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REVIEW

Protein palmitoylation: A potential therapeutic target in cardiovascular diseases

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Abstract Palmitoylation, an essential covalent attachment of a fatty acid (usually C16 palmitate) to cysteine residues within proteins, is crucial for regulating protein functionality and enzymatic activities. This lipid modification facilitates the anchoring of proteins to cellular membranes, dictating their subcellular distribution and influencing protein transport dynamics and intracellular positioning. Additionally, it plays a role in regulating protein degradation through the ubiquitin-proteasome system. Palmitoylation is implicated in the pathogenesis and progression of cardiovascular diseases by modulating substrates and prompting additional post-translational modifications, as well as by interacting with other molecular alterations. Moreover, an intervention strategy focusing on palmitoylation processes is anticipated to offer novel therapeutic avenues for cardiovascular pathologies and address extant challenges in clinical settings. This review consolidates current research on the role and importance of palmitoylation in cardiovascular diseases by exploring its regulatory functions, the catalyzing enzymes, and the involved substrates. It highlights recent discoveries connecting palmitoylation-targeted therapies to cardiovascular health and examines potential approaches and future challenges in cardiovascular treatment.

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1. Introduction

Originally identified in 1979, the mechanistic details and significance of palmitoylation remained unclear until 2002, primarily due to the lack of consensus sequences at modification sites and challenges in purifying membrane-bound enzymes responsible for attaching palmitate to proteins[1,2]. This changed with the discovery of a Ras protein acyltransferase in yeast (*Saccharomyces cerevisiae*)[2]. Currently, several technological advancements, such as using fluorescence techniques to assess the radioactivity of [^{3}H]-palmitate-labeled compounds and employing click chemistry for the separation and quantification of palmitoylated proteins, enable the determination of protein palmitoylation[3,4]. Palmitoylation is categorized into three types: *S*-palmitoylation, *N*-palmitoylation, and *O*-palmitoylation[5]. *S*-palmitoylation, the most prevalent form, involves the reversible addition of palmitic acid (PA)—a 16-carbon saturated fatty acid—to cysteine residues *via* thioester linkage[6,7]. This reversible nature is characterized by cycles of palmitoylation and depalmitoylation, rapidly regulated by extracellular signals, thereby dynamically controlling protein functionality[8,9]. In contrast, *N*-palmitoylation and *O*-palmitoylation are irreversible. *N*-palmitoylation, identified through Sonic Hedgehog analysis, involves attaching palmitate to the N-terminal cysteine, initially forming a thioester intermediate that becomes a stable amide bond[7,10]. *O*-Palmitoylation occurs through an oxyester linkage between cis Δ9 palmitate, a monounsaturated palmitate, and the hydroxyl group of either serine or threonine residues[5].

Palmitoylation occurs across various enzymes, including soluble and integral membrane proteins, necessitating acyltransferases for enzymatic reactions and functional integrity. *S*-Palmitoylation involves specific palmitoyl acyltransferases (PATs), identifiable by a conserved aspartic acid−histidine−histidine−cysteine (DHHC) motif within their cysteine-rich domain, forming the DHHC protein family[11]. The corresponding genes, designated zDHHC, reflect their zinc-binding capability and are sequentially numbered from 1 to 24, except for DHHC10's absence in *Homo sapiens*[12]. These PATs are predominantly located within the Golgi apparatus and endoplasmic reticulum, with presence in endosomes and the plasma membrane, playing roles in various post-translational modifications within the cellular environment[13-15]. Currently, the depalmitoylation process involves a limited number of enzymes, including acyl protein thioesterases APT1 and APT2, lysosomal enzymes PPT1 and PPT2, and the α/β-hydrolase domain family members ABHD17A, ABHD17B, and ABHD17C[4,16,17]. Additionally, the enzyme Porcupine, belonging to the membrane-bound *O*-acyltransferase (MBOAT) family, is implicated in the palmitoylation of WNT ligands, a critical step for proper WNT signaling, impacting both secretion and functionality of these ligands[18,19]. The unique and conserved structure of WNT is being increasingly recognized, facilitating the molecular-level understanding of WNT lipoylation by PORCN[20]. This insight is crucial for designing new drugs targeting WNT-related diseases, opening up novel therapeutic pathways. Additionally, Hedgehog acyltransferase (HHAT), an enzyme associated with the ER, catalyzes the N-terminus of Hedgehog precursors to form *N*-palmitoylation[21-23]. And part of the MBOAT family, HHAT's role in WNT is especially intriguing for developing innovative cancer therapies[24].

