermore, treatment with Pseurotin A elicited dose-dependent suppression of migration, colony formation, and PCSK9 expression in PC cell lines. Moreover, Pseurotin A effectively curbed the in vivo progression of PC-3 cells orthotopically xenografted in nude mice and thwarted both locoregional and distant tumor recurrences following primary tumor surgical excision.[117]

Colorectal Cancer

By modulating the epithelial–mesenchymal transition (EMT) and PI3K/AKT signaling pathways within tumor cells, PCSK9 plays pivotal roles in both the progression and metastasis of colon cancer. Concurrently, by controlling inhibitory factors and lactate levels, it significantly impacts the phenotype polarization of macrophages.[118] Moreover, PCSK9 expedites the development of colon cancer via the activation of the JAK2/STAT3/SOCS3 signaling cascades.[119] In the context of APC/KRAS-mutant colorectal cancer, PCSK9 promotes tumor progression by facilitating cholesterol uptake and triggering associated signaling cascades.[120] Berberine, a natural inhibitor of PCSK9, has the capacity to influence tumorigenesis and progression by regulating the expression of LDLR, HNF-1α, EGF-A, and SREGBP-2.[121]

Liver Cancer

HCV-positive patients typically exhibit elevated plasma PCSK9 protein levels compared with those of HCV-negative individuals.[8] Interestingly, tumor tissue from HCC patients presents significantly lower PCSK9 mRNA and protein levels and significantly higher LDLR levels than adjacent cirrhotic liver tissue.[122] Moreover, serum PCSK9 protein levels are significantly higher in patients with HCC than in patients with chronic liver disease without HCC, whereas high expression of PCSK9 is associated with poorer overall survival (OS).[123] In HepG2 cells, PCSK9 expression is correlated with the level of TNF-α.[124] An increase in PCSK9 expression is associated with drug resistance in certain cancers, contributing to their resistance to chemotherapeutic drugs.[93,125] A reduction in PCSK9 results in cholesterol accumulation within liver cancer cells, augmenting the proinflammatory actions of NF-κB and thereby limiting tumor growth.[126] Moreover, the loss of PCSK9 has been shown to result in elevated cholesterol levels in the liver, which can promote inflammation and carcinogenesis. This illustrates the intricate role of PCSK9 in liver disease and liver cancer, where it may confer some protective effects while potentially contributing to disease progression in certain instances.[127] PCSK9 interacts with GSTP1, thereby inhibiting the JNK signaling pathway and regulating apoptosis in HCC.[128]

Nanoparticles containing berberine can enhance the regulatory effects of berberine on PCSK9 expression in HepG2 cells.[129] Curcumin can downregulate the expression of PCSK9 by affecting the nuclear translocation of HNF-1α, resulting in increased uptake of LDL in HepG2 cells.[130] Increasingly, extracts, such as Sparassis crispa, Protium heptaphyllum gum resin extract, Scutellaria baicalensis, olive oil phenol extracts, and Welsh onion extract, are being shown to affect the occurrence and development of tumors by regulating the expression level of PCSK9.[131–135]

Ovarian Cancer

PCSK9 might also play a part in governing ovarian cancer cell fate. The inhibition of annexin A11, a protein implicated in conferring chemoresistance to ovarian cancer cells, could be under the control of PCSK9. These findings suggest that the latent capacity of PCSK9 modulates both apoptosis and drug resistance in ovarian cancer.[136] Moreover, synergistic interactions have been revealed between PCSK9 and its inhibitors and between PCSK9 and mTOR inhibitors. By perturbing ovarian cancer cell metabolism and signaling cascades, this combination amplifies therapeutic efficacy, opening new avenues for treatment optimization.[137]

Gastric Cancer

Both PCSK9 and transcriptional enhancer factor domain-containing protein 4 (TEAD4) are markedly overexpressed in stomach cancer (STAD). These proteins collaborate to bolster cancer stem cell (CSC) traits, with fatty acid metabolism (FAM) serving as a crucial mediator. Consequently, targeting the TEAD4/PCSK9/lipid axis could herald a novel therapeutic paradigm for quelling CSCs in STAD.[138] Additionally, PCSK9 has been shown to fuel gastric cancer metastasis and impede apoptosis by activating the MAPK signaling pathway and upregulating HSP70 expression.[139] Intriguingly, in esophageal cancer patients, those harboring higher levels of anti-PCSK9 antibodies appear to be better in the postoperative period.[140]

Other Cancers

In addition to its well-established role in modulating lipid metabolism, PCSK9 has emerged as a key regulator of cell death in lung adenocarcinoma, operating through diverse molecular pathways. For example, in A549 cells, PCSK9 orchestrates apoptotic processes by affecting mitochondrial and endoplasmic reticulum stress responses.[141,142] PCSK9 could also potentially hold a pivotal position in the genesis, progression, and therapeutic management of cholangiocarcinoma.[143–145] However, the precise mechanistic underpinnings and the exact nature of this correlation await further elucidation.[146,147] Nevertheless, certain malignancies, such as sebaceous carcinoma and pancreatic cancer, have established links to lipid metabolism, yet their associations with PCSK9 remain largely unexplored.[148,149] These uncharted territories require further investigation to fully elucidate the potential roles of PCSK9 in the oncogenic processes of these cancers.

Summary

PCSK9 plays complex and essential roles in cancer. PCSK9 not only indirectly influences the TME through regulating lipid metabolism but also directly affects immune cells, thereby affecting their occurrence, development, and therapeutic effects. The facts that PCSK9 has been extensively studied, and that numerous pharmacological agents have been extensively used and have achieved remarkable outcomes in the treatment of multiple diseases in the clinic, will provide many useful clues for its study in cancer.

Although PCSK9 has demonstrated significant potential across multiple cancers and promising progress has been made in the research of PCSK9, the role of PCSK9 in cancer has not been fully elucidated and further research is needed. For example, the specific mechanism of action of PCSK9 may differ among various tumor types. Furthermore, drug delivery of PCSK9 inhibitors to reach the tumor microenvironment effectively is also one potential challenge for can treatment. This is due to the unique of complex architecture of tumors and the presence of physiological barriers in TME that is completely different to liver.

Efforts should focus on delving deeper into the mechanisms by which PCSK9 regulates tumor immunity. This includes exploring the interactions between PCSK9 and other molecules to uncover its comprehensive role in cancer. In

addition, resistance mechanisms may develop, which may due to alternative ways are activated to evade the immune system or maintain their growth despite PCSK9 inhibition. Another important aspect is the clinical feasibility of combining PCSK9 inhibitors with existing cancer treatments, such as potential drug-drug interactions. Development of next-generation inhibitors with enhanced specificity and reduced off-target effects represents a key frontier. In the future, artificial intelligence may be used to make new breakthroughs in PCSK9-related drug development, tumor resistance, drug delivery, and drug combination. Such endeavors will definitely lay a solid theoretical foundation for the formulation of novel treatment strategies that target PCSK9 in cancer immunotherapy.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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