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REVIEW

Exploring the Pleiotropy of PCSK9: A Wide Range of Influences from Lipid Regulation to Extrahepatic Function

Huaru Wang[1], Guodong Tang[2,3], Jianqiang Wu[4], Xuzhen Qin[1]

[1]Department of Laboratory Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100730, People's Republic of China; [2]Department of Cardiology, Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing, 100730, People's Republic of China; [3]Department of Cardiology, Beijing United Family Hospital, Beijing, 100015, People's Republic of China; [4]Institute of Clinical Medicine, National Infrastructure for Translational Medicine, State Key Laboratory of Complex Severe and Rare Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College Hospital, Beijing, 100730, People's Republic of China

Correspondence: Xuzhen Qin, Email qxz_01@163.com

Abstract: In cardiovascular disease, the discovery of the proprotein convertase subtilisin/kexin type 9 (PCSK9) has undoubtedly opened a new chapter in regulating blood lipids. Since its first identification as a key regulator of low-density lipoprotein receptor (LDLR) degradation in 2003, the role of PCSK9 in cholesterol metabolism has been extensively studied. However, with further research, the pleiotropy of PCSK9 has gradually emerged, and its impact extends far beyond cholesterol metabolism in the liver. The purpose of this review is to systematically explore the pleiotropy of PCSK9, extending from its important role in lipid regulation to its extensive effects in extrahepatic tissues, and to reveal its potential role in cardiovascular health, nervous system function, and tumor biology. By integrating the latest research findings, this paper summarizes the complex mechanisms of action of PCSK9 in different biological processes and explores its potential and challenges as a therapeutic target.

Keywords: PCSK9, pleiotropy, blood lipid regulation, extrahepatic function

Introduction

In recent years, with the deepening of life science research, especially breakthroughs in gene and protein function analysis, PCSK9, an important regulator of lipid metabolism, has gradually attracted extensive attention from the scientific community for its multifaceted effects, such as anti-inflammatory, antitumor and antithrombotic effects. PCSK9 was originally discovered for its key role in the degradation of low-density lipoprotein cholesterol (LDL-C), which significantly affects blood lipid levels and has become a new target in cardiovascular disease therapy.[1] As the central organ for lipid metabolism in the human body, the liver is the primary target to inhibit PCSK9 synthesis. Targeting the PCSK9 synthesis pathway in the liver can effectively reduce plasma PCSK9 levels, enhance the expression and function of LDL receptors, and thereby achieve the goal of lowering plasma cholesterol levels. This approach may also provide new insights and methods for the treatment of lipid metabolism-related diseases such as atherosclerosis and hyperlipidemia. Recent clinical trials have further supported the central role of the liver in the regulation of PCSK9 synthesis. By employing various intervention strategies, including PCSK9 inhibitor drugs and gene editing technologies, successful inhibition of PCSK9 synthesis at the hepatic level has been achieved, accompanied by significant improvements in lipid metabolism. However, even with more research activities, the biological function of PCSK9 is far from fully understood. PCSK9 exerts a broad influence, transcending traditional boundaries and encompassing various aspects, from blood lipid regulation to functional modulation of extrahepatic tissues and organs, including the myocardium, pancreas, brain, and kidney.[2] This study aims to comprehensively explore the pleiotropy of PCSK9, analyze its complex molecular mechanisms impacting physiological and pathological processes, provide a theoretical basis for understanding its role in diverse diseases, and contribute to the development of novel therapeutic strategies.

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The Characteristics and Role of PCSK9 in Lipid Regulation

Basic Biological Characteristics of PCSK9

PCSK9, a secreted serine protease synthesized primarily by the liver, was originally named Neural Apoptosis Regulated Convertase-1 (NARC-1) and was found to be involved in regulating neural apoptosis.[3] The molecular structure of PCSK9 is complex and versatile. The PCSK9 protein is first synthesized as a 75 kDa precursor in the endoplasmic reticulum and contains an N-terminal signal peptide sequence, a domain, a catalytic domain, and a cysteine-rich C-terminal domain.[4] During its journey through the secreting pathway, PCSK9 undergoes autocatalytic cleavage precisely at the VFAQ152SIP sequence, giving rise to two distinct domains: a 13kDa primary fragment and a mature 62kDa PCSK9 domain. This composite heterodimer demonstrates an enhanced binding affinity and degradation efficacy towards LDLR. In contrast, a different circulating heterodimer form of PCSK9, composed of 55kDa and 13kDa fragments, is postulated to have a reduced binding affinity for LDLR. And the cleaved protein predominantly binds to the catalytic domain in noncovalent interactions to form a complex that is eventually secreted into the bloodstream.[1] Figure 1 shows the domain organization of PCSK9 and the basic biological characteristics of protease cleavage and final dimer formation.

The synthesis of PCSK9 begins in the endoplasmic reticulum (ER) and results in the formation of the mature PCSK9 protein through a series of autocatalytic reactions and posttranslational modifications (such as acetylation), which ensures that PCSK9 is properly folded and biologically active. Subsequently, PCSK9 is transported to the Golgi apparatus for further modification and processing and is ultimately released into the peripheral circulation through the secretion of the Golgi apparatus. Unlike most preprotein invertases, PCSK9 does not undergo secondary proteolytic cleavage after leaving the ER, making it the only subtilisin proteinase-like serine protease without a protein substrate.[5]

In the liver, PCSK9 performs its core function primarily through interactions with low-density lipoprotein receptors (LDLRs). When PCSK9 binds to the extracellular domain of LDLR, complex translocation to endosomes enhances the binding affinity of PCSK9 for LDLR under acidic conditions. This increased binding force promotes the degradation of LDLR in lysosomes, resulting in a decrease in the amount of LDLR on the cell surface. Since LDLR is the main receptor for the uptake and clearance of LDL-C by liver cells, this mechanism of action of PCSK9 directly affects the level of LDL-C in plasma.[6] In addition to LDLR, PCSK9 also regulates the degradation of other LDLR family members, such as very low-density lipoprotein receptor (VLDLR), apolipoprotein E receptor-2 (ApoER2), low-density lipoprotein receptor-associated protein 1 (LRP 1), and other cell surface proteins. For example, the degradation of scavenger receptor B (SR/CD36), angiotensin-converting enzyme 2 (ACE2), and toll-like receptor (TLR) affects lipid metabolism and the inflammatory response.[7] Figure 2 shows the various receptors that regulate cholesterol homeostasis that PCSK9 can cleat.

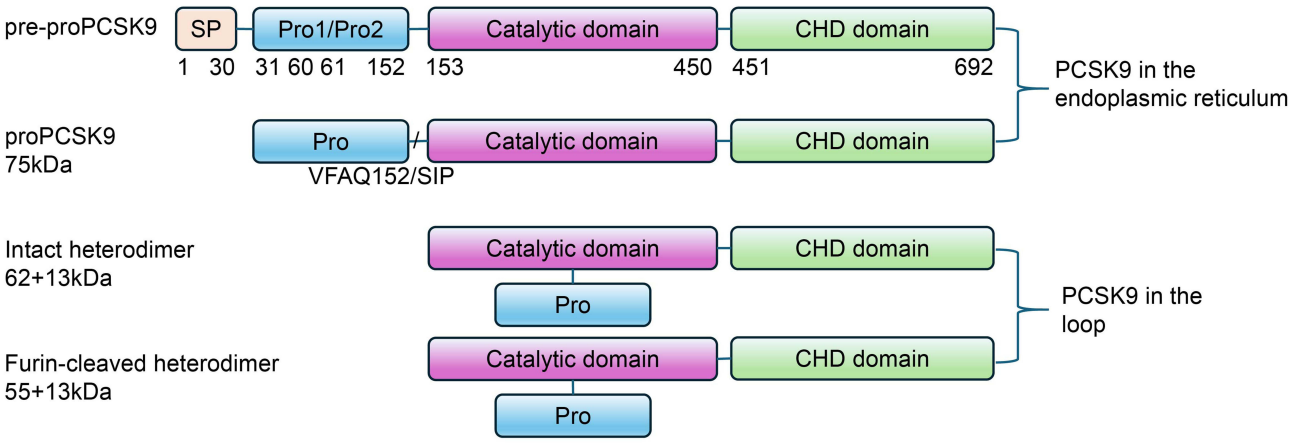

Figure 1 Domain organization, protease cleavage and final dimer formation of PCSK9.
Abbreviations: SP, Signal Peptide; Pro, Prodomain; CHD domain, Cysteine-His Rich Domain.

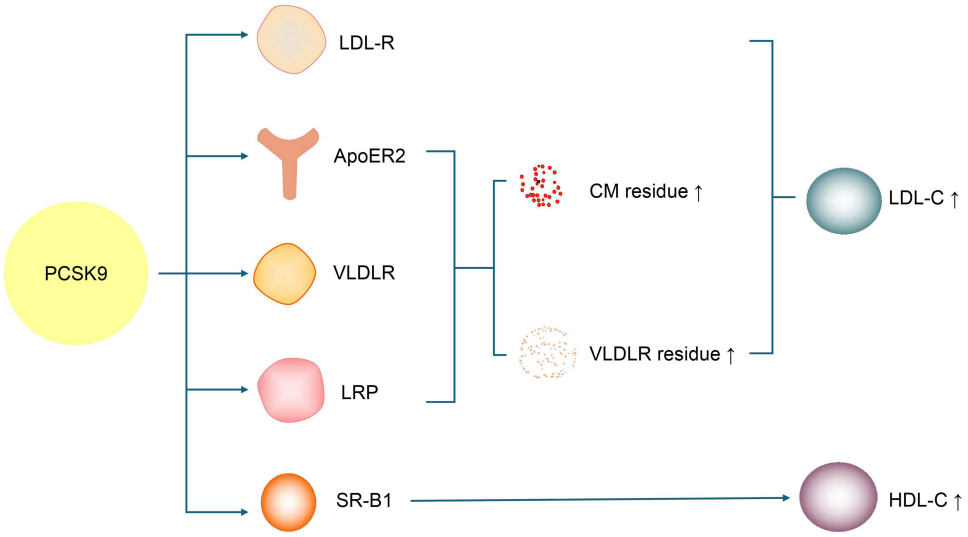

Figure 2 PCSK9 interacts with the cell surface receptors LDL-R, ApoER2, VLDLR, LRP, and SR-B1 to regulate cholesterol homeostasis. When ApoER2, VLDLR, and LRP are cleaved by PCSK9, the clearance of CM remnants, VLDL remnants, and LDL-C is impaired, resulting in their increased levels. Similarly, when LDL-R is cleaved by PCSK9, the clearance of LDL-C is also compromised, leading to an increase in its concentration. Furthermore, when SR-B1 is cleaved, the clearance of HDL-C is affected, causing an elevation in HDL-C levels.

