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Palmitoylation in cardiovascular diseases: Molecular mechanism and therapeutic potential

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ABSTRACT

Cardiovascular disease is one of the leading causes of mortality worldwide, and involves complex pathophysiological mechanisms that encompass various biological processes and molecular pathways. Post-translational modifications of proteins play crucial roles in the occurrence and progression of cardiovascular diseases, among which palmitoylation is particularly important. Various proteins associated with cardiovascular diseases can be palmitoylated to enhance the hydrophobicity of their molecular subdomains. This lipidation can significantly affect some pathophysiological processes, such as metabolism, inflammation by altering protein stability, localization, and signal transduction. In this review, we narratively summarize recent advances in the palmitoylation of proteins related to cardiovascular diseases and discuss its potential as a therapeutic target.

1. Introduction

Cardiovascular diseases (CVDs), including coronary artery disease, arrhythmia, heart failure, cardiomyopathy, and hypertension, remain among the leading causes of death worldwide, posing significant challenges to society and the economy [1–3]. Despite significant advances in the prevention and treatment of CVDs in recent years, a deeper understanding of its complex pathophysiologic mechanisms remains crucial for developing new therapeutic approaches. Protein post-translational modifications (PTMs) influence protein stability, localization, and molecular function by covalently linking functional groups to proteins, including ubiquitination, phosphorylation, glycosylation, methylation, acetylation, and glycation [4,5]. Various PTMs are involved in CVDs [6,7] and serve as potential targets and novel therapeutic strategies for CVDs. Among them, protein palmitoylation has emerged as a research hotspot due to its crucial role in CVDs.

Protein PTM involves the alteration of its structure and function through the covalent attachment of diverse chemical groups, including ubiquitin, phosphate, nitrosyl, oligosaccharide, and polysaccharide chains [8]. Palmitoylation is a reversible lipid modification in which the 16-carbon fatty acid palmitate is covalently attached to the cysteine (Cys) residues of target proteins via thioester bonds, catalyzed by

Abbreviations: CVDs, Cardiovascular diseases; PTMs, Protein post-translational modifications; Cys, Cysteine; PATs, Palmitoyl acyltransferases; FASN, Fatty acid synthase; ER, Endoplasmic reticulum; zDHHC, zinc finger DHHC; APTs, Acyl-protein thioesterases; PPTs, Palmitoyl protein thioesterase; ABHD17 A/B/C, α/β−hydrolase domain-containing proteins 17A/B/C; 2-BP, 2-Bromopalmitate; GSDMD, Gasdermin D; KChIP2, K^+ channel interacting protein 2; NOD1/2, Nucleotide oligomerization domain-like receptors 1 and 2; p-STAT3, Phosphorylated STAT3; NLRP3, NOD-like receptor protein 3; EGFR, Epidermal growth factor receptor; AMPK, AMP-activated protein kinase; β2-AR, β2-adrenergic receptor; TCR, T cell receptor; ATGL, Adipose triacylglyceride lipase; TAG, Triacylglycerol; PKC-δ, Protein kinase C-δ; Cav-2, Caveolin-2; TLR, Toll-like receptor; MAPK, Mitogen-activated protein kinase; MTOC, Microtubule-organizing center; LRR, Leucine-rich repeat; PCSK9, Proprotein convertase subtilisin/kexin type 9; CAD, Coronary artery disease; eNOS, Endothelial nitric oxide synthase; SNAP-23, Synaptosomal-associated protein of 23 kDa; AMI, Acute myocardial infarction; ECC, Excitation-contraction coupling; PM, Plasma membranes; DCM, Diabetic cardiomyopathy; TGR5, Takeda G-protein-coupled receptor 5; CaMKII, Calcium/calmodulin-dependent protein kinase II; ERα, Estrogen receptor α.

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palmitoyl acyltransferases (PATs) [9,10]. Palmitic acid is synthesized from fatty acids in hepatocytes by fatty acid synthase (FASN) through multiple catalytic steps [11]. This process begins with glucose uptake by hepatocytes, followed by glycolysis that produces pyruvate, which is then converted to palmitic acid via several enzymatic steps [12,13]. The reversible palmitoylation of proteins is maintained in dynamic equilibrium by PATs and de-palmitoylation enzymes [14,15]. Owing to the lipid bilayer structure of membrane components, lipid modifications increase the hydrophobicity of proteins and serve as their anchors to intracellular membranes (such as the nuclear membrane), specific membrane domains or lipid rafts. Thus, palmitoylation is instrumental in cellular localization, protein stability, signal transduction, and other cellular functions [11,16].

Multiple studies involving over 300 proteins have highlighted the association between palmitoylation and various tumors [16–19], neurological diseases [20–23], autoimmune diseases [24–27], hematological diseases [28], and CVDs [29–31]. The results indicate that abnormalities in palmitoylation are closely related to CVDs progression, suggesting that this modification could be a novel therapeutic target. However, a comprehensive overview of palmitoylation in CVDs remains lacking. Therefore, in this review, we focus on the role of palmitoylation in CVDs and discuss potential therapeutic strategies [14].

2. Palmitoylation

Protein acylation is a type of lipid modification in which fatty acids are attached to the peptide chains in the form of acyl groups. Depending on the acyl group acceptor, acylation can be further classified into N-acylation, S-acylation, and O-acylation [10]. S-acylation refers to the attachment of fatty acids to the thiol group of cysteine residues via a thioester bond (Fig. 1B). This reversible post-translational lipid modification mainly occurs in the Golgi apparatus, endoplasmic reticulum (ER), and other membrane components. It regulates physiological processes such as membrane receptor activity, ion channels and transporters, enzymatic reactions, signal transduction, and cell adhesion by influencing the structure, assembly, maturation, trafficking, and function of proteins [32,33]. S-acylation involves fatty acids such as palmitic, stearic, oleic, arachidonic, and eicosapentaenoic acids, with palmitic acid being the most abundant [34].

The enzymes that catalyze S-palmitoylation in proteins belong to the protein acyltransferase (PATs) family, a group of transmembrane proteins containing a highly conserved cysteine-rich DHHC domain (Asp-His-His-Cys). The genes encoding these enzymes are named as zinc finger DHHC (zDHHC) due to the DHHC motif forming a 51-amino acid zinc finger domain [33,35,36]. A total of 24 human zDHHC genes have been identified, named zDHHC1-24 (Table 1) [37–40]. Most zDHHC proteins are localized in the Golgi apparatus and ER, and some are found in the plasma membrane and mitochondria [41]. Changes in the expression of zDHHCs are closely associated with several conditions, including metabolic, cardiovascular, inflammatory, and neurological diseases, as well as tumors, thus providing potential targets for their diagnosis and treatment.

