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Clinical Application of PCSK9 Inhibitor in Tumor Therapy

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Abstract: Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9), a key protein secreted by the liver, initially emerged as a research focus in the cardiovascular field due to its central role in regulating lipid metabolism. With the deepening of research, the functional scope of PCSK9 and its inhibitors has continued to expand. They not only demonstrate remarkable efficacy in lipid management and the prevention/treatment of atherosclerotic cardiovascular disease (ASCVD) but also show enormous potential value in cancer prevention and control. Beyond indirectly regulating tumor progression by modulating lipid and inflammatory metabolism, PCSK9 may also exert direct effects on tumorigenesis and progression by participating in tumor cell proliferation, apoptosis signaling pathways, and immune regulation (e.g., influencing the expression of LDLR-related molecules on the surface of immune cells). However, no unified consensus has been reached in existing mechanistic studies. Regarding clinical evidence, there is heterogeneity among the results of multiple cohort studies and clinical trials. Some studies indicate that PCSK9 inhibitors do not significantly increase cancer risk or cancer-related mortality, and even some data suggest potential protective effects against specific types of tumors. Conversely, a small number of studies imply that long-term use may be associated with a slight elevation in the risk of certain cancers. Such discrepancies may stem from heterogeneity in sample size, follow-up duration, tumor types, and baseline characteristics of the study populations. Based on a review of numerous relevant studies, this article concludes that PCSK9 inhibitors may become a key therapeutic agent for cancer treatment in the future.

Keywords: PCSK9 inhibitors; Blood lipids; Tumors; Targeted therapy

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1. Introduction

Cancer has become a global health crisis. Despite continuous medical advancements, it remains the second leading cause of death worldwide, but is projected to become the primary cause by 2060 (with approximately 18.63 million deaths). The disease continues to rise globally, exacerbating the healthcare burden. In countries at the top quintile of socioeconomic development, cancer has surpassed cardiovascular diseases as the second leading cause

of death [1]. It is also a major contributor to disability-adjusted life years (DALYs). PCSK9 has evolved from a cholesterol-regulating factor into a pivotal node bridging metabolism and immunity, demonstrating significant research and clinical potential in oncology. PCSK9 regulates multiple proteins and signaling pathways in cancer, including JNK, NF-κB, and mitochondria-mediated apoptosis. Current evidence supports PCSK9 inhibitors as a potential strategy to reduce tumor risk and enhance immunotherapy efficacy, particularly in specific cancers such as breast, gastric and pancreatic cancers.

2. Exploring the role and mechanism of PCSK9 inhibitors in tumor prevention and control

2.1. Targeted regulation of digestive tract tumors

2.1.1. Stomach cancer, esophageal cancer

PCSK9 is closely associated with lipid levels, and its relationship with gastric cancer is equally significant. HDL-C serves as an independent risk factor for gastric cancer [2]. The study by Ghahremanfard *et al.* explicitly states that "serum lipid profile testing holds significant value in cancer progression," emphasizing that lipid profiles are not merely indicators of cardiovascular health but are also associated with the development of cancer [3]. Furthermore, basic research has demonstrated that PCSK9 gene and protein expression levels in gastric cancer tissues are significantly higher than in adjacent normal tissues, with expression increasing as the tumor progresses. These findings further confirm the association between PCSK9 and gastric cancer pathogenesis. Zoltan *et al.* demonstrated that assessing PCSK9 levels in elderly cancer patients enables risk stratification, where those with elevated expression may require intensified therapies (e.g., enhanced chemotherapy or immunotherapy) and closer survival monitoring [4].

Moreover, PCSK9 could serve as a cross-disease therapeutic target, targeting elderly patients with high PCSK9 levels, PCSK9 inhibitors may simultaneously improve lipid profiles, reduce inflammation, and indirectly enhance survival outcomes. Innovative Mendelian randomization (MR) studies targeting drug targets by Ding *et al.* have demonstrated a significant association between PCSK9 inhibitors and protective effects against gastric cancer (GC) [5]. Genetically, this evidence confirms that long-term use of statins, PCSK9 inhibitors, and other mainstream lipid-lowering drugs does not increase overall or specific cancer risks. It alleviates concerns among clinicians and patients about 'carcinogenicity of lipid-lowering drugs,' providing safety evidence for long-term lipid-lowering therapy in high-risk populations, such as cardiovascular disease patients.