Protein localization and function are regulated by various post-translational modifications (PTMs), involving the covalent attachment of functional entities, such as phosphates (as seen in phosphorylation) or lipid moieties (evident in lactylation or palmitoylation). Palmitoylation is among the most complex lipid-based PTMs in eukaryotes, affecting protein structure, intracellular trafficking, stability, activity, and oligomerization by enhancing protein lipophilicity[14,25]. It modulates protein−protein interactions, alters subcellular distribution, and directs proteins to specific intracellular compartments, impacting numerous cellular processes[26-29]. This reversible cysteine-based modification might also affect aging-related diseases due to oxidative stress[30]. The palmitoylation of WNT proteins significantly influences their secretion and interaction with Frizzled receptors, regulating neural processes like synaptogenesis and neurotransmission, and affecting neuronal synapses[31,32]. The WNT/β-catenin pathway is crucial for cell proliferation and stem cell pluripotency, linking it to various diseases[33]. Moreover, palmitoylation of the Stimulator of Interferon Genes (STING) serves as an activation mechanism, inducing the production of type I interferons and pro-inflammatory cytokines, which are vital for cancer immunotherapy[34-37].

Cardiovascular disease (CVD) incidence increases with age, being the leading cause of death worldwide[38]. Research from 1997 indicated palmitoylation's impact on vascular function by modulating nitric oxide synthase (eNOS)[39]. In 1998, its unique role in cardiac calcium channels was discovered[40]. Over the last four decades, evidence has linked protein palmitoylation to CVD incidence. Changes in the activity of protein acyltransferases and palmitoyl-protein thioesterases, regulating protein palmitoylation, can alter protein function by orchestrating protein scaffolding and membrane interaction[41], thereby affecting cardiovascular signal transduction and contributing to CVD etiology (Fig. 1). Understanding palmitoylation's effects on cellular and protein functions within the cardiovascular system is essential for comprehending disease etiology, developing therapeutic approaches, and creating effective preventive strategies. Modulating PTMs through specific substances is emerging as a promising future approach for prevention and treatment by manipulating protein functional groups. In CVD, delaying cellular senescence has been shown to impede disease progression. Previous studies have indicated that lipid metabolism anomalies can induce endothelial cell (EC) senescence *via* protein acetylation modifications mediated by acetyl-CoA, accelerating vascular senescence and fostering cardiovascular pathologies[42]. The palmitoylation process utilizes PA as a substrate. Recent research has shown that PA may promote aging and influence lipid metabolites, regulating biological functions and cellular signaling, ultimately leading to cardiovascular dysfunction[43,44]. Palmitoylation, as an emerging post-translational modification, shows promise for further exploration of biological aging. Recent advancements have provided significant insights, laying the groundwork for the development of similar therapeutic