Protein palmitoylation involves two steps. First, auto-palmitoylation, in which palmitoyl-CoA binds to the cysteine-rich DHHC domain of PATs via a thioester bond to form an intermediate [42], which occurs in the presence of a substrate [43]. Variations in the DHHC domain may contribute to the substrate specificity and functional diversity of DHHC enzymes. Cysteine residues within the DHHC domain are critical for the enzymatic activity of PATs, affecting their spatial structure and localization. Studies have shown that hydrogen bond interactions of key

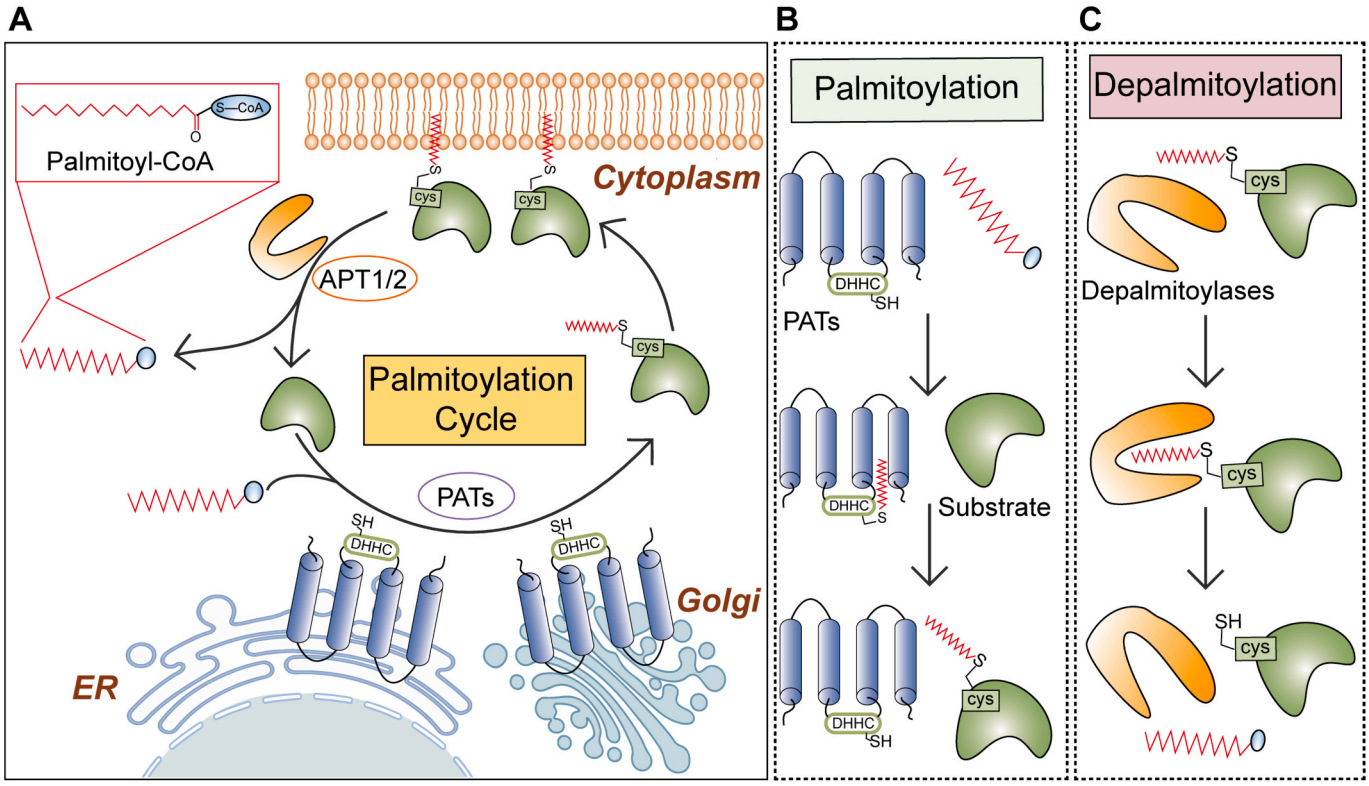

Fig. 1. Protein palmitoylation and depalmitoylation. (A) The dynamic cycle between palmitoylation and depalmitoylation. Proteins are palmitoylated by DHHC-PATs at endoplasmic reticulum (ER) or Golgi and then transferred to membrane components. Depalmitoylases (APT1/2, PPT1/2 and ABHD17) remove palmitate acid from substrates. (B) Palmitate from palmitoyl-CoA can be thioesterified to substrate proteins (green) by zDHHC-PATs (blue) with two steps. zDHHC-PATs first undergo an autopalmitoylation at the cysteine residue on its DHHC motif. Second, the palmitate group is transferred to a specific cysteine on a substrate protein. (C) Depalmitoylases remove palmitate groups from palmitoylated substrates. Among these enzymes, APT1/2 have a hydrophobic pocket to accept palmitate group and release fatty acid from the substrate. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
The subcellular localization, substrates, and associated diseases of PATs.

PATs	Localization	Substrates	Associated diseases
zDHHC1	ER	IGF2BP1, STING, NLRP3	colorectal cancer, uterine corpus endometrial, carcinoma [191–193]
zDHHC2	ER, Glogi	AGK, Gpm6a, AKAP150	Renal Cell Carcinoma, hepatocellular carcinoma, gastric adenocarcinoma [84,194,195]
zDHHC3	Glogi	IRHOM2, PD-L1, Cadm4, RARα, Rac1, VEGFR-1, GSDME-C, ACE2, VMP1	Nonalcoholic Steatohepatitis, pancreatic cancer, acute promyelocytic leukemia [22,196–198]
zDHHC4	Glogi	MAVS, GSK3β, KAI1	antitumor immunity、glioblastoma[26,86]
zDHHC5	PM	PKCδ, NOD1/2, INCENP, FAK, EZH2, Flotillin-1, NLRP3, CD36, SSTR5, Gasdermin D	fatty liver disease, triple negative breast cancer, Glioma, Lung Adenocarcinoma [66,93,199,200]
zDHHC6	ER	MYD88, PPARγ, AEG-1, NRas, DGKε	Sepsis, colon tumorigenesis, leukemia, hepatocellular carcinoma. [28,113,201,202]
zDHHC7	Glogi	STAT3, YAP1, mTOR, NLRP3, ATG16L1, Fas	hepatocellular carcinoma, ovarian clear cell carcinoma, colitis, Nonalcoholic Steatohepatitis prostate cancer, [68,203–206]
zDHHC8	Glogi	SLC7A11	Glioblastoma, epilepsy, schizophrenia [207–209]
zDHHC9	ER, Glogi	GRP78, Rab3gap1, NRAS, GLUT1, LDHA, cGAS, PD-L1	bladder cancer, heart failure, glioblastoma, leukemia [69,94,161,210]
zDHHC11	ER	TRAF6, MITA-IRF3, ATGL	Burkitt lymphoma, DLBCL, glioma [211–213]
zDHHC12	ER, Glogi	NLRP3, claudin-3	ovarian cancer, septic cardiomyopathy[173,214]
zDHHC13	ER, Glogi	MC1R, ULK1, MCAT, CTNND1, EGFR	Melanomagenesis, dermatitis, Oral Squamous Cell Carcinoma [96,215,216]
zDHHC14	ER	Gasdermin D, Kv1	myocardial infarction, CAD [144,190,217]
zDHHC15	Glogi	GP130, neuropilin-2	glioma[218,219]
zDHHC16	ER	PCSK9, SETD2	cancer, cardiomyopathy [19,220,221]
zDHHC17	Glogi	AKT, Oct4A, MAPK	HD, osteoporosis, atopic dermatitis, diabetes, and cancer [39,222,223]
zDHHC18	Glogi	cGAS, MDH2	Immunity, ovarian cancer, Gastrointestinal Stromal Tumors [25,75,224]
zDHHC19	ER	STAT3, p62, SQSTM1, Smad3	cervical cancer, glioblastoma [83,225]
zDHHC20	PM	YTHDF3, EGFR, ORAI1	pancreatic cancer [226]
zDHHC21	PM	5-HT1A, TRPV2, Caveolin-2, FASN, α1 Adrenergic Receptor	Acute myeloid leukemia, DLBCL, major depressive disorder [112,227,228]
zDHHC22	ER, Glogi	mTOR	estrogen receptor negative breast cancer [85]
zDHHC23	ER	GFAP, mTOR, PHF2	neuropathic pain, cancer [229,230]
zDHHC24	ER, Glogi	AKT, MAVS	liver tumorigenesis, immunity [38,39]

Localization data are from UniProt database and references. ER, endoplasm reticulum; PM, plasma membrane. CAD, coronary artery disease; DLBCL, Diffuse Large B-Cell Lymphoma; HD, Huntington disease.

amino acids in DHHC enzymes influence the selectivity of the acyl-binding pocket for different lengths of palmitoyl-CoA [44–46]. The two Zn^{2+} ions bound within the zinc finger-like domain of the DHHC enzymes may also modulate this selectivity.