PCSK9 Function Regulation in Lipid Regulation

The PCSK9 gene is located on the short arm of chromosome 1, and the encoded PCSK9 protein is expressed mainly in the liver, kidney, and small intestine.[8] The expression of PCSK9 is regulated by a variety of transcription factors, such as cholesterol regulatory element binding protein 2 (SREBP-2), forkhead framing O3 (FOXO3), hepatocyte nuclear factor-1 α (HNF1α), and Sirtuin 6 (SIRT6).[9,10] The most important of these transcription factors is sterol regulatory element binding protein-2 (SREBP-2), which is activated when the intracellular cholesterol level decreases. SREBP-2 promotes the expression of the PCSK9 and LDLR genes.[11] In addition, hormone and nutritional status and other metabolic signals can also regulate the expression of PCSK9; for example, insulin can upregulate the expression of PCSK9, which is particularly important in patients with metabolic syndrome.[12] Thyroid hormones and estrogen are also thought to regulate PCSK9 expression.[13,14] Moreover, the regulation of PCSK9 expression is also different in different nutritional states. One study revealed that high-oleic acid rapeseed oil or docosahexaenoic oil mixtures, marine n-3 polyunsaturated fatty acids, Mediterranean diets, etc, can reduce the PCSK9 concentration, whereas a high-sugar diet can increase the PCSK9 concentration.[15]

In addition, mutations and abnormal expression of PCSK9 are closely associated with a variety of cardiovascular disorders. PCSK9 mutations found in humans thus far include gain-of-function and loss-of-function mutations. Figure 3 shows the types and names of the mutations found in chronological order. Table 1 documents the structure, function, and clinical significance of PCSK9 mutations identified so far in chronological order. Gain-of-function mutations in PCSK9 cause familial hypercholesterolemia, which is characterized by significantly elevated LDL-C, leading to a significantly increased risk of early-onset coronary heart disease.[16] Conversely, loss-of-function mutations in PCSK9 reduce LDL-C levels and significantly reduce the incidence of cardiovascular events.[17] Two new PCSK9 loss-of-function mutations identified in the cohort study, E144K and C378W, reduce PCSK9 function through different mechanisms (the E144K mutation affects the PCSK9 protein maturation process, and the C378W mutation affects PCSK9 protein secretion). These findings provide new insights into the role of PCSK9 in cholesterol metabolism.[18]

Given the central role of PCSK9 in lipid regulation, drug development targeting PCSK9 has become an important direction in the field of lipid management. At present, a variety of PCSK9 inhibitors, such as monoclonal antibodies (evolocumab, alirocumab), have been widely used in clinical applications.[19] RNA interference-based drugs such as inclisiran, which has been approved by the FDA, are administered less frequently than traditional monoclonal antibodies and require only one injection every six months, increasing patient compliance.[20] Another drug under development is an oral PCSK9 inhibitor. Compared with injectable drugs, oral drugs provide patients with more convenient treatment options, such as MK-0616 and

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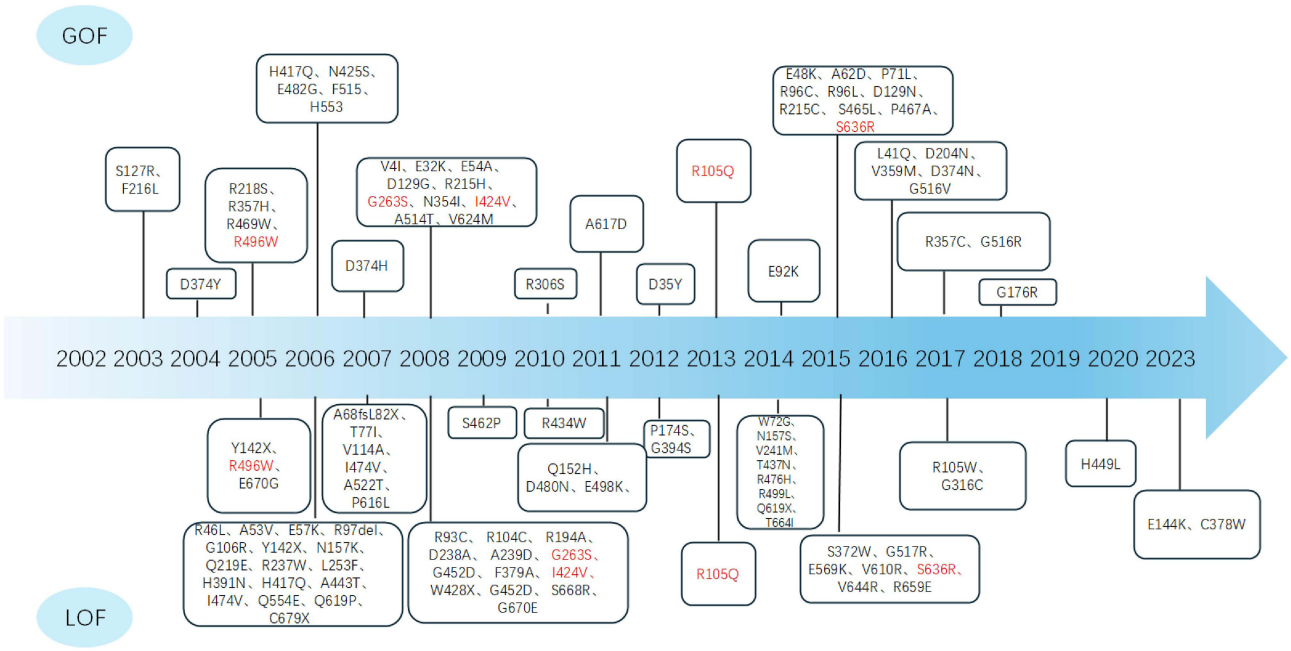

Figure 3 PCSK9 mutations identified in chronological order. Above the arrow is gain-of-function mutation, below the arrow is loss-of-function mutation, and the mutant gene marked in red is both gain-of-function mutation and loss-of-function mutation.

the fusion protein lerodalcibep. Although this approach is still in the clinical trial stage, if successful, it greatly simplifies the treatment process of PCSK9 inhibitors.[21,22] In addition, some cutting-edge research is exploring the use of gene editing technologies such as CRISPR to directly modify the PCSK9 gene to fundamentally address the problem of PCSK9 overexpression, which is still in its early stages and has been tested only in nonhuman primate and mouse models. This approach is promising for providing a solution for long-term or permanent cholesterol management in the future.[23] Table 2 describes PCSK9-based drugs and their unique properties.

Table 1 The Structural Features, Functional Consequences, and Clinical Implications of PCSK9 Mutations

Mutation	Structure	Function	Clinical Significance
Gain of Function			
S127R	The 127th serine (S) in the PCSK9 gene is replaced by arginine (R)	Enhanced PCSK9 and LDLR integration capability	Associated with familial hypercholesterolemia (FH)
F216L	The 216th phenylalanine (F) in the PCSK9 gene is replaced by leucine (L)	Enhanced PCSK9 and LDLR integration capability	Associated with an increased risk of cardiovascular disease
D374Y	The 374th aspartic acid (D) in the PCSK9 gene is replaced by tyrosine (Y)	Enhanced PCSK9 and LDLR integration capability	Associated with an increased risk of cardiovascular disease
R218S	The 218th arginine (R) in the PCSK9 gene is replaced by serine (S)	Change the binding affinity or binding way of PCSK9 and LDLR	Associated with an increased risk of cardiovascular disease
R357H	The 357th arginine (R) in the PCSK9 gene is replaced by histidine (H)	Enhanced PCSK9 and LDLR integration capability	Associated with an increased risk of cardiovascular disease
R469W	The 469th arginine (R) in the PCSK9 gene is replaced by tryptophan (W)	Change the binding affinity or binding way of PCSK9 and LDLR	People with this mutation may face a different risk of cardiovascular disease
H417Q	The 417th histidine (H) in the PCSK9 gene is replaced by glutamine (Q)	Change the binding affinity or binding way of PCSK9 and LDLR	This mutation may be closely related to an individual's cholesterol levels and cardiovascular disease risk
N425S	The 425th asparagine (N) in the PCSK9 gene is replaced by serine (S)	Enhanced PCSK9 and LDLR integration capability	Individuals with this mutation may be more likely to develop hypercholesterolemia
E482G	The 482nd glutamic acid (E) in the PCSK9 gene is replaced by glycine (G)	Change PCSK9 and LDLR combination capability or combination method	People with this mutation may face a different risk of cardiovascular disease

(*Continued*)

Table 1 (Continued).

Mutation	Structure	Function	Clinical Significance
F515L	The 515th phenylalanine (F) in the PCSK9 gene is replaced by leucine (L)	Change the binding affinity or binding way of PCSK9 and LDLR	People with this mutation may face a different risk of cardiovascular disease
H553R	The 553rd histidine (H) in the PCSK9 gene is replaced by arginine (R)	Change the binding affinity or binding way of PCSK9 and LDLR	People with this mutation may be at risk for cardiovascular disease
D374H	The 374th aspartic acid (D) in the PCSK9 gene is replaced by histidine (H)	Alter the binding properties of PCSK9 to LDLR, resulting in enhanced or diminished binding ability	People with this mutation may face a different risk of cardiovascular disease
V4I	The fourth valine (V) in the PCSK9 gene is replaced by isoleucine (I)	Alter the binding properties of PCSK9 to LDLR, resulting in enhanced or diminished binding ability	People with this mutation may face a different risk of cardiovascular disease
E32K	The 32nd glutamate (E) in the PCSK9 gene is replaced by lysine (K)	Enhanced PCSK9 and LDLR integration capability	Associated with an increased risk of cardiovascular disease
E54A	The 54th glutamic acid (E) in the PCSK9 gene is replaced by alanine (A)	Not entirely clear	Associated with a variety of cardiovascular diseases
D129G	The 129th aspartic acid (D) in the PCSK9 gene is replaced by glycine (G)	Enhanced PCSK9 and LDLR integration capability	Associated with the occurrence of autosomal dominant hypercholesterolemia (ADH)
R215H	The 215th arginine (R) in the PCSK9 gene is replaced by histidine (H)	Enhanced PCSK9 and LDLR integration capability	Associated with familial hypercholesterolemia (FH)
A514T	The 514th alanine (A) in the PCSK9 gene is replaced by threonine (T)	Not entirely clear	Not entirely clear
V624M	The 624th valine (V) in the PCSK9 gene is replaced by methionine (M)	It may change the binding affinity of PCSK9 with LDLR or affect the catalytic activity of PCSK9	Associated with familial hypercholesterolemia (FH)
R306S	The 306th arginine (R) in the PCSK9 gene is replaced by serine (S)	Change the way PCSK9 interacts with LDLR	Related to an individual's cholesterol levels and cardiovascular disease risk
A617D	The 617th alanine (A) in the PCSK9 gene is replaced by aspartic acid (D)	The results of current studies are inconsistent	Related to an individual's cholesterol levels and cardiovascular disease risk
D35Y	The 35th aspartic acid (D) in the PCSK9 gene is replaced by tyrosine (Y)	Change the binding ability of PCSK9 to LDLR, or affect the catalytic activity of PCSK9	Related to an individual's cholesterol levels and cardiovascular disease risk
E92K	The 92nd glutamic acid (E) in the PCSK9 gene is replaced by lysine (K)	Change PCSK9 and LDLR combination capability	Not entirely clear
E48K	The 48th glutamic acid (E) in the PCSK9 gene is replaced by lysine (K)	May change the binding ability of PCSK9 to LDLR and the secretion efficiency of PCSK9	Not entirely clear
A62D	The 62th alanine (A) in the PCSK9 gene is replaced by aspartic acid (D)	May alter the interaction of PCSK9 with LDLR or other related molecules	Its specific clinical significance still needs further study.
P71L	The 71st proline (P) in the PCSK9 gene is replaced by leucine (L)	May alter the interaction of PCSK9 with LDLR or other related molecules	Has important implications for cardiovascular disease risk and treatment strategies
R96C	The 96th arginine (R) in the PCSK9 gene is replaced by cysteine (C)	Change the binding ability of PCSK9 to LDLR, or affect the catalytic activity of PCSK9	Has important implications for cardiovascular disease risk and treatment strategies
R96L	The 96th arginine (R) in the PCSK9 gene is replaced by leucine (L)	Change the binding ability of PCSK9 to LDLR, or affect the catalytic activity of PCSK9	Has important implications for cardiovascular disease risk and treatment strategies
D129N	The 129th aspartic acid (D) in the PCSK9 gene is replaced by asparagine (N)	Change the binding affinity or binding way of PCSK9 and LDLR	Not entirely clear
R215C	The 215th arginine (R) in the PCSK9 gene is replaced by cysteine (C)	Change the ability to bind to LDLR and affects the stability of PCSK9	Not entirely clear
S465L	The 465th serine (S) in the PCSK9 gene is replaced by leucine (L)	May change the ability or stability of PCSK9 to bind to LDLR	May increase the risk of cardiovascular disease
P467A	The 467th proline (P) in the PCSK9 gene is replaced by alanine (A)	Change PCSK9 and LDLR combination capability	Associated with a variety of cardiovascular diseases

(*Continued*)

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Table 1 (Continued).