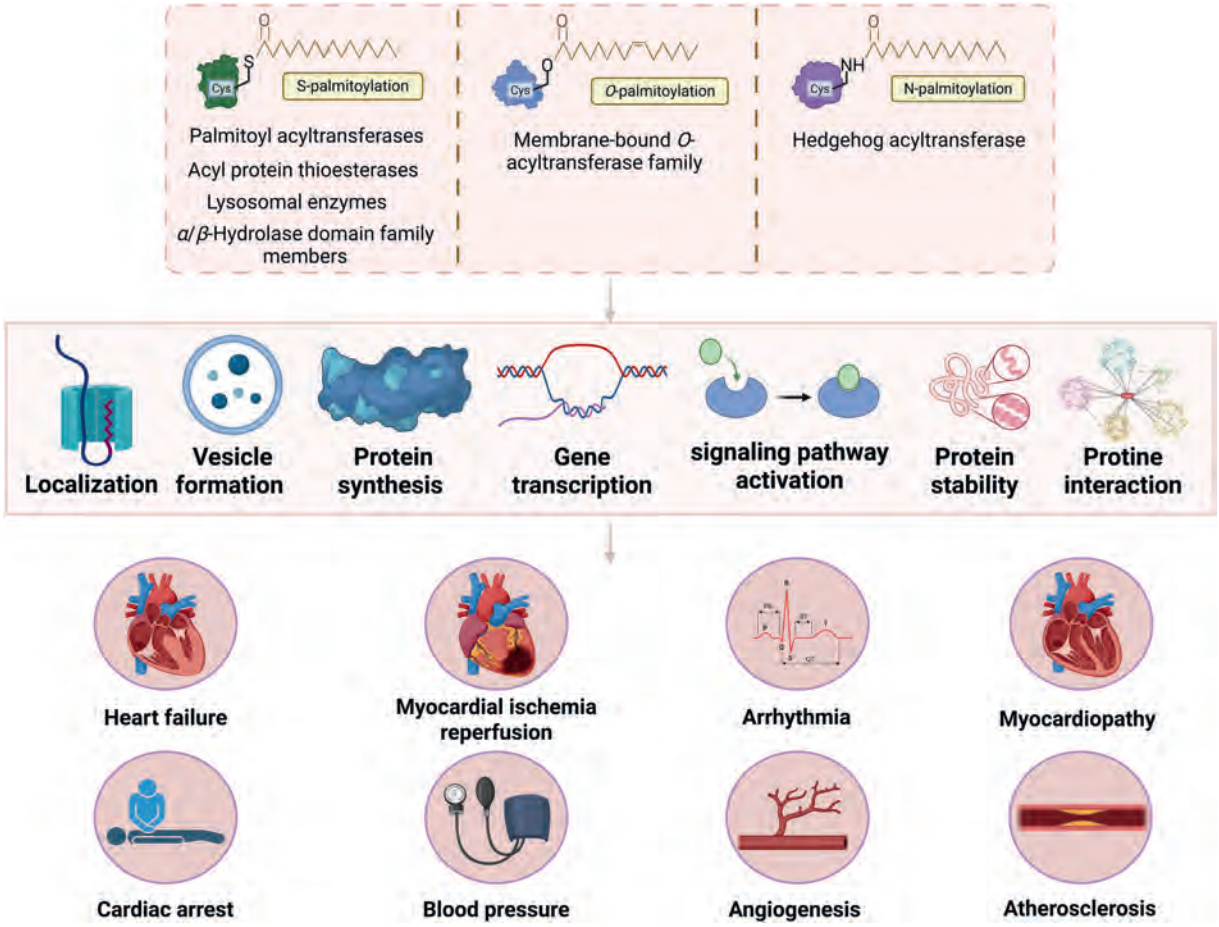

Figure 1 The mechanisms of palmitoylation and cardiovascular diseases. Palmitoylation can be divided into three types. It can induce heart failure, myocardial ischemia reperfusion, arrhythmia, myocardiopathy, cardiac arrest, blood pressure change, angiogenesis, atherosclerosis, and other cardiovascular diseases through changes in substrate localization, vesicle formation, protein secretion, gene transcription, signal pathway activity, protein stability, protein interaction and other changes of related enzymes.

approaches. Although palmitoylation is a relatively recent discovery among PTMs involved in protein activity regulation through protein−membrane interactions, its potential as a latent drug for disease mitigation through targeted therapies is evident. Nevertheless, many therapeutic agents utilizing this PTM are still in preclinical research, with only a few progressing to clinical trials. Despite the challenges in clinical adoption and utilization of palmitoylation, progress in understanding relevant pathways and biological functions in cardiovascular pathology, among other areas, highlights its considerable potential for specialized therapeutic interventions and precise disease modulation. Further empirical research is essential to validate the therapeutic efficacy of these interventions.