Xu *et al.*' s fundamental mechanism study, validated by cell experiments and animal models, elucidates the core molecular mechanism of GC development: "PCSK9 activates the MAPK signaling pathway by upregulating HSP70 (heat shock protein 70), thereby promoting GC cell metastasis and inhibiting apoptosis" [6]. This discovery provides a novel potential target for targeted therapy of GC. Simultaneously, esophageal cancer research has never stopped progressing. Researchers have for the first time revealed a close association between serum anti-PCSK9 antibody levels and postoperative prognosis in esophageal cancer patients. Specifically, higher antibody levels correlate with longer patient survival. This discovery provides a new research direction for clinical prognostic stratification and individualized management [7].

As mentioned above, the authors suggest that PCSK9 is directly involved in the progression of gastric cancer and may also indirectly influence it by regulating lipid metabolism. Therefore, PCSK9 inhibitors could suppress gastric cancer development through these dual mechanisms. However, the current understanding of its role in esophageal cancer remains unclear and requires further investigation to confirm.

2.1.2. Hepatocellular carcinoma

The mechanism of PCSK9 in hepatocellular carcinoma (HCC) has been preliminarily elucidated, where PCSK9 expression levels in HCC tissues are significantly lower than in adjacent normal tissues. *In vitro* experiments demonstrated that PCSK9 inhibits the Jun N-terminus kinase (JNK) signaling pathway by binding to glutathione S-transferase Pi1 (GSTP1), thereby suppressing HCC cell growth [8]. This discovery reveals the anticancer role of PCSK9 in HCC, providing a new molecular mechanism basis for targeted therapy of HCC. Alannan *et al.*'s data analysis reveals that PCSK9 serves as a cross-regulatory node between lipid metabolism and tumor immunity in HCC, suggesting it may function as a potential prognostic biomarker and therapeutic target [9]. This finding was reported by Jin *et al.*, the groundbreaking foundational research on drug repositioning and combination therapy for HCC has been successfully completed [10]. The core findings demonstrate that the established drug Flubendazole can significantly inhibit HCC progression through PCSK9-dependent inhibition, while enhancing the efficacy of first-line targeted therapy Lenvatinib and reducing its toxic side effects.

This provides a cost-effective and easily translatable new strategy for HCC treatment. For patients with HCC, particularly those intolerant to Lenvatinib, it offers a "cost-effective, low-toxicity, and highly efficient" combination therapy regimen. Moreover, Flubendazole's oral administration ensures high patient compliance. Additionally, in Xu *et al.*' s innovative basic research on enhancing immunotherapy sensitivity in liver cancer, PCSK9 was found to mediate immune evasion through dual mechanisms: inhibiting T cell function and upregulating PD-L1 [11]. Inhibition of PCSK9 blocks both pathways simultaneously. Directly blocking PCSK9 prevents T cell binding, restoring T cell cytotoxicity, while indirectly downregulating PD-L1 enhances antibody efficacy, creating a 'dual sensitization' effect. Thus, the absence of PCSK9 is not entirely beneficial to the organism, as noted by Ioannou *et al.* the PCSK9 gene knockout (KO) mouse model demonstrates that PCSK9 deficiency exacerbates non-alcoholic steatohepatitis (NASH) by promoting hepatic cholesterol accumulation and accelerates HCC development [12].