Mutation	Structure	Function	Clinical Significance
L41Q	The 41st leucine (L) in the PCSK9 gene is replaced by glutamine (Q)	Not entirely clear	To help more accurately assess their risk of cardiovascular disease
D204N	The 204th aspartic acid (D) in the PCSK9 gene is replaced by asparagine (N)	Change the catalytic activity of PCSK9 or its ability to bind to LDLR	May have an impact on cardiovascular disease risk
V359M	The 359th valine (V) in the PCSK9 gene is replaced by methionine (M)	Not entirely clear	May have an impact on cardiovascular disease risk
D374N	The 374th aspartic acid (D) in the PCSK9 gene is replaced by asparagine (N)	May change the ability or stability of PCSK9 to bind to LDLR	May have an impact on cardiovascular disease risk
G516V	The 516th glycine (G) in the PCSK9 is replaced by valine (V)	Not entirely clear	May have an impact on cardiovascular disease risk
R357C	The 357th arginine (R) in the PCSK9 gene is replaced by cysteine (C)	Not entirely clear	The risk of cardiovascular disease in mutation carriers may vary depending on the effect of the mutation on PCSK9 function
G516R	The 516th glycine (G) in the PCSK9 gene is replaced with arginine (R)	Not entirely clear	May have an impact on cardiovascular disease risk
G176R	The 176th glycine (G) in the PCSK9 gene is replaced with arginine (R)	Not entirely clear	May have an impact on cardiovascular disease risk
Loss of Function			
Y142X	The mutation is located on exon 3 of the PCSK9 gene, and as a result of the mutation, translation is prematurely terminated, resulting in a truncated, non-functional PCSK9 protein	The mutation resulted in loss of function of PCSK9 protein, which could not effectively promote LDLR degradation	Individuals with the Y142X mutation have significantly lower plasma LDL-C levels than normal, about 28 to 40% lower
E670G	The 670th glutamate (E) in the PCSK9 gene is replaced by glycine (G)	Mutations may result in changes in the binding ability, stability, or other functional properties of PCSK9 to LDLR	Individuals who carry this mutation (especially the GG genotype) may be at higher risk of CVD
R46L	The 46th arginine (R) in the PCSK9 gene is replaced by leucine (L)	The binding ability of PCSK9 and LDLR is weakened	Patients who carry the R46L mutation have a significantly lower risk of cardiovascular disease than those who do not
A53V	The 53rd alanine (A) in the PCSK9 gene is replaced by valine (V)	Not entirely clear	Not entirely clear
E57K	The 57th glutamic acid (E) in the PCSK9 gene is replaced by lysine (K)	Not entirely clear	Not entirely clear
R97del	The 97th amino acid is deleted	It may seriously interfere with the binding ability of PCSK9 to LDLR, or lead to complete loss of function of PCSK9 protein	Individuals who carry this mutation may face a higher risk of cardiovascular disease
G106R	The 106th glycine (G) in the PCSK9 gene is replaced by arginine (R)	May change PCSK9's ability to combine with LDLR	May result in reduced or lost PCSK9 function, reducing the risk of cardiovascular disease
Y142X	A nonsense mutation in tyrosine (Y) at position 142 causes the translation process to end prematurely at this location, resulting in a truncated PCSK9 egg	Loss of PCSK9 protein function	In people with this mutation, plasma LDL-C levels are significantly reduced, and the risk of cardiovascular disease is correspondingly reduced
N157K	The 157th asparagine (N) in the PCSK9 gene is replaced by lysine (K)	May change PCSK9's ability to bind to LDLR or the stability of PCSK9	The PCSK9 function may be weakened or lost
Q219E	The 219th glutamine (Q) in the PCSK9 gene is replaced by glutamic acid (E)	May change PCSK9's ability to bind to LDLR or the stability of PCSK9	Associated with cardiovascular disease risk
R237W	The 237th arginine (R) in the PCSK9 gene is replaced by tryptophan (W)	May change PCSK9's ability to combine with LDLR	Patients who carry the R237W mutation have lower LDL-C levels and a lower risk of cardiovascular disease
L253F	The 253th leucine (L) in the PCSK9 is replaced by phenylalanine (F)	Not entirely clear	Associated with cardiovascular disease risk
H391N	The 391th histidine (H) in the PCSK9 gene is replaced by asparagine (N)	Mutation may disrupt the normal binding ability of PCSK9 to LDLR	Not entirely clear

(*Continued*)

Table 1 (Continued).

Mutation	Structure	Function	Clinical Significance
H417Q	The 417th histidine (H) in the PCSK9 gene is replaced by glutamine (Q)	Change the binding ability of PCSK9 to LDLR, or affect the catalytic activity of PCSK9	Associated with cardiovascular disease risk
A443T	Amino acid 443 in PCSK9 protein is mutated from alanine (A) to threonine (T)	Change the catalytic activity of PCSK9 or its ability to bind to LDLR	Not entirely clear
I474V	The 474th isoleucine (I) in the PCSK9 gene is replaced by valine (V)	Not entirely clear	Associated with cardiovascular disease risk
Q554E	The 554th glutamine (Q) in the PCSK9 gene is replaced by glutamate (E)	May change PCSK9's ability to bind to LDLR or the stability of PCSK9	Not entirely clear
Q619P	The 619th glutamine (Q) in the PCSK9 gene is replaced by proline (P)	May change the catalytic activity of PCSK9 or its ability to bind to LDLR	Not entirely clear
C679X	A nonsense mutation at amino acid 679 in the PCSK9 protein causes the amino acid at this position to be replaced by a stop codon	Resulting in loss of function of PCSK9 protein	In people with this mutation, plasma LDL-C levels are significantly reduced
A68fsL82X	Frameshift occurs from amino acid 68, resulting in an early stop codon (X) at what should have been the 82nd amino acid.	Resulting in loss of function of PCSK9 protein	Patients who carry the mutated gene may have a lower risk of cardiovascular disease due to reduced LDL-C levels
T77I	The 77th threonine (T) in the PCSK9 is replaced by isoleucine (I)	May change the catalytic activity of PCSK9 or its ability to bind to LDLR	Not entirely clear
V114A	The 114th valine (V) in the PCSK9 is replaced by alanine (A)	May change the catalytic activity of PCSK9 or its ability to bind to LDLR	Not entirely clear
I474V	The 474th Isoleucine (I) in the PCSK9 is replaced by valine (V)	May change the catalytic activity of PCSK9 or its ability to bind to LDLR	Not entirely clear
A522T	The 522nd alanine (A) in the PCSK9 is replaced by threonine (T)	May change the catalytic activity of PCSK9 or its ability to bind to LDLR	Not entirely clear
P616L	The 616th Proline (P) in the PCSK9 is replaced by leucine (L)	Not entirely clear	Not entirely clear
R93C	The 93rd arginine (R) in the PCSK9 is replaced by cysteine (C)	May change the catalytic activity of PCSK9 or its ability to bind to LDLR	Not entirely clear
R104C	The 104rd arginine (R) in the PCSK9 is replaced by cysteine (C)	May change the catalytic activity of PCSK9 or its ability to bind to LDLR	Not entirely clear
R194A	The 104rd arginine (R) in the PCSK9 is replaced by alanine (A)	May change PCSK9's ability to combine with LDLR	Not entirely clear
D238A	The 238th aspartic acid (D) in the PCSK9 is replaced by alanine (A)	May change the catalytic activity of PCSK9 or its ability to bind to LDLR	Not entirely clear
A293D	The 293th alanine (A) in the PCSK9 is replaced by aspartic acid (D)	May change the catalytic activity of PCSK9 or its ability to bind to LDLR	Not entirely clear
G452D	The 452nd glycine (G) in the PCSK9 is replaced by aspartic acid (D)	May change the catalytic activity of PCSK9 or its ability to bind to LDLR	Not entirely clear
S668R	The 668th serine (S) in the PCSK9 gene is replaced by arginine (R)	May change the catalytic activity of PCSK9 or its ability to bind to LDLR	Not entirely clear
G670E	The 670th glycine (G) in the PCSK9 gene is replaced with glutamate (E)	May change the catalytic activity of PCSK9 or its ability to bind to LDLR	Not entirely clear
S462P	The 462nd serine(S) in the PCSK9 gene is replaced by proline (P)	May change the catalytic activity of PCSK9 or its ability to bind to LDLR	Not entirely clear
R434W	The 434th arginine (R) in the PCSK9 is replaced by tryptophan (W)	May change the catalytic activity of PCSK9 or its ability to bind to LDLR	Not entirely clear
Q152H	The 152nd glutamine (Q) in the PCSK9 gene is replaced by histidine (H)	Reduce blood lipid levels in the body	Prevention of cardiovascular disease
D480N	The 480th aspartic acid (D) in the PCSK9 gene is replaced by asparagine (N)	Not entirely clear	Not entirely clear
E498K	The 498th glutamic acid (E) in the PCSK9 gene is replaced by lysine (K)	May change the binding ability of PCSK9 to LDLR, or affect the catalytic activity of PCSK9	May have an impact on cardiovascular disease risk
P174S	The 174th Proline (P) in the PCSK9 is replaced by serine (S)	May change the binding ability of PCSK9 to LDLR, or affect the catalytic activity of PCSK9	Not entirely clear

(*Continued*)

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Table 1 (Continued).