In this comprehensive review, we aim to elucidate the regulatory pathways and mechanisms of palmitoylation in cardiovascular diseases. We will collate and review key biomolecular targets and conceptual therapeutic strategies, while also identifying potential diagnostic and treatment modalities for clinical application. This specialized analysis provides an in-depth examination of the modulatory effects of palmitoylation substrates and catalyzing enzymes, particularly those associated with cardiopathological conditions, underscoring the need for continued research in this area. In essence, this discourse offers a detailed explication of the implications and clinical applications of palmitoylation, laying the groundwork for new perspectives and academic support that advance precision medicine for cardiovascular diseases.

2. Palmitoylation in cardiac diseases

Palmitoylation plays a critical role in various cardiac diseases and has been widely studied to understand its relationship with common conditions. In myocardial hypertrophy and heart failure (HF)-related cardiac dysfunction, the expression, modification, and malfunction of proteins involved in excitation-contraction coupling are key factors[45]. Pathological changes in the function of excitation-contraction coupling proteins during heart disease are often due to alterations in PTM regulation, particularly lipid modifications like palmitoylation[46]. During the reoxygenation phase of hypoxic myocardium, palmitoylation induces massive endocytosis (MEND) reactions that coincide with mitochondrial permeability transition pore (PTP) opening, contributing to reoxygenation injury in ischemia/reperfusion (I/R) events[47]. Additionally, changes in palmitoylation significantly impact myocardial cell excitability, increasing channel availability and extending action potential duration[48]. Genetic deficiencies related to palmitoylation can disrupt multiple pathways in myocardial

disease progression, highlighting its importance in cardiac development and function.

2.1. Palmitoylation in HF

2.1.1. PATs in HF

Palmitoylation at cysteine 418 of estrogen receptor beta (ERβ) is critical for its translocation to the membrane and its biological function. And membrane-associated ERβ inhibits AngII-induced SMAD3 phosphorylation and nuclear localization *via* 17β-estradiol (E2)/ERβ signaling, thereby attenuating AngII-induced cardiomyocyte hypertrophy and fibrosis responses[49]. While the precise mechanisms and interplay between palmitoylation and cardiac protection require elucidation, it is hypothesized that palmitoylation may confer cardioprotection by modulating membrane dynamics and ERβ localization. Beyond ERβ, the palmitoylation of other receptors, such as adrenergic receptor (AR), has been observed. β1-AR undergoes *S*-palmitoylation at multiple cysteine residues within its C-terminal domain, specifically at positions Cys392, Cys393, and Cys414[50]. Mutation of the distal cysteine residue, Cys414, affects agonist-mediated internalization of β1-AR, implicating potential effects on receptor sensitivity, downregulation, or sequestration. These findings underscore the therapeutic potential of targeting receptor palmitoylation in the management of cardiomyocyte function and heart diseases[50,51]. Subsequent investigations have elucidated that the cardiomyocyte-specific palmitoyl acyltransferase DHHC5 undergoes palmitoylation within its C-terminal domain, a crucial process for β-AR mediated signal transduction[52]. This lipid modification of DHHC5 occurs within the caveolae, lipid-raft microdomains involved in β-AR signaling pathways implicated in cardiovascular pathologies such as HF, significantly influencing membrane retention post β-AR pathway activation. These signaling pathways facilitate the enzymatic activity of DHHC5, modulating its isoform-specific functionality and substrate specificity within cardiomyocytes[52]. The potential of DHHC5 in cardiomyocytes is significant, with emerging research suggesting its intricate role and possible future application as a therapeutic target. Insulin enhances the palmitoylation of zDHHC5, a palmitoyl-transferase family member on the plasma membrane, which triggers fatty acyl-CoA synthesis and subsequent palmitoylation at Cys-739 of the cardiac sodium-calcium exchanger (NCX1). Research indicates that insulin, in the context of HF due to resistance, can modulate the architecture and functionality of NCX1, paving the way for innovative pharmacological treatments aimed at improving cardiac performance[53]. Further, Main et al.[45] investigated palmitoylation processes in animal models of left ventricular hypertrophy (LVH) and HF, and human HF specimens, revealing an inconsistency in zDHHC5 expression and NCX1 palmitoylation across these models and clinical samples. Notably, zDHHC5 levels increased in LVH but decreased in HF, while NCX1 palmitoylation was reduced in LVH and increased in human HF, indicating that palmitoylation rate is not solely dependent on zDHHC5 expression. Despite existing knowledge, the intricate regulatory machinations of zDHHC5 activity and its substrate palmitoylation warrant further investigation. Another *S*-acyltransferase, zDHHC9, palmitoylates Rab3gap1, leading to spatial separation from Rab3a, increasing Rab3a GTP levels, formation of Rab3a-positive peripheral vesicles, and impairing exocytosis that restricts atrial natriuretic peptide (ANP) release[54]. Overexpression of zDHHC9 also suggests ANP dysregulation, a clinical biomarker for heart disease severity, indicating a potential therapeutic target for natriuretic peptide signaling in HF[54]. Additionally, Rac1, a Ras-related C3 botulinum toxin substrate, has been identified as a novel target for the *S*-acyltransferase zDHHC3. Elevated zDHHC3 expression enhances RhoGTPase signaling, contributing to cardiac hypertrophy[55]. ZDHHC3 and zDHHC7 regulate RhoGTPase activity on the cytoplasmic surface of the Golgi apparatus in cardiomyocytes, promoting heart disease and HF[55]. Increased zDHHC3 expression can enhance Rac1 palmitoylation and membrane localization, activating other RhoGTPase family members, leading to myocardial hypertrophy and HF[55]. Among them, DHHC7 has been identified as a palmitoyltransferase for junctional adhesion molecule C (JAM-C), with *S*-palmitoylation occurring at the membrane-proximal cysteine residues Cys-264 and Cys-265, facilitating JAM-C localization in tight junctions[56]. While *S*-palmitoylation of JAM-C has been implicated in cancer metastasis, given the association of JAM-C with leukocyte transendothelial migration, angiogenesis, and other functions, the role of DHHC7-mediated JAM-C palmitoylation in the cardiovascular system warrants further investigation[56]. Recent findings indicate that upregulated expression of ZDHHC17 enhances SARM1 palmitoylation, which subsequently targets P4HA1 to promote collagen deposition and myocardial fibrosis, thereby accelerating fibrotic progression—a potential key mechanism underlying heart failure[57]. Identifying the interaction sites between SARM1 and P4HA1, as well as the specific palmitoylation sites on SARM1, may offer promising therapeutic targets for anti-fibrotic interventions[57].