3. Depalmitoylation

Protein depalmitoylation involves the removal of long-chain fatty acids linked via thioester bonds from the cysteine residues in proteins. Depalmitoylation is a complex process involving the participation of multiple enzymes, and can be divided into two types: enzyme-catalyzed and non-enzyme-catalyzed depalmitoylation (Fig. 1C). Essential enzymes regulating depalmitoylation (Table 2) include acyl-protein thioesterases (APTs), palmitoyl protein thioesterase (PPTs), and ABHD family thioesterase (α/β −hydrolase domain-containing proteins 17A/B/C, ABHD17A/B/C). They catalyze the hydrolysis of thioester bonds to dissociate and replace substrates on a membrane [18,47–49]. APT1/2 proteins are primarily located in the membrane components of cells, and APT1 can also function in the mitochondria [50]. Studies show that APT2 captures and hydrolyzes long-chain fatty acids from target proteins into hydrophobic pockets and hydrolyzes them [51]. PPTs are mainly found in lysosomes, where the catalytic Ser115-His289-Asp233 triad in PPT1 forms ester bonds to hydrolyze acyl chains [52].

Non-enzymatic depalmitoylation refers to the interaction of certain small molecular compounds with related enzymes, thereby promoting depalmitoylation. 2-Bromopalmitate (2-BP) is a non-specific palmitoylation inhibitor that covalently binds to PATs, inhibits the attachment of palmitoyl groups and promotes depalmitoylation indirectly [53,54]. ML348 and ML349 act as selective inhibitors of APT1/2 isoenzymes [55,56]. Palmostatin B alters the conformation of the enzyme by non-covalently binding to the active site of APT1 [57], reducing its affinity for substrates and thus inhibiting depalmitoylation. Depalmitoylation plays an essential role in various diseases (Table 2), including neurological disorders, cancer, inflammation, and pyroptosis, by regulating protein membrane localization, stability, and conformational changes [48].

Intriguingly, it forms a dynamic cycle with palmitoylation (Fig. 1A), where it reverses the effects of palmitoylation at times, triggering substrate alteration through precise spatiotemporal control (Table 3). For instance, zDHHC7 mediates S-palmitoylation of Gasdermin D (GSDMD) at the Cys192 site, enhancing its interaction with caspases and subsequent cleavage. GSDMD can then translocate to the plasma membrane, where GSDMD can also be depalmitoylated by APT2, facilitating its oligomerization. This cyclic process exerts spatiotemporal control over GSDMD activation during pyroptosis [58].

The dynamics of palmitoylation vary depending on multiple factors, including the type of protein and cells. In T cell activation, palmitoylation turnover can occur within minutes. Extracellular signals can induce dynamic changes in palmitoylation. For instance, TCR activation in T cells triggers alterations in the palmitoylation of proteins such as

Table 2
The subcellular localization, substrates, and associated diseases of depalmitoylases.

Enzyme	Localization	Substrates	Associated diseases
APT1	PM, ER, Nucleus Membrane	β-catenin, CD36, H-Ras, Caveolin-2, Vangl2	Renal fibrosis, Diabetes, Atherosclerosis, HD, Peripheral Artery Disease [30,31,89,225,231]
APT2	PM	MAVS, MC1R, TNF-R1, p-STAT3, GSDMD-NT, AKT	Colitis, innate immunity, melanoma [38,68,88]
PPT1	Lysosome	NLRP3, AEG-1, CSPα, GFAP, Gpx1, AMPAR, HSP90α	Inflammation, hepatocellular carcinoma, hyperandrogenism, neurodegenerative pathology, Neuronal ceroid lipofuscinosis [87,136,202,232–235]
PPT2	Lysosome	/	ovarian cancer [236]
ABHD17	PM	PSD-95, MAP6, N-Ras	cancer [95,237,238]

ER, endoplasm reticulum; PM, plasma membrane. HD, Huntington disease.

Table 3
The dynamic cycle between palmitoylation and depalmitoylation.

Enzymes	Substrate	Function
APT1 and zDHHC5	CD36	Facilitate fatty acid uptake [122]
APT1 and zDHHC5	NCX1	Modulates the structure and change cytosolic Ca [152]
APT1 and zDHHC9	β-catenin	Regulate the abundance and nuclear translocation [30]
APT1 and zDHHC9	Vangl2	Regulate the cell surface distribution of Vangl2 [239]
APT1 and zDHHC19	Flotillin-1	Regulate lysosomal degradation [225]
APT1 and zDHHC19	p62	Regulate protein degradation via autophagy [79]
APT1 and zDHHC21	Caveolin-2	Control signal transduction [90]
APT2 and zDHHC7	STAT3	Change the localization on nucleus and membrane [68]
APT2 and zDHHC7	GSDMD	Promote the translocation to plasma membrane and oligomerization of GSDMD [58]
APT2 and zDHHC13	MC1R	Modulate signal transduction [88]
APT2 and zDHHC24	MAVS	Modulate antiviral signal transduction [38]
PPT1/2 and zDHHC6	AEG-1	Influence tumor-progression [202]

Lck and LAT [59]. Additionally, activation of GPCR (G protein-coupled receptor) signaling pathways can modulate the palmitoylation of Gα proteins [60]. Intracellular signaling molecules and environmental changes, such as calcium ions, phosphorylation, and dephosphorylation, also influence palmitoylation [32]. Furthermore, the activity of depalmitoylating enzymes can regulate the dynamic equilibrium of palmitoylation.

4. Physiological function of palmitoylation

4.1. Membrane localization and intracellular trafficking

Addition of long-chain fatty acids to substrate proteins alters their hydrophobicity and conformation, thus increasing their affinity for membrane structures [11]. This modification improves the transport of proteins between different membrane components in the cells, affecting their cellular localization, which is crucial for maintaining cell function. Peripheral membrane proteins attach to the cell membrane through PTMs such as S-palmitoylation. The Golgi apparatus is often viewed as a transit station for PATs to modify peripheral membrane proteins before transporting them to their final destinations such as the plasma membrane [61]. Numerous reports have shown that palmitoylation can serve as a sorting signal to guide proteins to specific membranes [11,62,63]. In cardiomyocytes, the K^+ channel interacting protein 2 (KChIP2) is a regulatory protein that modulates multiple cardiac ion channels and transporters in the plasma membrane. Its palmitoylation status determines its subcellular distribution in cardiomyocytes. Palmitoylated KChIP2 accumulates on the plasma membrane, whereas non-palmitoylated KChIP2 exhibits better cytoplasmic mobility and faster nuclear import [64].