Mutation	Structure	Function	Clinical Significance
G394S	The 394th glycine (G) in the PCSK9 gene is replaced with serine (S)	May change the binding ability of PCSK9 to LDLR, or affect the catalytic activity of PCSK9	Not entirely clear
W72G	The 72nd tryptophan (W) in the PCSK9 gene is replaced by glycine (G)	Change LDLR degradation rate and cholesterol metabolism	Not entirely clear
N157S	The 175th asparagine (N) in the PCSK9 gene is replaced by serine (S)	Change the binding affinity or binding way of PCSK9 and LDLR	May have an impact on cardiovascular disease risk
V241M	The 241st valine (V) in the PCSK9 is replaced by methionine (M)	May result in increased or decreased binding affinity with LDLR	Early screening and prevention of cardiovascular diseases may be important.
T437N	The 437th threonine (T) in the PCSK9 is replaced by asparagine (N)	May change binding affinity with LDLR	Early screening and prevention of cardiovascular diseases may be important.
R476H	The 476th arginine (R) in the PCSK9 is replaced by histidine (H)	May change binding affinity with LDLR	Early screening and prevention of cardiovascular diseases may be important.
R499L	The 476th arginine (R) in the PCSK9 is replaced by leucine (L)	May change the catalytic activity of PCSK9 or its ability to bind to LDLR	Associated with cardiovascular disease risk
Q619X	Amino acid 619 of PCSK9 gene is mutated from glutamine (Q) to stop codon (X)	Promote the endocytosis and degradation of LDLR, thereby reducing the amount of LDLR on the cell surface	People who carry this mutation may have a lower risk of cardiovascular disease
T664I	The 664th threonine (T) in the PCSK9 gene is replaced by isoleucine (I)	May change the catalytic activity of PCSK9 or its ability to bind to LDLR	Not entirely clear
S372W	The 372nd serine(S) in the PCSK9 gene is replaced by tryptophan (W)	May change the catalytic activity of PCSK9 or its ability to bind to LDLR	Associated with cardiovascular disease risk
G517R	The 517th glycine (G) in the PCSK9 gene is replaced with arginine (R)	May change the catalytic activity of PCSK9 or its ability to bind to LDLR	Associated with cardiovascular disease risk
E569K	The 569th glutamic acid (E) in the PCSK9 gene is replaced by lysine (K)	Change PCSK9 and LDLR combination capability or combination method	Associated with cardiovascular disease risk
V610R	The 610th valine (V) in the PCSK9 is replaced by arginine (R)	May change the catalytic activity of PCSK9 or its ability to bind to LDLR	Associated with cardiovascular disease risk
V644R	The 664th valine (V) in the PCSK9 is replaced by arginine (R)	May change the catalytic activity of PCSK9 or its ability to bind to LDLR	Associated with cardiovascular disease risk
R659E	The 659th arginine (R) in the PCSK9 is replaced by glutamate (E)	May change the catalytic activity of PCSK9 or its ability to bind to LDLR	Associated with cardiovascular disease risk
R105W	The 105th arginine (R) in the PCSK9 gene is replaced by tryptophan (W)	May change the catalytic activity of PCSK9 or its ability to bind to LDLR	Not entirely clear
G316C	The 316th glycine (G) in the PCSK9 gene is replaced with cysteine (C)	May change PCSK9's ability to bind to LDLR or the stability of PCSK9	May have an impact on cardiovascular disease risk
H449L	The 449th histidine (H) in the PCSK9 gene is replaced by leucine (L)	May change PCSK9's ability to bind to LDLR or the stability of PCSK9	Associated with cardiovascular disease risk
E144K	The 144th glutamic acid (E) in the PCSK9 gene is replaced by lysine (K)	May change the catalytic activity of PCSK9 or its ability to bind to LDLR	Associated with cardiovascular disease risk
C378W	The 378th cysteine (C) in the PCSK9 gene is replaced by tryptophan (W)	May change PCSK9's ability to bind to LDLR or the stability of PCSK9	Associated with cardiovascular disease risk
Gain of Function and Loss of Function			
R496W	The 496th arginine (R) in the PCSK9 is replaced by tryptophan (W)	Not entirely clear	Not entirely clear
G263S	The 263th glycine (G) in the PCSK9 gene is replaced with serine (S)	Not entirely clear	Not entirely clear
I424V	The 424th Isoleucine (I) in the PCSK9 is replaced by valine (V)	Not entirely clear	Not entirely clear
R105Q	The 105th arginine (R) in the PCSK9 is replaced by glutamine (Q)	Not entirely clear	Not entirely clear
S636R	The 636th serine (S) in the PCSK9 is replaced by arginine (R)	Not entirely clear	Not entirely clear

Table 2 Drugs Based on PCSK-9 and Their Properties

Drug	Type	Indications	Method of Administration	Side Effects	Whether It Has Been Marketed	In Which Generation of Drugs Does It Belong
Evolocumab	Human IgG2 monoclonal antibody	The treatment for homozygous familial hypercholesterolemia in adults or adolescents over 12 years of age is also applicable to patients with hyperlipidemia who are intolerant to statins.	Subcutaneous injection	Injection site reactions, allergic reactions, and other adverse effects may occur.	Yes	The first generation
Alirocumab	Fully human monoclonal antibody	Prevention of cardiovascular disease, treatment of hypercholesterolemia and mixed dyslipidemia.	Subcutaneous injection	The following adverse events may occur: injection site reactions, pruritus, upper respiratory symptoms, influenza-like illness, and allergic reactions, etc.	Yes	The first generation
Tafolecimab	Fully human monoclonal antibody	The primary indication is hypercholesterolemia.	Subcutaneous injection	No detailed figures have been released	No	The first generation
Bococizumab	Humanized monoclonal antibody	Patients with hypercholesterolemia who have a poor response to or are intolerant of statins, as well as patients with familial hypercholesterolemia (FH)	Subcutaneous injection	In clinical trials, it was found that some patients developed anti-drug antibodies against Bococizumab, resulting in decreased efficacy and increased adverse reactions.	No	The first generation
Inclisiran	Small interfering RNA (siRNA)	The treatment of primary hypercholesterolemia or mixed dyslipidemia	Subcutaneous injection	Injection site reactions may occur.	Yes	The second generation
MK-0616	Oral small - molecule inhibitor of PCSK9	The primary indication is hypercholesterolemia.	Oral administration	Gastrointestinal discomfort, headache, muscle pain, and abnormal liver function may occur.	No	The third generation
Lerodalcibep	Small recombinant fusion protein	Treatment of adults with ASCVD and individuals at very high or high risk for ASCVD, including those with heterozygous familial hypercholesterolemia	Subcutaneous injection	No detailed figures have been released	No	The third generation
Recaticimab	Humanized IgG1 monoclonal antibody	It is indicated for the treatment of adults with nonfamilial hypercholesterolemia or mixed dyslipidemia, and can also be used in combination with statins or other lipid-lowering therapies.	Subcutaneous injection	Injection site reactions may occur.	Yes	It has not been explicitly mentioned in the publicly available information.
Ongericimab	Fully human monoclonal antibody	It is indicated for patients with primary hypercholesterolemia, mixed hyperlipidemia, or heterozygous familial hypercholesterolemia.	Subcutaneous injection	No detailed figures have been released	No	It has not been explicitly mentioned in the publicly available information.
Ebronucimab	Fully human IgG1 monoclonal antibody	It is indicated for patients with primary hypercholesterolemia, mixed hyperlipidemia, or heterozygous familial hypercholesterolemia.	Subcutaneous injection	Injection site reactions, allergic reactions, and other adverse effects may occur.	It is already available in certain regions or countries, but its availability may vary depending on local regulatory approvals.	It has not been explicitly mentioned in the publicly available information.

The Pleiotropic Mechanism of PCSK9

Inflammatory Response Regulation

PCSK9 not only plays a role in lipid metabolism but also participates in regulating the inflammatory responses through a variety of mechanisms. First, PCSK9 increases the uptake of oxidized low-density lipoprotein (ox-LDL) by upregulating the expression of plant hemagglutinin-like oxidized low-density lipoprotein receptor 1 (LOX-1) on cells. Ox-LDL can be used as a ligand to bind to macrophage pattern recognition receptors (such as TLR4) and activate inflammatory signaling pathways such as the NF-κB pathway, thereby upregulating the expression of inflammatory cytokines and promoting the inflammatory response.[24,25] Second, owing to their ability to recognize and bind ox-LDL, the scavenger receptor protein family can promote the uptake and accumulation of lipids by monocytes and macrophages to form foam cells. When PCSK9 is abnormally expressed, it can enhance the SR-mediated inflammatory response by increasing the level of ox-LDL.[25] Third, PCSK9 can also induce the degradation of LRP1 and ApoER2 in macrophages, increase the secretion of inflammatory cytokines by activating the TLR4/NF-κB pathway, and downregulate ATP-binding cassette transporter A1 (ABCA1) in macrophages to inhibit cholesterol efflux, thus playing a proinflammatory role.[26] In hyperlipidemia, PCSK9 can also affect inflammatory changes in monocytes, including the upregulation of C-C chemokine receptor type 2 (CCR2) expression and increased migration to monocyte chemokine protein 1 (MCP-1).[27] The PCSK9 monoclonal antibody can reduce the expression and migration ability of CCR2 in monocytes, reduce tumor necrosis factor-α (TNF-α), and increase the secretion of the anti-inflammatory cytokine IL-10.[28] Fourth, PCSK9 is expressed in vascular smooth muscle cells (VSMCs) of atherosclerotic plaques, which can induce LOX-1 expression and promote inflammatory proliferation and the migration of VSMCs by increasing the production of reactive oxygen species (ROS).[29] The emergence of PCSK9 inhibitors can reduce the oxidative stress of endothelial cells, reduce the production and accumulation of ox-LDL, inhibit the secretion of inflammatory mediators, and thus reduce damage to endothelial cells and the inflammatory response of the blood vessel wall. Some PCSK9 inhibitors, such as aliciumab, and some drugs that can indirectly regulate PCSK9 levels (such as Angiosofacia pills) can also downregulate the expression of proinflammatory factors, such as TNF-α and interleukin-6 (IL-6), and increase the expression of anti-inflammatory factors, such as IL-10.[30,31] In animal models of hyperlipidemia and atherosclerosis, the inhibition of PCSK9 also reduces the levels of M-CSF-1 and other proinflammatory factors, such as VEGF-A. M-CSF-1 is an important stimulating factor for monocyte and macrophage migration, and a decrease in its level can reduce the recruitment of monocytes to the blood vessel wall, thereby alleviating the inflammatory response of the blood vessel wall and the occurrence of atherosclerosis. A decrease in the VEGF-A level can lead to downregulation of the expression of intercellular adhesion molecule-1 (ICAM-1) in endothelial cells, thereby reducing the adhesion of monocytes to the vascular endothelium and

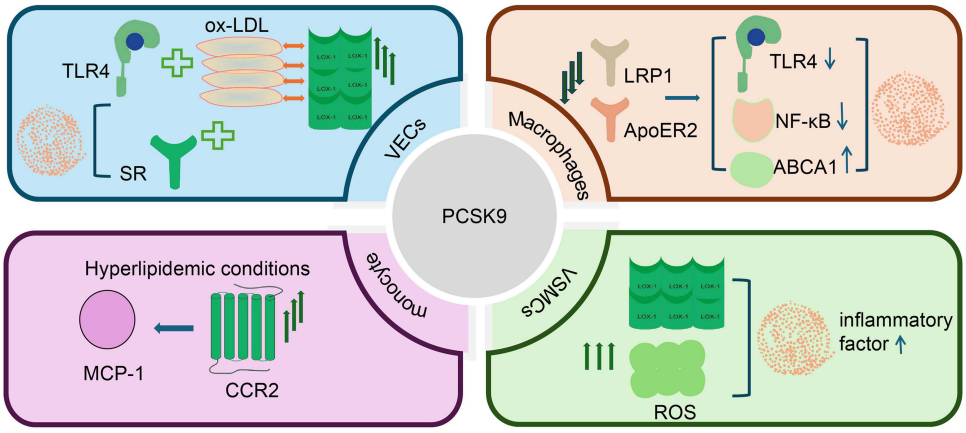

Figure 4 Proinflammatory mechanism of PCSK9 in surface receptor proteins of different cells, such as vascular endothelial cells, monocytes, macrophages, and vascular smooth muscle cells.