2.1.2. Depalmitoylases in HF

Previous research has demonstrated that the dynamic palmitoylation of NCX1 is facilitated by palmitoyltransferase zDHHC5 and reversed by thioesterase APT1, with the state transition between palmitoylation and depalmitoylation being contingent on the conformational equilibrium of NCX1[58].

2.1.3. MBOAT family in HF

The involvement of WNT signaling in cardiovascular pathologies is increasingly recognized. Porcupine, a membrane-bound *O*-acyltransferase, is instrumental in the palmitoylation-driven secretion and distribution of WNT proteins[59]. The pharmacological agent Wnt-C59, a potent Porcupine enzyme inhibitor, has shown efficacy in improving myocardial function both *in vivo* and *in vitro* by inhibiting the WNT/β-catenin signaling pathway[59]. This compound notably reduces the synthesis of Wnt3a and β-catenin proteins, as well as the transcription of WNT target genes, including cyclin D1 and *c-Myc*. Utilizing a model of transverse aortic constriction in adult male mice, Wnt-C59 administration resulted in a pronounced attenuation of pathological myocardial hypertrophy, fibrosis, and myocyte apoptosis[59]. The Wnt-3a protein undergoes palmitoylation at Ser209 under Porcupine catalysis, essential for Wnt-3a secretion from the ER in L cells[60]. Its role in cardiac tissue through a similar mechanism remains to be explored.

Palmitoylation impacts HF by modifying substrate localization, activating HF-related pathways, and influencing the secretion of HF-associated proteins. Various mechanisms and pathways underscore the strong link between palmitoylation and HF.