Multiple zDHHCs are involved in palmitoylation and play important roles in protein localization and function within cells, serving as important regulatory mechanisms in cell biology. zDHHC3 palmitoylates VMP1 at Cys263 and Cys278, facilitating its transfer from the cytoplasm to the plasma membrane [65]. zDHHC5 modifies the nucleotide oligomerization domain-like receptors 1 and 2 (NOD1 and NOD2) at multiple cysteine sites, increasing their localization and function on the endosomal and plasma membrane [66]. Moreover, zDHHC5 can catalyze the palmitoylation of Cys456 on FAK, enhancing its localization from the cytoplasm to the plasma membrane, leading to the autophosphorylation and activation of downstream pathways, such as PI3K/AKT. S-palmitoylation is essential for maintaining its membrane localization [67]. zDHHC7 catalyzes the palmitoylation of STAT3 at Cys108, directing its localization to the membrane rather than the nucleus. This promotes the activation and phosphorylation of STAT3, as well as its interaction with proteins such as JAK2. Conversely, APT2 regulates phosphorylated STAT3 (p-STAT3) and transports it to the nucleus [68]. Additionally, the glucose transporter GLUT1, a transmembrane protein, is palmitoylated at Cys207 by zDHHC9, maintaining its localization in the plasma membrane and thereby affecting glucose absorption [69].

4.2. Protein stability and degradation

Multiple studies have shown that PTMs function in maintaining protein stability by altering protein degradation [4]. In eukaryotic cells, protein degradation pathways include the ubiquitin proteasome system and the lysosomal pathway (including autophagy) [70,71].

Dynamic palmitoylation affects protein stability indirectly by disturbing ubiquitination. Ubiquitin ligases can be palmitoylated, such as E3 ubiquitin ligase PHF2 and FBXL2. PHF2 is palmitoylated by zDHHC23, which in turn disturbs the stability of sterol regulatory element-binding protein 1c (SREBP1c) by enhancing the ubiquitin-dependent degradation function of PHF2 [72]. Depalmitoylated FBXL2 is enriched on the ER, facilitating the ubiquitin-mediated degradation of IP3R3 [73]. zDHHC1 and zDHHC2 modify Gpm6a at Cys17, 18, and 246, mediating the formation of lipid rafts to stabilize Procr protein [74]. zDHHC4 modifies MAVS at Cys79, promoting its stability and activation by modulating ubiquitination [26]. The expression of MDH2 is typically regulated by the combined effects of TRIM21-mediated ubiquitination and USP5-mediated deubiquitination. While MDH2 can also be palmitoylated by zDHHC18 at Cys138, which prevent its ubiquitination and thereby improve its stability [75].

Palmitoylation also regulates autophagy. S-palmitoylation mediated by zDHHC5 can reduce the autophagic degradation of NOD2 and enhance NF-κB signaling [76]. zDHHC7 modifies the E3 ubiquitin ligase ATG16L1 at Cys153, thereby catalyzing the lipidation of MAP1LC3/LC3 and the formation of autophagosomes, indicating a regulatory function of palmitoylation in autophagy [77]. zDHHC12 modifies NOD-like receptor protein 3 (NLRP3) at Cys844, to promote its degradation via the autophagy via chaperone-mediated autophagy [78]. The autophagy receptor p62 is modified by zDHHC19 at Cys289 and Cys290, accelerating the degradation of p62 via the autophagy pathway and the autophagic clearance of ubiquitinated proteins [79]. Programmed death ligand 1 (PD-L1) is modified by zDHHC3 at Cys272, enhancing its stability by preventing PD-L1 ubiquitination, while depalmitoylation promotes PD-L1 degradation through the lysosomal pathway [80].

4.3. Signal transduction

Palmitoylation of proteins alters their cellular localization and stability, like signal transduction-related proteins, thereby regulating signaling pathways in cells [11]. There are dozens of pathways relevant to palmitoylation involving tumors, autoimmune diseases, neurological disorders, and CVDs. These pathways include epidermal growth factor receptor (EGFR) signaling pathway [81], G protein-coupled receptor (GPCR) signaling pathway [82], TGF-β/Smad3 pathway [83], PI3K-AKT-mTOR pathway [84,85], WNT-β-Catenin pathway [22], GSK3β-EZH2-STAT3 pathway [86], androgen receptor (AR) pathway [87], MC1R pathway [88], H-Ras-MAPK pathway [89], IR/Cav-2/IRS-1/Akt pathway [90], TNF-R1 pathway [91] NF-κB pathway [92], and PKCδ/NLRP3-related neuroinflammatory pathways [93].

Notably, the interaction between some special enzymes with PATs has an indirect effect on the modification of substrates and their signaling pathways. The localization to the plasma membrane is essential for N-Ras protein to activate downstream pathways. RAB27B, a RAB family small GTPase, interacts with zDHHC9 to palmitoylate N-Ras at Cys181 [94], allowing it to migrate from the Golgi to the cell membrane,

while ABHD17 can prompt the depalmitoylation of NRAS [95]. Moreover, the regulation of zDHHC9 by RAB27B can also influence the signaling of the NRAS/c-RAF/MEK/ERK pathway in leukemia [94]. In oral squamous cell carcinoma, RAB27A maintains the localization of the EGFR at the plasma membrane by modulating the zDHHC13-mediated palmitoylation, thereby activating downstream signalling [96]. Furthermore, some protein phosphorylation can also coordinate with palmitoylation. The phosphorylation of zDHHC13 by AMP-activated protein kinase (AMPK) boosts the zDHHC13-mediated palmitoylation of MC1R, increasing downstream signalling of MC1R-RHC [97]. zDHHC7 palmitoylates STAT3, strengthening its membrane recruitment and JAK2 phosphorylation, whereas APT2 depalmitoylates p-STAT3 and facilitate it transport to the nucleus [68].

In the cardiovascular system, some pathways may be regulated by palmitoylation. For instance, the β2-adrenergic receptor (β2-AR) is targeted to the plasma membrane via palmitoylation of its C-terminus, where it transmits signals through interactions with G proteins [98–100]. Multiple pathways are involved in pathological cardiac hypertrophy [101], such as small GTPases (H-Ras, N-Ras, and Rac1) [102], which associate with the plasma membrane dynamically and subsequently activate downstream effectors. Rac1 is modified at Cys178 by zDHHC3 and transported to cholesterol-rich regions where it is activated. The palmitoylated Rac1 triggers downstream MAPK and NADPH signaling, leading to cardiac hypertrophy [102,103]. Lipid rafts, a microdomain abundant in cholesterol and sphingolipids within the cell membrane, and closely correlated with signal transduction. zDHHC20 modifies the ORAI1 channel protein at the Cys143, targeting it to cholesterol-rich lipid raft, thereby activating T cell receptor (TCR) signaling [104].