Abbreviations: SR, Scavenger Receptor; TLR4, Toll-Like Receptor 4; ABCA1, ATP-Binding Cassette Transporter A1; ApoER2, Apolipoprotein E Receptor 2; NF-κB, Nuclear Factor kappa-light-chain-enhancer of activated B cells; MCP-1, Monocyte Chemoattractant Protein-1; CCR2, C-C Chemokine Receptor Type 2; VECs, Vascular Endothelial Cells; VSMCs, Vascular Smooth Muscle Cells.

further reducing the inflammatory response of the vascular wall, both of which are non-LDL-C-dependent anti-inflammatory mechanisms.[32] The proinflammatory mechanism of PCSK9 is shown in Figure 4.

In recent years, relevant studies have investigated the inflammatory response of PCSK9 in specific diseases. Marinelli et al[33] reported for the first time that elevated serum PCSK9 levels can be used as a potential biomarker of ulcerative colitis (UC) disease activity. The study included 112 adults who had been diagnosed with UC for more than 6 months and were divided into different disease activity groups on the basis of Mayo scores (a tool used to assess the severity of ulcerative colitis and the effectiveness of treatment). The results revealed that in UC patients, serum PCSK9 levels were significantly positively correlated with commonly used biomarkers such as C-reactive protein (CRP), fecal calponin (FC), and disease activity scores, suggesting that the PCSK9 level reflects disease activity and inflammation in UC. Deng et al[34] explored the relationships between serum PCSK9 levels and disease activity, the proportion of T helper cells (Th1/Th2/Th17 cells), and the clinical response to TNF (tumor necrosis factor inhibitor) treatment in UC patients. These authors reported that serum PCSK9 levels were positively correlated with disease activity, C-reactive protein (CRP), total Mayo score, and the proportion of Th 1 and Th 17 cells in UC patients. These results can help clinicians provide personalized treatment options for UC patients to improve the outcome of the disease.

Tumor Immune Regulation

In recent years, the role of PCSK9 in tumorigenesis and development has gradually been recognized. PCSK9 is involved in the proliferation, apoptosis, invasion, and migration of tumor cells through various mechanisms, as well as the regulation of immune cells in the tumor microenvironment, indicating its potential value in tumor therapy. First, PCSK9 may regulate the cholesterol metabolism of tumor cells, thereby affecting their proliferation and differentiation. Since cholesterol is an important part of the cell membrane and crucial for cell growth and survival, PCSK9 may promote the growth and metastasis of tumor cells by affecting the uptake and utilization of cholesterol.[35] Second, PCSK9 can promote the apoptosis of tumor cells by influencing apoptosis-related factors such as XIAP and survivin, mitochondrial apoptosis, endoplasmic reticulum stress, and other pathways, thereby mediating the genesis and progression of tumors. In addition, PCSK9 is significantly correlated with tumor invasion and metastasis, which has been confirmed in melanoma cells, and other studies have shown that PCSK9 deletion can also reduce the liver metastasis of tumor cells.[36]

PCSK9 can also interact with cancer-promoting signaling pathways to influence tumor growth and spread. For example, there is a potential link between PCSK9 and the regulation of the cancer-promoting signaling pathway PI3K/AKT, and intervention in this pathway may be helpful for antitumor therapy. In hepatocellular carcinoma (HCC), palmitoylation of PCSK9 enhances its interaction with PTEN, a tumor suppressor, leading to the degradation of PTEN via the lysosomal pathway, thereby activating the AKT pathway and promoting cancer cell growth.[37] In colon cancer, Wang et al[38] reported that PCSK9 can promote the progression of colon cancer by regulating EMT (Epithelial–Mesenchymal Transition) and the PI3K/AKT signaling pathway and affect macrophage polarization, mediating M1/M2 polarization by regulating MIF (macrophage migration inhibitor) and lactate levels.

In the regulation of tumor immune response, the downregulated expression of PCSK9 may increase the level of major histocompatibility complex (MHC) protein class I molecules on the surface of tumor cells, thus promoting the invasion and killing of cytotoxic T cells into the tumor and enhancing the antitumor immune response.[39] Furthermore, PCSK9 has been shown to enhance the effectiveness of anti-PD-1 and anti-PD-L1 (immune checkpoint inhibitors).[40] In addition, the inhibition of PCSK9 can increase the number of tumor-infiltrating lymphocytes, especially CD8+ killer T cells, thereby enhancing the antitumor immune response.[41]

Other studies have suggested that there is a correlation between PCSK9 expression and neovascularization. PCSK9 may be an antiangiogenic gene. Since angiogenesis is one of the key steps in tumor growth and spread, overexpression of PCSK9 may inhibit tumor growth and metastasis.[42]

Thrombosis Regulation

An increasing number of studies have shown that PCSK9 is involved in the regulation of thrombosis and has an important effect on platelet function and coagulation factors. First, PCSK9 can indirectly activate platelets by reducing the consumption of lipoproteins and promote the overactivation of platelets. Second, PCSK9 can bind to the CD36 receptor independently of the LDL-R pathway and directly promote platelet activation and thrombosis. In mouse models of mesenteric arteriolar

thrombosis damaged by $FeCl_3$, PCSK9 was found to significantly increase thrombosis formation.[43] NOX-2 (the catalytic unit of NADPH oxidase) also plays an important role in this process, accelerating the oxidation of lipoproteins by producing reactive oxygen species (ROS), which in turn promotes platelet activation.[44] Third, ox-LDL induces the expression of tissue factor (TF), a key factor in the clotting cascade, in human monocytes in a TLR4-dependent manner, and its increased expression further promotes the clotting process, thereby increasing the risk of thrombosis.[45] Liu et al[46] first explored the function of endogenous SIRT6 (silencing-regulatory factor 2 related enzyme 6) in platelets in a mouse model and reported that the absence of SIRT6 led to increased expression and release of PCSK9 in platelets, thus activating the MAPK signaling pathway and promoting platelet activation and thrombosis. These findings suggest that in the future, SIRT6-based agonists may be used to prevent and treat thrombotic diseases and that enhancing the expression of SIRT6 in platelets through gene editing technology may constitute a new therapeutic strategy.

Furthermore, PCSK9 can also affect the clotting process and promote thrombosis by regulating coagulation factors and the fibrinolysis system. PCSK9 promotes the clotting process by increasing the production of thrombin, which is at the heart of the clotting cascade and converts fibrinogen into fibrin, which can lead to thrombosis. When Silvino et al[47] explored the role of PCSK9 and thrombin production in familial hypercholesterolemia (FH), and they reported that the thrombin production potential of patients treated with statins alone or combined with ezetimibe was significantly reduced, indicating that the PCSK9 level was significantly increased in patients with FH. It is closely related to dyslipidemia and abnormal thrombin production. Second, increased plasma PCSK9 levels were positively correlated with multiple clotting indicators. In a mouse septicemia model, the inhibition of PCSK9 improved coagulation dysfunction and reduced the D-dimer level, prothrombin time (PT), activated partial thromboplastin time (APTT), and other coagulation markers in septicemic mice.[48] Wang et al[49] also confirmed that PCSK9-deficient mice presented a significant reduction in thrombosis in a venous thrombosis model, that the activity of clotting factors in PCSK9-deficient mice was reduced, and that platelet activation was inhibited. However, a subsequent study did not find significant antithrombotic effects of PCSK9 inhibitors. The study included 40 patients with FH who received evolocumab and alirocumab treatment. D-dimer and fibrinogen levels in patients were detected before and after treatment as markers for evaluating thrombosis. After treatment with PCSK9 inhibitors, the median D-dimer level decreased to 0.31 mg/L (IQR 0.25–0.59 mg/L), and the median fibrinogen level increased to 3.4 g/L (IQR 2.98–3.62 g/L). However, none of these changes reached statistical significance ($p = 0.37$ and $p = 0.38$). Owing to the small sample size and limited observation period in this study, the possibility of more subtle or long-term antithrombotic effects of PCSK9 inhibitors cannot be completely ruled out.[50]

On the other hand, PCSK9 promotes the expression of plasminogen activation inhibitor-1 (PAI-1), inhibits the activity of tissue-type plasminogen activator(tPA), and reduces fibrinolysis, which further increases the risk of thrombosis and stabilization. Levine et al reported in both mouse and human studies that PAI-1 inhibition was positively correlated with PCSK9.[51] A recent study evaluating the effects of PCSK9 inhibitors on lipid parameters, inflammation, coagulation, and fibrinolysis indices in patients after myocardial infarction also revealed that TC, LDL-C, and TG levels were correlated with coagulation and fibrinolysis parameters (such as thrombin-activated fibrinolysis inhibitor, PAI-1, etc) before treatment with PCSK9 inhibitors. These associations weakened or disappeared after treatment, suggesting that PCSK9 inhibitors may indirectly affect the coagulation and fibrinolysis systems by lowering lipid levels.[52] Moreover, since factor VIII is a key accelerator in the clotting pathway, PCSK9 may indirectly promote the clotting response by affecting its production and activation, but this has not been proven by current studies.[53]

Expression and Function of PCSK9 in Extrahepatic Tissues

PCSK9 is expressed mainly in the liver, but in recent years, its expression and function in extrahepatic tissues have gradually attracted increasing attention. Figure 5 shows the expression and function of PCSK9 in different tissues and organs.