This finding overturns the previous notion that "PCSK9 inhibition is exclusively beneficial" and provides critical safety evidence for clinical use of PCSK9 inhibitors. The study reveals PCSK9's dual role in liver diseases, while prior research focused on its lipid-lowering and cardiovascular protective effects, this investigation confirms that "in metabolic disorders (e.g., NASH), PCSK9 deficiency/inhibition may promote hepatic lesions through cholesterol accumulation." This paradigm shift challenges the single-benefit hypothesis and offers essential guidance for clinical application: Patients with concurrent NASH or high hepatic cholesterol risk should undergo regular monitoring of liver cholesterol levels and NASH progression to avoid indiscriminate use of PCSK9 inhibitors.

2.1.3. PDAC: Proprotein convertase

PCSK9 is primarily synthesized and secreted by hepatocytes, with minor production and release from the kidneys, pancreas, intestines, and adipose tissue. Its core mechanism involves binding to low-density lipoprotein (LDL) receptors, thereby blocking their recycling process and ultimately leading to elevated blood LDL-C levels, which induces dyslipidemia [13]. It indicates a positive correlation between PCSK9 levels and the severity of HTGP. PCSK9 serves as a biomarker for predicting liver and lung colonization. Elevated PCSK9 levels direct liver-preferring cells toward lung colonization, whereas PCSK9 knockout redirects lung-preferring cells to liver colonization, thereby establishing PCSK9's necessity and sufficiency for secondary organ site preference [14].

2.1.4. Control and management of colorectal tumors

APC and KRAS are the two most critical driver mutations in colorectal cancer (CRC). They often work in concert, with APC driving the initiation phase and KRAS the progression phase, jointly driving tumor development, proliferation, drug resistance, and metastasis. These mutations are key targets for molecular subtyping and clinical treatment decisions in this disease. In a cohort of CRC patients, researchers studied isogenic cell lines and transgenic mice [15]. We established that APC/KRAS mutant CRC induces de novo cholesterol biosynthesis, accompanied by elevated geranylgeranyl-1,2-diphosphate (GGPP), a metabolite essential for KRAS activation. PCSK9, a top-upregulated cholesterol-related gene, demonstrates that depletion of PCSK9 inhibits APC/KRAS mutant CRC cell growth *in vitro* and *in vivo*, whereas overexpression of PCSK9 induces tumorigenesis. Here, the results indicate that PCSK9 promotes APC/KRAS mutant CRC and is a therapeutic target [15]. Our data collectively demonstrate that PCSK9 is a carcinogen in APC/KRAS mutant CRC. PCSK9 inhibitors inhibit the growth of APC/KRAS mutant CRC *in vitro* and *in vivo*.

Multidimensional translational studies combining cell experiments, animal models, and human colon cancer samples by Porcheron *et al.* conclusively demonstrate that either single or combined silencing of PCSK7/PCSK9 (proprotein convertase family members) significantly inhibits colon cancer metastasis by enhancing T cell cytotoxicity [16]. The dual-silencing approach outperforms single-silencing, providing a novel strategy for immunotherapy targeting advanced metastatic colon cancer. In conclusion, PCSK9 inhibitors can not only directly inhibit colorectal tumors through signaling pathways but also enhance the efficacy of PD-1 inhibitors as adjuvant therapy.

2.2. Exploration of the correlation of breast cancer

Research data confirms that metabolic syndrome is a key risk factor for breast cancer, with lipid levels showing a significant correlation to disease risk [17–19]. Cholesterol and its metabolites not only provide "energy or raw materials" for tumor cells, but also actively participate in breast cancer pathophysiology by activating oncogenic signaling pathways and modulating hormone receptor activity. These compounds thus function as "active regulatory factors" in cancer progression, rather than mere "passive nutrients." Kitahara *et al.*'s study has found that high total cholesterol (≥ 240 mg/dl) is significantly positively associated with the risk of prostate cancer in men (HR = 1.24,95% CI:1.07–1.44), colon cancer (HR = 1.12,95% CI:1.00–1.25), and breast cancer in women (HR = 1.17,95% CI:1.03–1.33), with a clear dose-response trend [20]. Clinical testing has revealed that serum PCSK9 levels in breast cancer patients are significantly higher than in healthy individuals, and patients have elevated TC and LDL-C levels, as well as reduced HDL-C levels [21]. This correlation suggests that PCSK9 may influence breast cancer development by regulating lipid metabolism or directly modulating the tumor microenvironment. Although direct evidence for PCSK9 inhibitors in breast cancer treatment remains limited, the combined measurement of serum PCSK9 and lipid profiles has been validated as a valuable tool for early screening, diagnosis, and precision therapy and lay the foundation for follow-up intervention studies [21].