5. Palmitoylation in CVDs

5.1. Coronary artery disease

Coronary artery disease (CAD) is one of the general cardiovascular diseases, with the outcome of myocardial infarction, heart failure, ischemic cardiomyopathy, and stroke [105–107]. While atherosclerosis is one of the primary pathological processes leading to CAD and some other CVDs (Fig. 3A) [108]. The initiation of atherosclerosis involves multiple factors, including lipid and cholesterol metabolism, endothelial integrity, and inflammation. The functions of endothelial cells, macrophages, and smooth muscle cells are crucial in the progression of atherosclerosis [109,110]. In recent years, escalating evidence has shown that PTMs including ubiquitination, glycosylation, and palmitoylation contribute in the progression of atherosclerosis [14].

As described above, the proteins involved in multiple lipid hemostasis can be palmitoylated. Palmitoylation is a common lipid modification that plays a wide-ranging role in intracellular lipid metabolism, including the regulation of lipid absorption and synthesis (Fig. 2), modulation of lipid metabolic pathways, and lipid signal transduction [111–116]. On the surface of macrophages, CD36 can recognize, bind, and internalize ox-LDL, inducing inflammation and mediating the formation of foam cells, thus participating in the occurrence and development of atherosclerosis [117,118]. oxHDL activates CD36 by increasing its palmitoylation, enhancing the bind of CD36 to lipid rafts in serum and activating downstream signaling mediators [119]. Lipid rafts are essential for CD36 to uptake fatty acid [120]. Wang et al. reports that CD36 is palmitoylated by zDHHC4 and zDHHC5 when transported from the ER to Golgi and localizing on the membrane [121]. And it must be depalmitoylated by APT1 before endocytosing the fatty

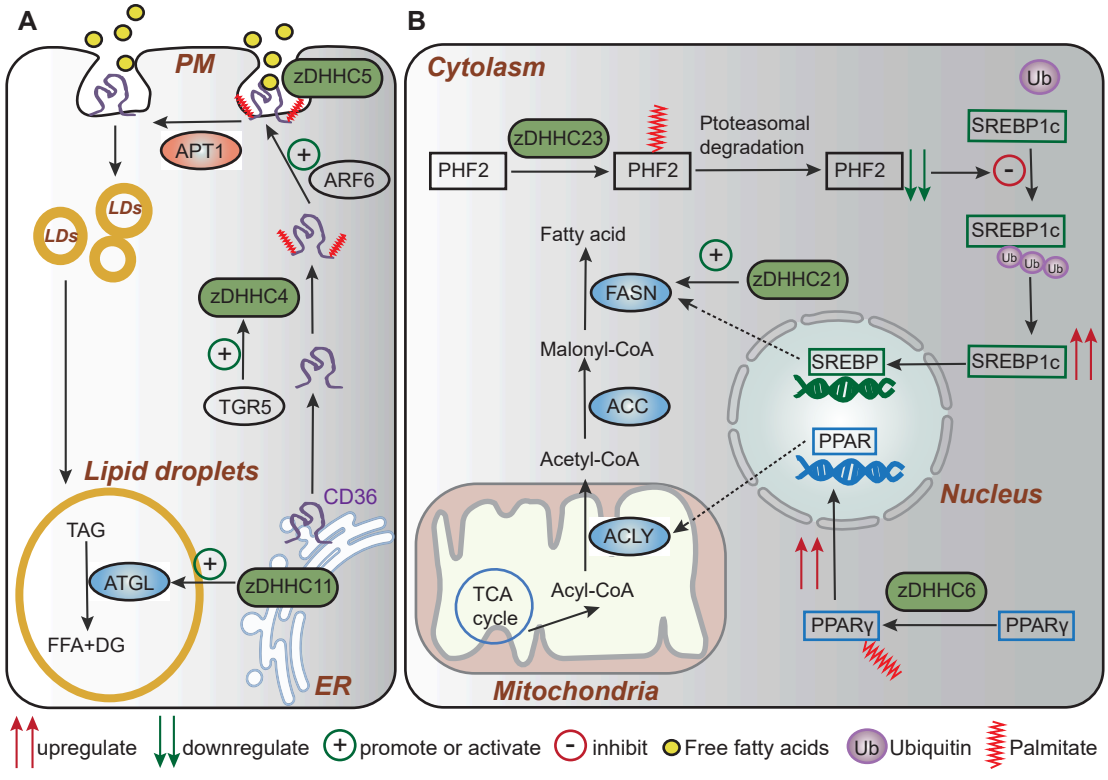

Fig. 2. Palmitoylation in lipid uptake and synthesis. (A) CD36 (purple) is palmitoylated by zDHHC4 when transported from the endoplasm reticulum (ER) to Golgi. ARF6 promotes the migration of palmitoylated CD36 to the plasma membrane (PM). zDHHC5 maintains its localization on the membrane. FAs bind to CD36 in a caveolae on the plasma membrane of adipocytes. APT1 depalmitoylates CD36, initiating CD36-mediated caveolar endocytosis. The endocytosed vesicles deliver FAs to lipid droplets for storage. zDHHC11 activates ATGL and accelerates lipid breakdown and β-oxidation in lipid droplets. (B) FASN and ACLY are crucial enzymes in the synthesis of fatty acids. zDHHC6 palmitoylates transcription factor PPARγ and increases its nuclear translocation, upregulation ACLY. zDHHC23 palmitoylates PHF2 and enhances its ubiquitination degradation. And the decrease of PHF2 downregulate the ubiquitination of SREBP1c, increasing the level of FASN. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

acids. The results uncover the necessity of dynamic palmitoylation on the uptake of fatty acids [122].

Endothelial dysfunction is an early marker of atherosclerosis. Endothelial cells release factors such as nitric oxide (NO) to maintain vascular tone, exerting anti-atherosclerotic effects [123]. Endothelial nitric oxide synthase (eNOS) in endothelial cells is the key enzyme responsible for NO synthesis. Palmitoylation of eNOS by zDHHC21 in endothelial cells localizes it to the cell membrane and stimulates the production of NO [124], which helps maintain vascular function and regulates vasodilation and contraction. In mice with zDHHC21 functional deficiency, endothelial cells exhibit barrier dysfunction. zDHHC21-mediated palmitoylation of PLCβ1 activates downstream pathways involved in endothelial inflammation [125]. Endothelial-derived APT1 mediates the interaction of macrophages and endothelial cells, participating in the occurrence of atherosclerosis by regulating the Ras/MAPK pathway [89]. Additionally, S-palmitoylation of ciliary proteins in endothelial cells is crucial for maintaining endothelial ciliary function. And the accumulation of triglycerides that inhibits S-palmitoylation can lead to cilia shedding [126].

Palmitoylation regulates inflammation with the mechanism involving inflammatory signalling pathways [24], the release of inflammatory mediators [127], and the functional regulation of inflammatory cells [128]. Palmitoylation has an impact on the activation and regulation of various inflammatory signalling pathways, such as Toll-like receptor signalling (TLR) [129], NOD1/2 signalling [66,76], cytokine receptor-mediated signalling [68], nuclear factor κB (NF-κB) pathway [130] and MAPK pathway [28,131,132]. NLRP3 can be palmitoylated by zDHHC1 [133], zDHHC5 [134], zDHHC7 [135]. When PPT1-mediated depalmitoylation is suppressed, the stability of NLRP3 is enhanced, leading to excessive activation of the inflammasome [136].