Cardiovascular System

PCSK9 is most significantly expressed in the liver, but small amounts of PCSK9 are also expressed in cardiomyocytes, especially in cardiac muscle fibers and the vascular endothelium. PCSK9 expression in myocardial tissue may be regulated by a variety of factors, including genetic variation, environmental factors, hormone levels, nutritional status, etc. In particular, signaling pathways associated with cardiometabolic and inflammatory processes are likely to modulate

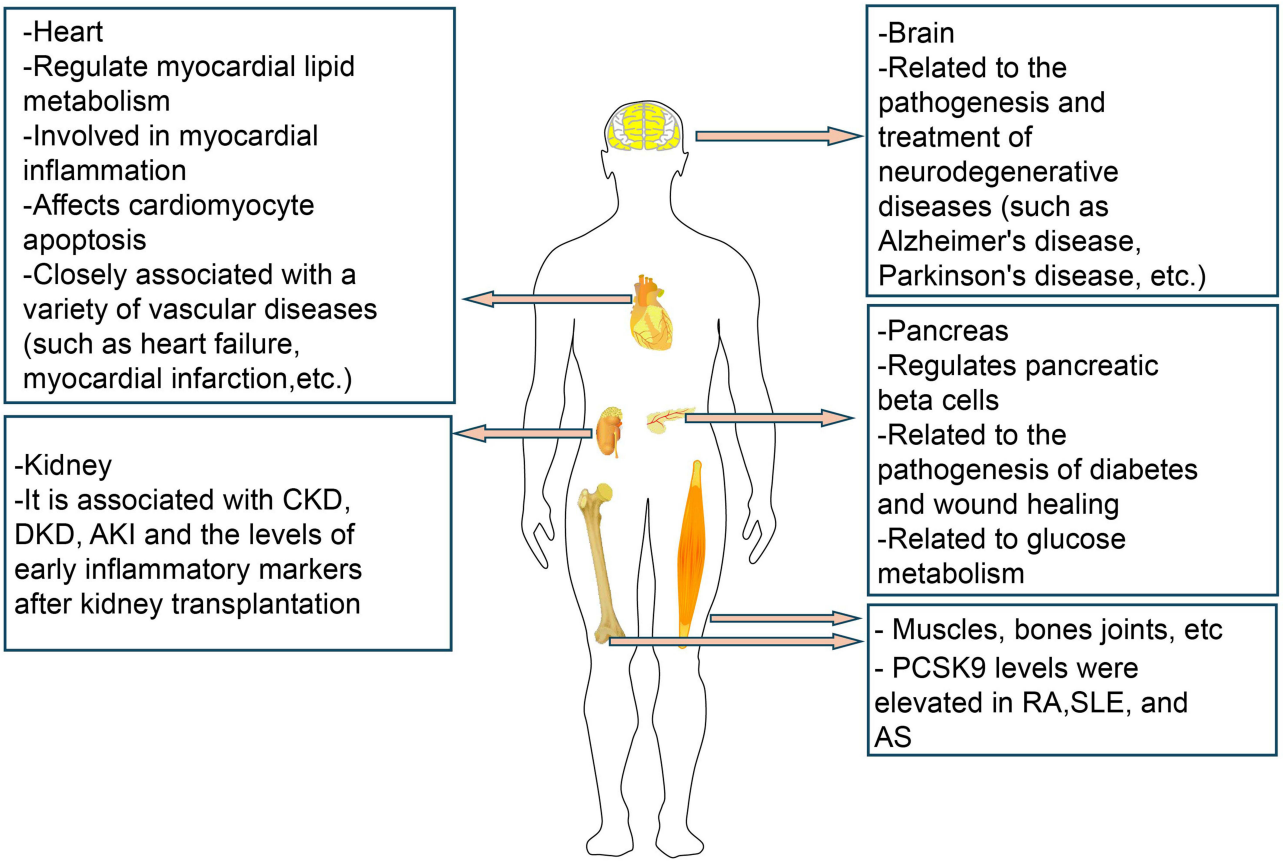

Figure 5 Expression and function of PCSK9 in the kidney, heart, brain, pancreas, muscle, bone and joints.

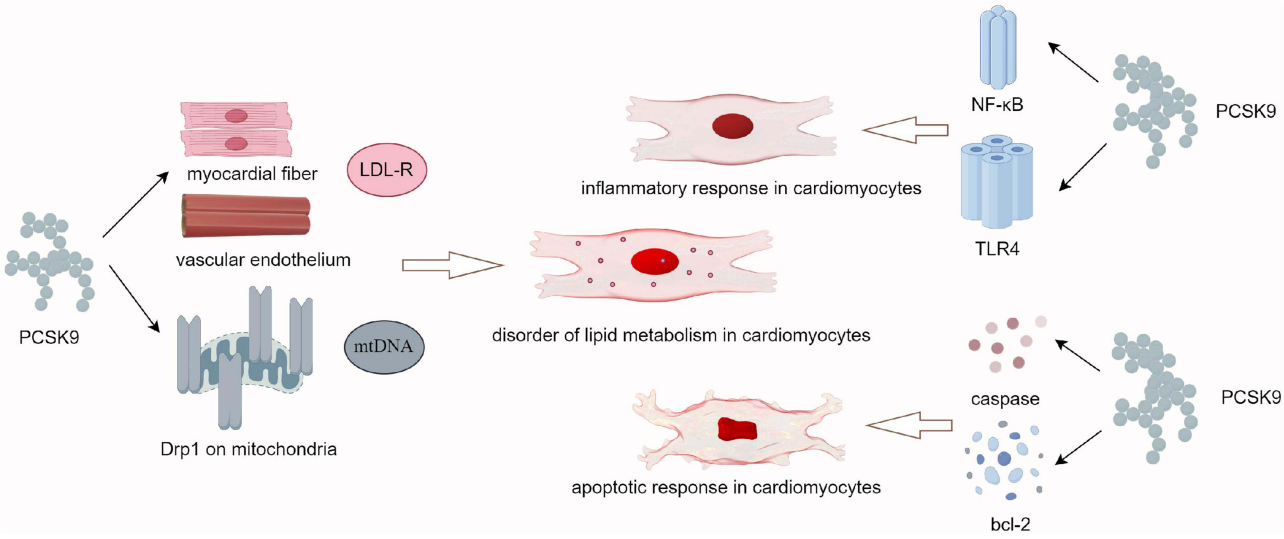

Figure 6 PCSK9 participates in myocardial cell inflammation, apoptosis, and lipid metabolism disorders through various pathways.

the expression levels of PCSK9. Figure 6 illustrates the diverse pathophysiological processes in which PCSK9 is involved within cardiomyocytes.

The function of PCSK9 in the myocardium is first to regulate myocardial lipid metabolism. PCSK9 affects the uptake and metabolism of LDL-C by cardiomyocytes by regulating the stability of LDLR.[54] Second, PCSK9 expressed and

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released by cardiomyocytes can act on cardiomyocytes and impair their function in an autocrine manner.[55] On the other hand, PCSK9 can promote mitochondrial division by directly or indirectly regulating the expression and activity of Drp1 (dynamic associated protein 1), which not only destroys the integrity of mitochondria but also may lead to mitochondrial DNA (mtDNA) damage and dysfunction, thus further aggravating myocardial damage.[56]

In addition, PCSK9 can participate in the myocardial inflammatory response, which is one of the important mechanisms of the occurrence and development of cardiovascular diseases. The expression of PCSK9 in cardiomyocytes is closely related to the inflammatory response. By activating specific signaling pathways (NF-κB, TLR4, etc), it upregulates the expression of inflammatory factors, thus participating in the process of myocardial inflammation.[57] PCSK9 can also influence the infiltration and activation of immune cells such as macrophages in myocardial tissue, further aggravating the myocardial inflammatory response. During ventricular remodeling after myocardial infarction, PCSK9 can affect cardiac function by regulating macrophage polarization. The inhibition of PCSK9 can reduce M1 macrophage polarization and promote M2 polarization, which is mediated through the activation of the TLR4/MyD88/NF-κB signaling pathway.[58] The Notch1 signaling pathway also plays a role in this remodeling process and can regulate the transformation of myocardial infarction-induced cardiac fibroblasts (CFs) into myocardial fibroblasts (CMFs). PCSK9 inhibitors prevent the transdifferentiation of CFs into CMFs by increasing the expression of Notch1, thus reducing the degree of fibrosis. Improves heart function.[59] Another signaling pathway, Pink1/Parkin, has been found to play an important role in cardiomyocyte injury induced by hypoxia/reoxygenation (H/R), which affects the fate of cardiomyocytes through the regulation of mitochondrial autophagy. Interference with the Pink1/Parkin pathway may provide a new strategy for the prevention and treatment of H/R-related cardiovascular diseases.[60]

Additionally, PCSK9 can affect the apoptosis of cardiomyocytes, which is an important pathological characteristic of heart diseases such as heart failure. PCSK9 may affect the apoptotic process of cardiomyocytes by regulating specific apoptosis-related genes or signaling pathways (such as the Caspase family and the Bcl-2 family). Inhibition of PCSK9 may help reduce the number of apoptotic cardiomyocytes and protect myocardial function.[61,62] While exploring the relationships among PCSK9, mtDNA damage, and death, researchers have reported that PCSK9 causes mtDNA damage through several mechanisms, such as increased expression of mtDNA damage markers (such as 8-OHdG). mtDNA damage may trigger the activation of the NLRP3 inflammasome and induce pyroptosis. In the context of chronic myocardial ischemia, this process is significantly amplified.[63]

PCSK9 is also closely associated with a variety of cardiovascular diseases. In myocardial ischemia–reperfusion models, upregulation of PCSK9 exacerbates myocardial injury.[55] IL-10 can also play a protective role in myocardial ischemia–reperfusion injury by regulating lipid metabolism and inflammation mediated by phospholipid oxidation.[64] In a mouse model of ischemic heart disease, PCSK9 expression was significantly upregulated around the infarct area, which was closely related to cardiac systolic dysfunction, whereas the use of PCSK9 inhibitors or PCSK9 gene knockout mice significantly reduced the infarct size and significantly improved cardiac functions, such as the ejection fraction and left ventricular systolic force.[65] Moreover, PCSK9 indirectly leads to elevated cholesterol levels by promoting the degradation of LDLR, which in turn promotes the development of atherosclerosis. Atherosclerosis affects the blood supply to coronary arteries and increases the risk of heart attack.[66] In addition, overexpression of PCSK9 is associated with heart failure, which may promote the deterioration of cardiac structure and function by affecting cholesterol metabolism and cardiomyocyte energy metabolism.[67]

The expression and function of PCSK9 in myocardial tissue are highly important for maintaining heart health. However, a recent study has revealed that PCSK9 is expressed only minimally in the hearts of mice, rats, and humans, suggesting that its direct regulatory role in cardiac function remains unclear. This finding is controversial compared to previous studies, which proposed that PCSK9 might act locally in the heart, particularly under pathological conditions. Current evidence primarily supports the notion that PCSK9 is secreted into the bloodstream by the liver and exerts indirect effects on cardiac function by modulating lipid metabolism and inflammatory responses. Furthermore, the inhibition of PCSK9 synthesis in the liver has been shown to be comparable in efficacy to monoclonal antibody-mediated PCSK9 inhibition, further confirming the liver as the primary source of PCSK9. Additionally, research has found that hepatic PCSK9 expression levels may change with age, and overexpression of PCSK9 might accelerate liver aging. During the aging process, elevated PCSK9 levels may be associated with cardiac dysfunction, and PCSK9 inhibitors have been shown to ameliorate age-related liver diseases such as non-alcoholic steatohepatitis (NASH) as well as aging-related cardiovascular dysfunction. While improving hepatic steatosis and inflammation, PCSK9 inhibitors

may also confer cardioprotective effects by enhancing lipid metabolism and reducing oxidative stress. Monitoring circulating PCSK9 levels could facilitate early identification and intervention for age-related cardiovascular diseases. Future studies are needed to further elucidate the direct mechanisms of PCSK9 in the heart, particularly in the context of aging and metabolic diseases, and to evaluate the long-term efficacy and safety of PCSK9 inhibitors in patients with cardiovascular and liver diseases, especially their potential protective effects on cardiac function.[68,69]

The specific signal transduction pathway of PCSK9 in cardiomyocytes and its function under different pathological conditions should be further studied in the future. At the same time, targeted drug research for PCSK9 should also be strengthened to develop safer and more effective treatments.