A study published by Wenbin *et al.* revealed that a common lineage mutation in the PCSK9 gene (rs562556, V474I) promotes breast cancer metastasis by targeting low-density lipoprotein receptor-related protein 1 (LRP1) [22]. This provides the first direct evidence of genetic susceptibility to breast cancer metastasis and suggests that anti-PCSK9 therapies could become a novel strategy for prevention. By integrating human genetics, functional experiments, and mechanism analysis, the study elucidated the molecular mechanism by which PCSK9 V474I mutation promotes metastasis through LRP1 degradation and validated the preclinical

efficacy of anti-PCSK9 therapies. These findings not only offer a new genetic explanation for breast cancer metastasis but also pave the way for developing precision therapies to "prevent metastatic cancer." Future large-scale clinical trials are needed to verify the safety and effectiveness of this strategy, as well as to explore synergistic effects with other targeted drugs (such as EMT inhibitors) [23]. A chimeric virus-like particle (cVLP) vaccine targeting PCSK9 was developed and validated in a preclinical HER2-positive breast cancer model for its efficacy when combined with the cVLP-HER2 vaccine. The results demonstrated that this combination strategy significantly enhanced anti-tumor immune responses, inhibited tumor growth, and prolonged survival. The core mechanism involves improving the tumor immune microenvironment through PCSK9 targeting, providing a novel combination approach for HER2-positive breast cancer immunotherapy. This highlights the pivotal role of PCSK9 inhibitors in breast cancer treatment, underscoring the continued importance of advancing research in this field.

3. The effect of PCSK9 on tumor

Foreign research studies confirm that PCSK9 mediates tumor cell proliferation, invasion, and migration by regulating EMT (epithelial-mesenchymal transition) and the PI3K/Akt signaling pathway [24]. Indirectly, PCSK9 inhibitors, novel lipid-lowering agents, may influence tumors through lipid metabolism. Hyperlipidemia accelerates tumor development by promoting inflammation, oxidative stress, and angiogenesis, while tumor cells elevate lipid levels by remodeling lipid metabolism to meet their energy demands [25]. The efficacy of lipid-lowering drugs in tumor prevention and control varies. PCSK9 inhibitors demonstrate non-lipid-lowering anticancer effects (e.g., in GC prevention), overcoming the limitations of conventional lipid-lowering drugs and providing a new research direction for the interdisciplinary field of 'blood lipids-tumor'[25].

4. Conclusion

PCSK9 inhibitors are currently primarily used to lower blood lipids, though their efficacy in treating various cancers remains under investigation. Most of their mechanisms are still unclear, necessitating further data collection to elucidate these pathways and enhance cancer treatment strategies. This development offers a promising approach for patients undergoing prolonged radiotherapy, chemotherapy, or surgery. However, due to the relatively short market availability of PCSK9 inhibitors, adverse reaction data remain limited. Clinical evidence for their use in pregnant women, nursing mothers, and patients with severe hepatic or renal impairment is insufficient and requires further validation. In other disease treatments involving inflammation and lipid management, PCSK9 inhibitors show significant relevance to conditions like osteoarthritis and organ transplantation. For our rapidly evolving society, whether PCSK9 inhibitors will bring benefits or challenges to cancer patients remains to be seen. Future research should focus on large-scale, multicenter clinical studies to thoroughly explore the mechanisms and long-term effects of PCSK9 inhibitors across multiple therapeutic areas, facilitating their transition from basic research to clinical application and providing comprehensive solutions for multidisciplinary disease management.

Disclosure statement

The authors declare no conflict of interest.

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