Thrombosis is a critical part in the progression of atherosclerosis to myocardial infarction [137]. Palmitoylation of proteins associated with thrombosis is essential for the activation of platelet [138–140]. Synaptosomal-associated protein of 23 kDa (SNAP-23) contains a domain with five closely spaced cysteines. The palmitoylation of SNAP-23 by zDHHC2 maintains its localization on the membrane [141]. While APT1-mediated depalmitoylation inhibits the binding of SNAP23 to the cell membrane and ultimately affects the secretion of platelet granule [142]. Moreover, palmitoylation of STING in platelet may contribute to septic thrombosis via overactivation of platelet [143]. zDHHC14 palmitoylates the GSDMD at Cys192, facilitating it localize to cytomembrane. The palmitoylation of GSDMD aggravates pyroptosis in cardiomyocyte, promoting acute myocardial infarction (AMI) [144].

5.2. Cardiac arrhythmias

The occurrence and development of cardia arrhythmia are closely related to abnormalities in myocardial cell ion channels function, extracellular matrix, inflammatory response, and excitation–contraction coupling in cardiomyocytes [145,146]. Palmitoylation mainly affects arrhythmia by regulating the activity and expression of various ion channel proteins, including sodium, potassium, and calcium channels (Fig. 3B) [147–150].

Multiple subunits (α, β, FXYD) of the transmembrane sodium/potassium pump can be palmitoylated. The α3 subunit (phospholemman), which is specifically expressed in cardiomyocytes, inhibits the activity of sodium/potassium pump when palmitoylated. The activity of the sodium-calcium exchanger 1 (NCX1) depends on the transmembrane sodium concentration gradient. Thus slight intracellular changes of sodium induced by the palmitoylation of phospholemman can also affect calcium levels, impacting the contraction of cardiomyocytes [151]. Meanwhile, zDHHC5 palmitoylates NCX1 at Cys739 on the cell surface, repressing its activation and decreasing intracellular calcium concentration, whereas APT1 catalyzes the depalmitoylation of NCX1 [152]. The sodium channel Nav1.5 affects the initiation of cardiac action potentials and conduction. The palmitoylation at Cys981 increases its sensitivity, leading to enhanced cardiomyocytes excitability [148]. The Kv1.5 potassium channel current is a major current during the repolarization of atrial action potentials. Palmitoylation at Cys593 increases potassium current on the cell surface, increasing the risk of arrhythmias [153].

Cardiac excitation–contraction coupling (ECC) is a physiological process by which cardiac myocytes convert electrical signals into mechanical contractions [154]. Palmitoylation significantly regulates the ECC process by affecting ion channels, receptors, and signaling molecules [155]. L-type calcium channel (Cav1.2) is crucial to the action potential plateau phase in cardiac myocytes. Palmitoylation of Cav1.2 can enhance its anchoring to the membrane [156], stabilizing its function and allowing more efficient calcium entry into cells. This triggers the opening of calcium release channels, such as ryanodine receptor. Opening of these channels promotes the release of calcium ions from the sarcoplasmic reticulum and ultimately leading to myofilament contraction [157,158]. Junctophilins (JPH1-JPH4) are critical for ECC by connecting endoplasmic/sarcoplasmic reticulum (ER/SR) with plasma membranes (PM). In ventricular myocytes, JPH2 can be palmitoylated and binds to lipid-raft domains in PM, enhancing ER/SR-PM tethering [159].

5.3. Cardiomyopathy

Palmitoylation is closely related to the pathogenesis of various cardiomyopathies by intervening processes such as apoptosis, inflammatory response, cardiac remodeling, and energy metabolism (Fig. 3C). In cardiomyocytes, β- adrenergic signaling stimulates the palmitoylation of Gαs and Gαi by zDHHC5, modulating downstream signaling associated with heart failure [160]. And zDHHC3/7 palmitoylated Rac1 at the Golgi, regulating the downstream signaling and cardiac remodeling [103]. Palmitoylation of Rab3gap1 by zDHHC9 in cardiomyocytes affects the release of atrial natriuretic peptide [161], thereby participating in the development of heart failure caused by dilated cardiomyopathy.

Calcium/calmodulin-dependent protein kinase II (CaMKII) plays a central role in the development of pathological cardiac remodeling and heart failure [149,162–164]. The palmitoylation of cardiac calcium handling proteins, such as CaMKII, affects calcium signal transduction, which may lead to cardiomyocyte dysfunction [165,166].The excessive activation of CaMKII is one of the important pathological mechanisms in dilated cardiomyopathy, hypertrophic cardiomyopathy, and heart failure [167]. Palmitoylation increases CaMKII activity, significantly disrupting calcium homeostasis and causing cardiomyocyte death. Caveolin-3, a membrane-associated protein in cardiomyocytes, can be palmitoylated, enhancing its localization in lipid rafts [168]. Mutations in Caveolin-3 are closely related to certain types of hereditary cardiomyopathies, and the regulation of its membrane localization and function by palmitoylation is associated with cardiomyopathy pathogenesis [168,169].

Palmitoylation plays an important role in the pathogenesis of diabetic cardiomyopathy by modulating insulin signaling [170], fatty acid metabolism [90], and membrane-associated proteins functions in cardiomyocytes. Further research on these modification mechanisms is expected to provide new therapeutic targets for diabetic cardiomyopathy. In cardiomyocytes, the palmitoylation of SNAP23, GLUT4 and CD36 modulates lipid-Induced insulin resistance [171]. The bile acid receptor, Takeda G-protein-coupled receptor 5 (TGR5), is involved in metabolic regulation and myocardial protection. The deletion of TGR5 gene upregulates zDHHC4-mediated palmitoylation of CD36, promoting its localization on the plasma membrane and increasing cardiac fatty acid uptake. This highlights the potential of targeting TGR5 for diabetic cardiomyopathy treatment [172]. Vaccarin enhances the palmitoylation of NLRP3 by acting on zDHHC12, leading to the inactivation of the NLRP3 inflammasome and alleviating septic cardiomyopathy [173]. Abnormal palmitoylation is closely related to the pathogenesis of cardiomyopathy, so future research should consider this modification as a