Endocrine System

PCSK9 plays an important role in the pancreas and is expressed mainly in pancreatic beta cells, and its expression level is regulated by many factors, such as insulin and glucose. Locally produced PCSK9 can regulate the expression of LDLR in pancreatic beta cells, further affecting the accumulation of cholesterol esters and insulin secretion, and changes in cholesterol levels can affect the formation, transport, and release of insulin particles. The absence of PCSK9 may lead to a toxic accumulation of cholesterol in pancreatic cells, thus impairing insulin secretion function.[70,71] PCSK9 also regulates the number and function of β cells by influencing their proliferation and apoptosis.[72] Several surface proteins closely related to the function of β cells, such as insulin receptors and glucose transporters, have been studied, and it has been found that PCSK9 may regulate gene transcription and translation of these surface proteins by influencing signal transduction pathways in β cells, such as the MAPK and PI3K/Akt pathways. PCSK9, through its secreted form outside the cell, may also interact with other cellular or matrix components to indirectly affect the expression of beta-cell surface proteins.[73] Figure 7 shows the relevant mechanism of action of PCSK9 in islet beta cells.

Vascular endothelial dysfunction caused by diabetes is an important cause of poor healing of diabetic foot ulcers. Gao et al revealed a new mechanism by which diabetes induces PCSK9 to promote VEGFR2 ubiquitination, thereby inhibiting vascular endothelial function and diabetic wound healing. In addition, they reported that the application of a PCSK9 monoclonal antibody can significantly improve the vascular function and wound healing of diabetic mice, providing a new treatment method for clinically promoting the wound healing of diabetic foot ulcers.[74] Genetic association studies have revealed that PCSK9 genetic variants are associated with an increased risk of type 2 diabetes. These findings suggest that PCSK9 may play an important role in the pathogenesis of diabetes, but the specific molecular mechanism still needs to be further explored.[75] Furthermore, through multi-omics Mendelian randomization studies, Rosoff et al investigated the effects of PCSK9 and HMGCR inhibition on type 2 diabetes in five populations. Their findings revealed that PCSK9 inhibitors, while reducing LDL cholesterol, significantly lowered the risk of type 2 diabetes compared to HMGCR inhibitors. This suggests that PCSK9

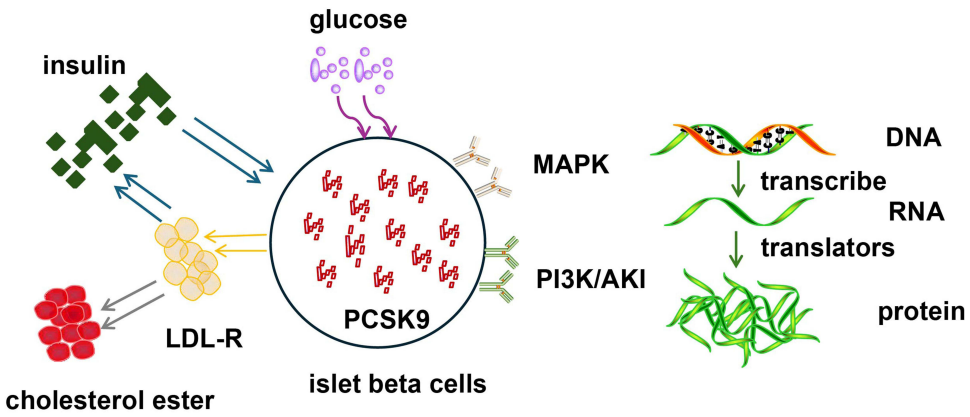

Figure 7 The mechanisms underlying the role of PCSK9 in the regulation of pancreatic β-cell function. Insulin and glucose regulate the expression of PCSK9 in islet beta cells, and locally produced PCSK9 regulates the expression of LDLR, affecting the release of cholesterol ester and insulin. In addition, PCSK9 can also regulate the gene transcription and translation of the surface proteins of islet beta cells by affecting the MAPK and PI3K/Akt signaling pathways.

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inhibition not only improves lipid metabolism but may also offer superior metabolic safety, providing critical evidence to support its practical application in clinical settings.[76]

Although PCSK9 inhibitors have shown excellent performance in reducing LDL-C, their effects on glucose metabolism have been the focus of research. Multiple clinical trials and meta-analyses have shown that PCSK9 inhibitors have no harmful effects on glucose metabolism and may even improve blood sugar control in some cases.[77] Animal experiments have confirmed this point. High inactivation of PCSK9 in pancreatic beta cells does not affect glucose homeostasis or insulin secretion in mice,[78] and Momtazi-Borojeni et al[79] reduced PCSK9 levels via immune mechanisms, effectively improving the blood glucose level and glucose tolerance of diabetic rats. It also reduces LDL-C levels. However, some studies suggest that PCSK9 inhibitor treatment may cause mild hyperglycemic reactions, especially in individuals with diabetes. Most of these hyperglycemic reactions are reversible and can be reversed after withdrawal. In experimental mouse models, both female and male PCSK9-deficient mice fed a Western diet or a normal diet presented varying degrees of elevated blood sugar.[80]

The mechanism of action of PCSK9 in the pancreas and diabetes is becoming clear. The discovery of exenatide and other drugs has also provided new ideas for the diagnosis and treatment of diabetes. When diabetic patients receive statin therapy, the combined use of exenatide may help reduce the adverse effects of statins on islet beta cells and improve insulin secretion function.[81] Future studies should further reveal the specific mechanism of action of PCSK9 in diabetes and its complications and explore the potential application of PCSK9 inhibitors in diabetes treatment. Moreover, the development of drugs targeting PCSK9 will lead to more options for the treatment of metabolic diseases such as diabetes.

Urinary System

The kidney is not only an important excretory organ of the human body but also plays a role in cholesterol metabolism and excretion. Studies have shown that PCSK9 is expressed in the kidney, especially in the renal tubules, which may affect the excretion process of cholesterol. PCSK9 affects the excretion of cholesterol by affecting the stability of LDLR in the renal tubules, consequently affecting renal health.[82] Figure 8 shows the mechanism of action of PCSK9 in different kidney diseases.

In experimental models of chronic kidney disease (CKD), PCSK9 levels are elevated.[83] The abnormal expression of CD36 in renal tubular epithelial cells and podocytes may lead to excessive lipid accumulation in cells and then cause damage to renal tubular epithelial cells and podocytes, and PCSK9 can reduce the above process by affecting the expression of CD36.[84,85] By lowering LDL-C levels, PCSK9 inhibitors can reduce the burden on the glomeruli and slow the process of inflammation and fibrosis, thereby protecting kidney function. Preliminary clinical trial results suggest that PCSK9 inhibitors have a protective effect on kidney function in patients with CKD. PCSK9 inhibitors also have good safety and tolerance in patients with moderate renal function decline.[86] In the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial, the PCSK9 inhibitor evolocumab was able to effectively reduce LDL-C levels (approximately 50–60%) in patients with CKD at all stages, reducing the risk of primary endpoint events, and the safety was consistent in patients at all stages.[87] In patients with CKD who are at high cardiovascular risk, PCSK9 inhibitors may also be an important option for intensive lipid-lowering therapy and combination therapy.[88]

The role of PCSK9 in diabetic nephropathy (DKD) has also been a hot topic in recent years. Elevated PCSK9 levels can lead to glomerular lipid accumulation and promote the glomerular inflammatory response and fibrosis process. PCSK9 can also affect the function and survival of podocytes; regulate signaling pathways in podocytes (such as the Akt/mTOR pathway); affect the proliferation, differentiation, and apoptosis of podocytes; and participate in the progression of diabetic nephropathy.[89] Animal experiments revealed that PCSK9 is expressed in both DKD model mice and Hyperglycemia Preconditioning Adaptation (HGPA) cells and is closely related to the intensification of renal inflammation. In diabetic nephropathy, increased mtDNA damage leads to the activation of the cGAS/STING signaling pathway. By triggering a series of inflammatory cascades, the inhibition of PCSK9 levels inhibits the activation of signaling pathways and reduces inflammation.[90] Another study compared the expression of PCSK9 in the glomerular tissues of DKD patients and normal controls and reported that PCSK9 expression was downregulated in the glomerular tissues of DKD patients and decreased in podocytes in an animal model of diabetes. This downregulation is closely related to

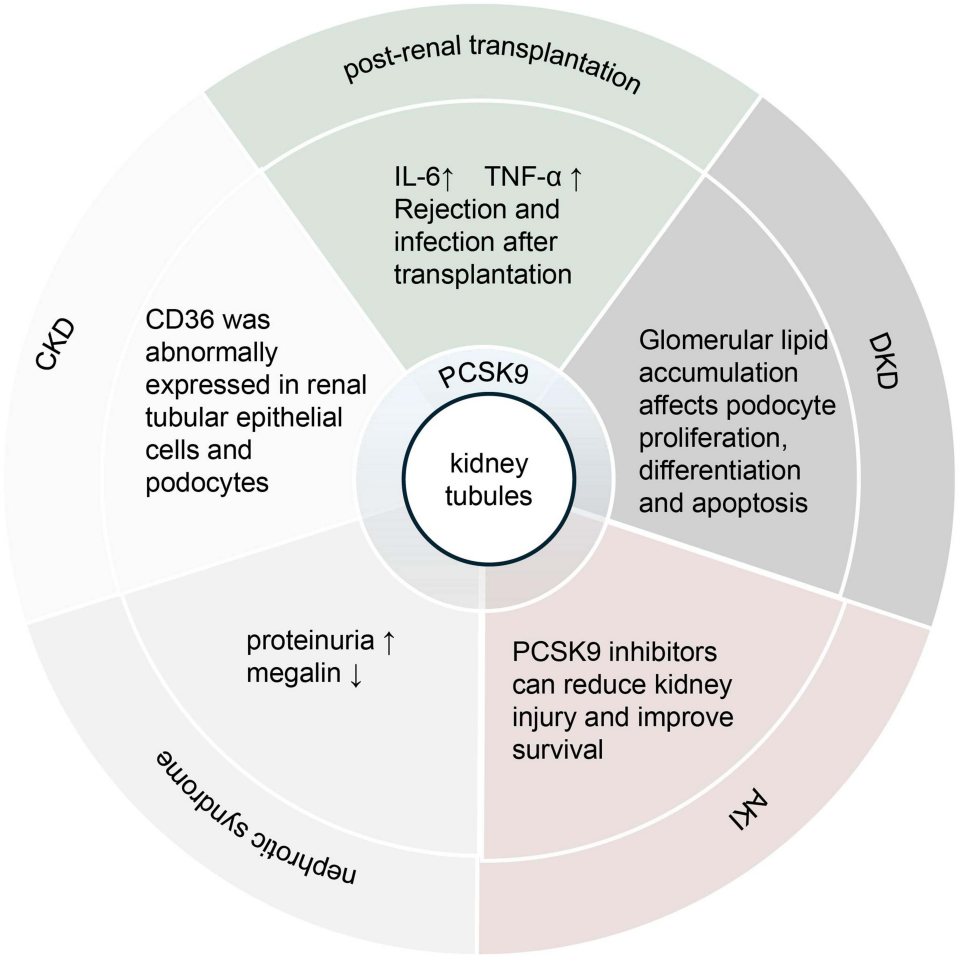

Figure 8 The mechanism of action of PCSK9 in different kidney diseases.

increased lipid accumulation, mitochondrial dysfunction, cell apoptosis, and kidney injury.[91] Future studies could explore the specific mechanism of PCSK9 in DKD and develop drugs that target PCSK9 to provide new strategies for the treatment of DKD.

PCSK9 is also associated with inflammatory biomarkers in the early stage after kidney transplantation. In the early stage after kidney transplantation, the serum PCSK9 level in patients fluctuates to a certain extent, and some studies suggest that the level of PCSK9 is decreased, which may be related to the use of immunosuppressants and the improvement in cholesterol metabolism after transplantation. The increase in PCSK9 levels in most patients may be accompanied by increases in IL-6, TNF-α, and other inflammatory factors, suggesting that PCSK9 may be involved in the inflammatory reaction process after transplantation and that patients with higher PCSK9 levels may be more prone to complications such as rejection and infection after transplantation.[92] In posttransplant treatment, the PCSK9 inhibitor evolocumab, in combination with statins, is safe and effective, significantly reduces lipid levels, and does not increase the risk of cardiovascular events. Although the study sample size was limited and the observation period was relatively short, the results still support the potential use of PCSK9 inhibitors in patients with elevated cardiovascular risk after kidney transplantation.[93] In addition, among kidney transplant patients, the risk of new-onset diabetes (NODAT) is significantly increased in patients with higher serum PCSK9 levels.[94]

The presence of proteinuria, a common symptom of CKD, indicates damage to the glomerular filtration membrane and may accelerate the decline in kidney function. In patients with nephrotic syndrome, there is a significant positive correlation between the level of PCSK9 and the degree of proteinuria, and the more severe the proteinuria is, the higher the circulating PCSK9 level is.[95,96] Some studies have revealed a new mechanism by which PCSK9 exacerbates proteinuria in nephrotic

syndrome, that is, the effect of PCSK9 on megalin in proximal renal tubules. PCSK9 can promote megalin transport to lysosomes, resulting in the degradation of megalin, thus reducing its quantity and function in proximal renal tubules. Owing to the decrease in megalin, the proximal renal tubules are less able to reabsorb protein, causing more protein to be excreted in the urine, thus exacerbating proteinuria.[82] In patients with refractory nephrotic syndrome, PCSK9 inhibitors had significant lipid-lowering effects, urinary protein levels were also reduced in some patients, and no serious adverse reactions occurred in these patients during the observation period. A few patients experienced mild discomfort, such as pain at the injection site and muscle pain, but none of these symptoms affected the continuation of treatment.[97] In animal models, PCSK9 inhibitors improved the structure and function of podocytes in mouse nephrotic syndrome models, alleviated podocyte injury and apoptosis, restored podocyte barrier function, and thus reduced proteinuria excretion.[98] These findings provide new targets and ideas for the treatment of nephrotic syndrome and provide an experimental basis for the future development of specific drugs targeting PCSK9.

In the pathological process of acute kidney injury (AKI), the expression of PCSK9 is significantly upregulated, and its level is closely related to the severity and prognosis of AKI. Treatment with PCSK9 inhibitors can significantly reduce the pathological changes and renal damage associated with AKI and improve the survival rate of patients. In addition, in contrast to media-induced AKI in patients with acute myocardial infarction and patients with atherosclerotic cardiovascular disease receiving interventional therapy, treatment with PCSK9 inhibitors significantly improved the incidence of AKI, as well as renal function indicators.[99,100] A pharmacovigilance study revealed AKI-related signals associated with PCSK9 inhibitors, revealing the protective effect of PCSK9 inhibitors on AKI, especially when combined with common nephrotoxic drugs, PCSK9 inhibitors can still reduce the risk of AKI caused by these drugs.[101]

As novel therapeutic approaches, PCSK9 inhibitors show great potential in the treatment of kidney disease. By lowering LDL-C levels, PCSK9 inhibitors effectively reduce cardiovascular risk, protect renal function, and reduce proteinuria. However, its long-term safety and drug costs still need to be further studied and addressed. In the future, with the in-depth exploration of the mechanism of PCSK9 and its inhibitors and the development of more clinical trials, the use of PCSK9 and its inhibitors is expected to become an important means of treating kidney disease and bring more benefits to patients.

Nervous System (Brain)

PCSK9 was initially identified in primary cerebellar neurons[102] and was originally described as NARC-1 (neurodegenerative regulatory convertase 1). Studies that transfected NARC-1 into primary cultures of telencephalic cells on day 13.5 showed that NARC-1 promoted the recruitment of undifferentiated neural progenitor cells into neuronal lineages. These findings suggest that NARC-1 is involved in the differentiation of cortical neurons.[3] In addition, some studies have shown that PCSK9 is related to cholesterol metabolism and the synaptic formation of neurons and plays an important role in neuronal migration and apoptosis.[103] PCSK9 is also able to influence cholesterol metabolism in astrocytes in vitro and affect neuronal health by reducing the supply of cholesterol to neurons.[104]

PCSK9 not only plays a significant role in cholesterol metabolism but is also related to the pathogenesis and treatment of neurodegenerative diseases (such as Alzheimer's disease and Parkinson's disease). A previous study revealed that patients with AD had elevated levels of PCSK9 in the cerebrospinal fluid and the prefrontal cortex of the brain and that levels in the cerebrospinal fluid were positively correlated with a variety of AD-related markers.[105,106] β-Amyloid protein (Aβ) is a major pathological feature of AD. PCSK9 indirectly regulates the production and deposition of Aβ by affecting cholesterol metabolism and aggravates the pathological process of AD by interfering with the Aβ clearance pathway.[107] In a 5XFAD transgenic mouse model, in PCSK9 knockout mice, the pathological process of Aβ was effectively alleviated, neuroinflammation was relieved, and cognitive dysfunction was improved.[108] In the 5XFAD mouse model, deletion of the PCSK9 gene significantly reduced microglial proliferation, astrocyte reactivity, and Aβ aggregation, while improving performance on hippocampal-dependent spatial memory tasks. These findings support a protective role of PCSK9 deficiency against Aβ pathology, neuroinflammation, and cognitive decline.[109] In addition, PCSK9 can affect the expression of Aβ by degrading BACE1 (β-site amyloid precursor protein lyase-1) and affecting the apoptosis-related processes of neurons.[110] Some LOF mutations in PCSK9 (loss-of-function mutations) have also been shown to reduce the risk of developing AD.[111] In PD patients, an increase in the PCSK9 level is often associated with lipid metabolism disorders, and the level of PCSK9 is significantly correlated with several lipid parameters.[112] Moreover, HMGCR

inhibitors have been found to increase the risk of PD development.[111] Additionally, studies utilizing Mendelian randomization methods have investigated the effects of PCSK9 inhibitors and HMGCR inhibition on cognitive function. The results indicate that, compared to traditional HMGCR inhibitors, PCSK9 inhibitors may be associated with a lower risk of inducing cognitive impairment while effectively reducing cholesterol levels.[113]

Mendelian randomization studies have revealed that PCSK9 inhibitors significantly reduce the risk of amyotrophic lateral sclerosis (ALS) and increase the risk of PD.[114] Lipid-lowering drugs do not affect the risk of AD, but genetic variants associated with PCSK9 inhibitors are predicted to increase the risk of AD, in contrast with the protective effect of PCSK9 inhibitors against cardiovascular diseases such as coronary artery disease (CAD).[115] There are also gene editing technologies, such as CRISPR-Cas9, that can effectively reduce PCSK9 levels by directly modifying PCSK9 genes or related regulatory genes, thereby mitigating negative effects on the nervous system. One animal experiment revealed that mice in which the SORL1 gene (low-density lipoprotein receptor-associated protein 1, an important nerve cell membrane protein) was knocked out via gene-editing techniques such as CRISPR/Cas9 presented significant impairments in cognitive function. Typical pathological changes in SAD (sporadic Alzheimer's disease), such as Aβ deposition and neuron loss, were found in mouse brain tissue.[116] Furthermore, PCSK9 inhibitors have demonstrated potential therapeutic effects in neurodegenerative diseases and alcoholic liver disease. Studies using a rat model with a 12% ethanol liquid diet revealed that chronic alcohol exposure results in increased hepatic PCSK9 expression. Administration of the monoclonal antibody alirocumab significantly reduced hepatic PCSK9 expression while enhancing low-density lipoprotein receptor expression, thereby alleviating alcohol-induced hepatic steatosis, inflammation, oxidative stress, and hepatocyte damage. Research by Josephin et al found that alirocumab can mitigate alcohol-induced brain injury and oxidative stress, influence neuroimmune activity, and spare cognitive function, providing a novel perspective for PCSK9-based therapy in central nervous system disorders such as alcohol use disorder. Although the underlying mechanisms remain unclear, the potential of PCSK9 in the neurological domain warrants further exploration. (Lee et al, 2019; Wagner et al, 2024).

There are complex interactions between PCSK9 and the nervous system. With further research, we hope to reveal more about the new mechanisms of PCSK9 in neurological diseases and develop more effective treatment strategies to address these challenges.

Immune System (Autoimmune Disease)

At present, the direct mechanism between PCSK9 and autoimmune diseases is limited, but PCSK9 inhibitors have shown some potential in the treatment of certain autoimmune diseases. Drug target Mendelian randomization (MR) analysis revealed that PCSK9 inhibitors increased the risk of asthma and Crohn's disease while reducing the risk of systemic lupus erythematosus.[117] Elevated levels of PCSK9 were detected in the serum of patients with rheumatoid arthritis and systemic lupus erythematosus, and the inhibition of PCSK9 reduced the risk of both.[118,119] Moreover, PCSK9 inhibitors can reduce the risk of atrial fibrillation in mouse models of rheumatoid arthritis,[120] and a short-term decrease in PCSK9 during the treatment of ankylosing spondylitis (AS) suggests a good prognosis for patients. By inhibiting PCSK9 in a mouse model of experimental autoimmune myocarditis (EAM), myocardial inflammation and damage in mice were also inhibited.[121] As research on PCSK9 continues, scientists are exploring possible new mechanisms between PCSK9 and autoimmune diseases. For example, PCSK9 may be involved in the pathogenesis of autoimmune diseases by influencing specific signaling pathways or gene expression. In addition, with the development of high-throughput technologies such as single-cell sequencing and proteomics, researchers will be able to gain a deeper understanding of the specific mechanism of action of PCSK9 in autoimmune diseases, providing a theoretical basis for the development of new treatments.

Conclusion

In conclusion, the pleiotropic roles of PCSK9 extend beyond lipid regulation, offering significant clinical implications. While its ability to lower LDL-C is well-established, emerging evidence highlights PCSK9's involvement in immune modulation, glucose metabolism, and neuroprotection. These findings open new therapeutic avenues for immune-related diseases, metabolic disorders such as diabetes, and neurodegenerative conditions. Future studies should prioritize clinical trials to assess the efficacy and safety of PCSK9-targeted therapies across diverse disease states. Additionally, further

exploration of PCSK9's mechanisms in non-liver tissues and its interactions with key signaling pathways, such as inflammatory and insulin pathways, is essential to identify novel therapeutic targets. In summary, by deepening our understanding of PCSK9's pleiotropic effects, we can develop more precise and effective strategies to address not only cholesterol-related diseases but also a broader spectrum of complex conditions. This will ultimately enhance its clinical relevance and application in practice.

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Disclosure

The authors report no conflicts of interest in this work.

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