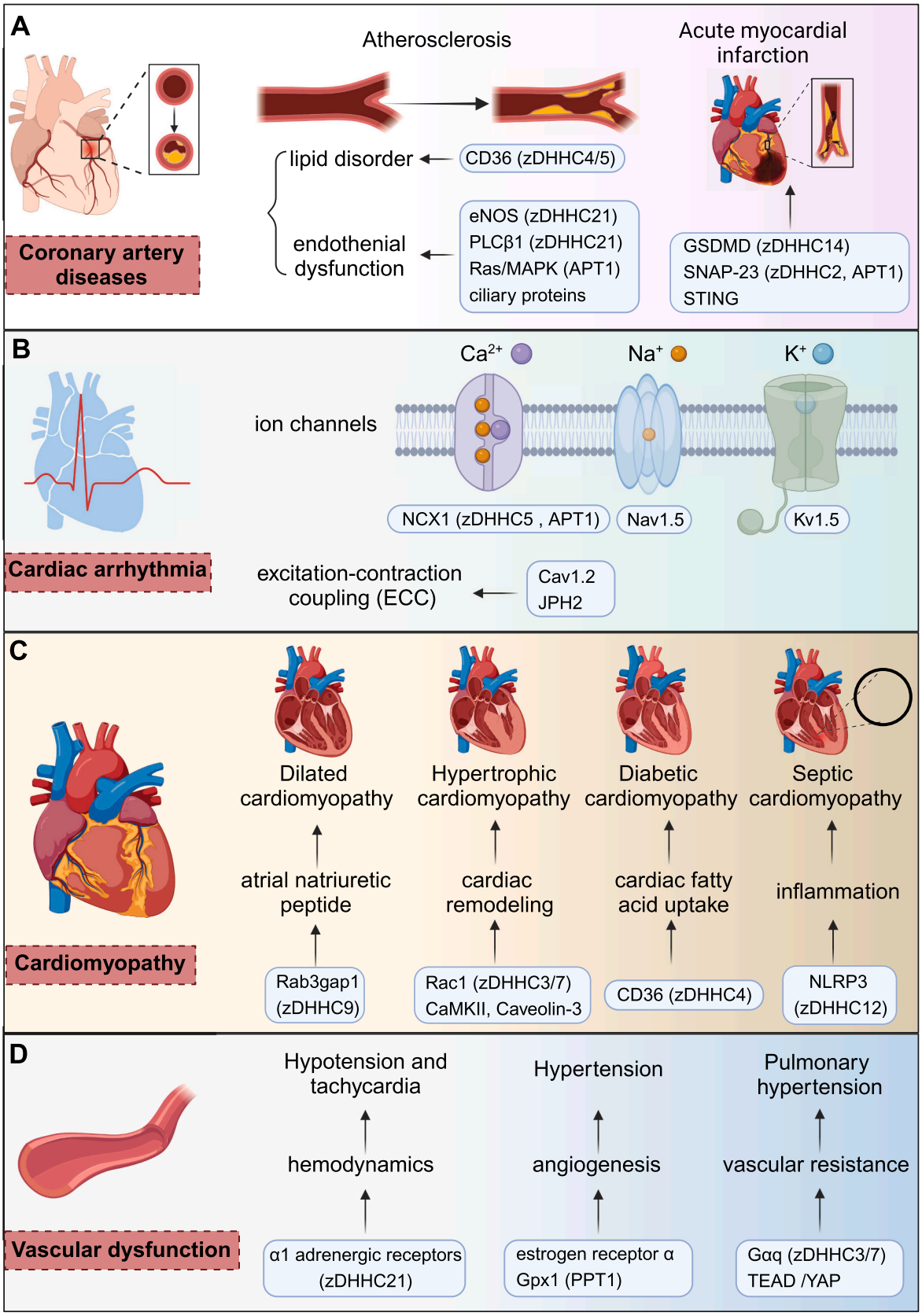

Fig. 3. Palmitoylation functions in the cardiovascular diseases. Summary of palmitoylation involved in the progression of cardiovascular diseases. Schematic representation of (A) coronary artery diseases, (B) cardiac arrhythmia, (C) cardiomyopathy, and (D) vascular dysfunction. Proteins in blue boxes are substrates that can be palmitoylated, followed by the corresponding enzymes in parentheses. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

potential therapeutic target.

5.4. Vascular dysfunction

NO is a crucial determinant of vascular integrity and blood pressure homeostasis [174,175]. As referred above, palmitoylation of eNOS can regulate hemodynamics through adjusting vasodilation and contraction. Palmitoylation may affect the activity and expression levels of angiotensin receptors, thereby influencing vascular tone and blood pressure (Fig. 3D). Elevated blood glucose reduces APT1 activity in endothelial cells, increasing R-Ras palmitoylation and impairing vascular function [176]. In mice with functional deficiency of the protein zDHHC21, the function of vascular α1 adrenergic receptors is weakened, leading to altered hemodynamics and reduced vascular tone, which manifests in vivo as hypotension and tachycardia [177]. Mice lacking the palmitoylation site on estrogen receptor α (ERα) show increased sensitivity to estrogen, preventing atherosclerosis and hypertension induced by angiotensin II [178]. Besides, the dynamic palmitoylation of Gpx1 plays a pivotal role in angiogenesis. PPT1 diminishes the protein stability of Gpx1 by depalmitoylation, restraining angiogenesis [179].

Pulmonary arterial hypertension is a chronic cardiovascular disease characterized by progressive increases in pulmonary artery pressure and vascular resistance. The palmitoylation of Gαq mediated by zDHHC3 and zDHHC7 alters the association with thromboxane receptors, thereby affecting hypoxic pulmonary arterial hypertension [180]. The activation of YAP promotes pulmonary hypertension, and the palmitoylated TEAD site is buried within the deep hydrophobic pocket of the YAP binding domain, rather than on the exterior of the protein [181]. However, the function of TEAD palmitoylation remains unclear and requires further investigation. Currently, research on palmitoylation in diseases caused by abnormal blood pressure is limited, warranting further study.

6. Therapeutic strategies

Recent studies have shown that palmitoylation can serve as a prognostic biomarker and therapeutic target in various diseases [8]. The treatment strategies based on the target of palmitoylation has significant potential (Fig. 4). PATs, APTs, and PPTs are key enzymes that regulate palmitoylation. And targeting these enzymes represents a potential strategy to treat diseases related to palmitoylation dysregulation [182]. For example, GNS561, a clinical-stage PPT1 inhibitor, effectively combats hepatocellular carcinoma by regulating lysosomal function [183]. In addition to directly targeting related enzymes, developing drugs that target specific palmitoylated proteins is also a potential therapeutic strategy. For instance, inhibiting the palmitoylation of Ras may effectively block Ras-mediated tumor growth [95]. Palmitoylation is mediated by long-chain saturated fatty acids such as palmitic acid. Therefore, the fatty acid in the diet can potentially influence palmitoylation. A high-saturated fatty acid diet may exacerbate the risk of palmitoylation dysregulation, such as promoting liver tumorigenesis through palmitoylation and AKT activation [39]. Furthermore, several chemical inhibitors and small molecule drugs that can regulate palmitoylation have been developed through high-throughput screening and drug design [80,184,185]. 2-BP, a broad-spectrum inhibitor of palmitoylation, has been used to study the role of palmitoylation in various cellular processes. However, 2-BP can cause widespread cytotoxic reactions and

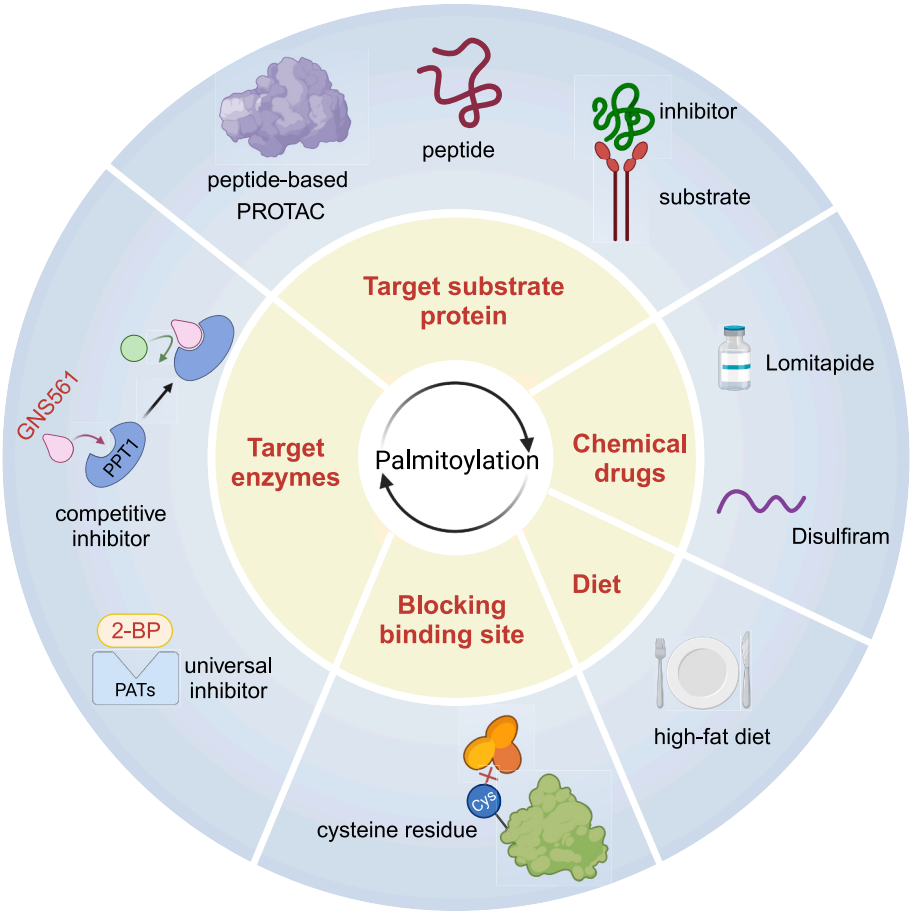

Fig. 4. Therapeutic strategies of palmitoylation. Key enzymes, substrate proteins, and cysteine residues are considered therapeutic targets. GNS561 binds to PPT1 competitively and 2-BP inhibits palmitoylation widely. Several chemical inhibitors, small molecule drugs and fatty acid in the diet can potentially influence palmitoylation.

lacks specificity. Therefore, it is necessary to develop more selective and safer compounds that target specific enzymes for precise therapy. Palmitoylation may exhibit significant individual variation due to different genotypes and environmental factors. Personalized treatment can be developed by assessing palmitoylation or the expression levels of related enzymes in patients.

As mentioned earlier, palmitoylation is involved in physiological processes of the cardiovascular system, such as angiogenesis [176,186], glucose and lipid metabolism [172,187–189], regulation of myocardial contractility, and inflammation. Some studies suggest that targeting palmitoylation in cardiovascular system could serve as a potential therapeutic strategy. For instance, endothelial cell ciliary proteins influenced by S-palmitoylation can be restored through drugs or palmitic acid-rich diets, which significantly improves endothelial cilia and alleviates atherosclerosis in male mice, providing a feasible intervention for the prevention and treatment of atherosclerosis [126]. The proprotein convertase subtilisin/kexin type 9 (PCSK9) is palmitoylated by zDHHC16 at cysteine Cys600. A PCSK9-derived peptide was developed and verified to competitively inhibit the palmitoylation of PCSK9, enhancing antitumor effects by hindering the phosphorylation of AKT [19]. APT1 can influence the localization and function of H-Ras via depalmitoylation. The miR-138-APT1 axis may partially contribute to atherosclerosis by regulating the H-Ras-MAPK pathway and hBP transport. These findings elucidate the potential mechanisms underlying atherosclerotic CVDs, identifying possible diagnostic and therapeutic targets [89]. miR-574-5p can promote the proliferation of vascular smooth muscle cells and inhibit apoptosis by suppressing zDHHC14 expression, indicating that miR-574-5p is a factor associated with CAD and could serve as a potential therapeutic target for CAD [190]. Disulfiram can target the palmitoylation of GSDMD as a potential clinical intervention for myocardial pyroptosis [144]. Nonetheless, the precise molecular mechanisms and biological effects of palmitoylation in many CVDs remain unclear, warranting further research to clarify its therapeutic potential.

7. Conclusion and perspectives

The complexity of CVDs requires thorough explorations of their pathological mechanisms from multiple perspectives in order to develop more effective treatments. Palmitoylation, as an important molecular mechanism regulating protein function, has received increasing attention for its role in CVDs (Table 4). This review emphasizes the physiological function of dynamic palmitoylation cycle in cells, including altering subcellular localization, protein stability, and signal transduction. And its potential key role in lipid hemostasis, inflammation is elucidated. In cardiovascular diseases, palmitoylation acts in cardiac function and vascular health by the integrated action on signal transduction, lipid hemostasis and inflammation. Therefore, understanding the specific role of palmitoylation in diseases can also help identify new biomarkers for the early diagnosis and risk assessment of cardiovascular diseases.

In summary, palmitoylation is a PTM that regulates multiple key processes in the cardiovascular system by affecting protein localization, stability, and function. Research on palmitoylation provides new biological insights and points to potential therapeutic targets. Despite challenges, we hope to uncover the full scope of palmitoylation in CVDs and ultimately develop new therapeutic approaches through deeper mechanistic studies and technological advancements. Future research should focus on the specific regulation of palmitoylation in combination with small molecule drugs, gene editing technologies, and metabolic interventions to reduce potential side effects and provide more options for precision medicine.

Ethics approval and consent to participate

Not applicable.

Table 4
Functions and roles of enzymes in the cardiovascular system.

Disorder	Enzymes	Substrate	Function
Atherosclerosis	zDHHC4 and zDHHC5	CD36	regulate lipid uptake in macrophages
	zDHHC21	eNOS	stimulate the production of NO in endothelial cells
	zDHHC21	PLCβ1	activates endothelial inflammation
	APT-1	R-Ras	regulating Ras/MAPK pathway and vascular function
	zDHHC14	GSDMD	aggravate pyroptosis in cardiomyocyte and promote AMI
	DHHC3/7/17 and APT1	SNAP-23	affects the secretion of platelet granule
Cardiac arrhythmias	zDHHC5 and APT1	NCX1	impact Ca^{2+} concentration and contraction of cardiomyocyte
	/	Nav1.5	increase sensitivity and excitability of cardiomyocytes
	/	Kv1. 5	increases potassium current on the cell surface
	/	Cav1.2	Regulate Excitation-Contraction Coupling
Cardiomyopathy	zDHHC5	Gαs and Gαi	Modulate heart failure
	zDHHC3/7	Rac1	Regulate cardiac remodeling
	zDHHC9	Rab3gap1	affect dilated cardiomyopathy
	/	CaMKII	cardiomyocyte dysfunction
	/	Caveolin-3	hereditary cardiomyopathy
	zDHHC4	CD36	diabetic cardiomyopathy, DCM
	zDHHC12	NLRP3	alleviate septic cardiomyopathy
Vascular dysfunction	zDHHC21	α1 adrenergic receptor	alter hemodynamics and cause hypotension and tachycardia
	/	ERα	prevent atherosclerosis and hypertension induced by angiotensin
	PPT1	Gpx1	restrain angiogenesis
	zDHHC3 and zDHHC7	Gαq	affecting hypoxic pulmonary arterial hypertension

Consent for publication

Not applicable.

CRediT authorship contribution statement

Rongli Wang: Writing – review & editing, Writing – original draft, Visualization, Investigation, Conceptualization. **Yi He:** Writing – original draft, Methodology. **Yan Wang:** Supervision, Funding acquisition. **Jing Wang:** Writing – review & editing, Writing – original draft, Funding acquisition. **Hu Ding:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

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Declaration of competing interest

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

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