2.2. Palmitoylation in myocardial ischemia-reperfusion

2.2.1. PATs in myocardial ischemia reperfusion

The expression of DHHC5 and DHHC2 acyltransferases regulates Na/K pump activity, Ca transients, and MEND responses[47]. During hypoxic cardiac tissue reoxygenation, the signaling pathway

from mitochondrial PTP opening to DHHC5 acyltransferase and endocytic enzyme is activated[47]. The MEND reaction occurs upon PTP opening, where enhanced palmitoylation of cardiac membrane proteins may trigger endocytosis and muscle damage, suggesting that inhibiting palmitoylation could alleviate reperfusion injury[47]. This protective mechanism may also apply to vascular ECs and fibroblasts during reperfusion. Howie and colleagues detailed how DHHC5 targets the cardiac phosphoprotein phospholemman (PLM), showing that palmitoylation at PLM's Cys40 residues near the plasma membrane inhibits the Na^+ pump and regulates myocardial contractility, with significant implications for cardiac function[61]. DHHC5 is also implicated in HF-related diseases[52], suggesting a possible specific mechanism connection. The identified site in ischemia-reperfusion may aid in pinpointing and studying the site in HF. PLM is essential for maintaining intracellular Na^+ levels in cardiomyocytes, affecting various cellular functions, including mitochondrial-driven contractility[62]. Cyclophilin-D (CypD), a known mitochondrial PTP regulator, exhibits cardioprotective effects when its critical *S*-acylation site cysteine 202 (C202) is mutated to serine (C202S)[63]. This mutation prevents CypD oxidation and translocation to PTP during ischemia, desensitizing PTP and providing cardiac protection[63]. Reduced PTP activity and I/R injury were observed in CypD C202S knockout mice[47,62,63].

2.3. Palmitoylation in arrhythmia

The pathogenesis of arrhythmia involves ion channels and electron transport proteins, which are susceptible to alterations *via* post-translational modifications[64]. The interplay between ion channels and transporters regulates action potential duration, effective refractory period, and Ca^{2+} cycling, thereby orchestrating excitation-contraction coupling and normal cardiomyocyte function[65]. Specifically, PLM affects cardiac sodium pumps through palmitoylation of C40 and C42 residues within its intracellular domain[66]. This post-translational modification, triggered by phosphorylation, aids PLM in regulating sodium pumps[66]. PLM phosphorylation activates sodium pumps and can prevent calcium overload and arrhythmia by limiting intracellular Na increase during β-AR stimulation, offering insights into the role of palmitoylation[67]. Conversely, antioxidant protein peroxidase 6 interacts with PLM in a glutathione-dependent manner and depalmitoylates PLM[68]. This interaction is likely due to protein peroxidase 6's thioesterase activity, which allows it to undergo nucleophilic attack via its reactive thiol, leading to protein depalmitoylation and linking the palmitoylation of PLM and sodium pump activity to cellular glutathione levels[68]. And Pei et al.[48] identified that the cardiac voltage-gated sodium channel undergoes palmitoylation. The channel has four palmitoylation sites, and mutations at the Cys981 site enhance the channel's inactivation in a closed state, nullifying depalmitoylation sensitivity and reducing myocardial cell excitability[48]. This modification is linked to both acquired and congenital arrhythmias and other cardiac channelopathies[48]. Similarly, the α1C subunit of Ca (v)1.2 L-type Ca channels is regulated by palmitoylation at specific sites, the channel's amino terminus and I−II linker, affecting voltage sensitivity and increasing the risk of arrhythmias like ventricular tachycardia and ventricular fibrillation[69]. These arrhythmias can lead to HF, warranting further investigation. Additionally, potassium channels are closely associated with palmitoylation. The voltage-dependent potassium channel Kv1.5 undergoes cysteine palmitoylation at its COOH terminus, specifically at C593. Deficiency or mutation at this site decelerates channel internalization, augmenting surface channel density and potassium currents[70]. Given the significant role of Kv1.5 in atrial arrhythmia[71], the study of its palmitoylation modification presents a promising research avenue.

2.4. Palmitoylation in myocardiopathy

2.4.1. PATs in myocardiopathy

Zhou and colleagues discovered that the enzyme palmitoyl acyltransferase Aph2, also known as Ablphilin 2 or zf-DHHC16, catalyzes the palmitoylation of phospholamban (PLN), promoting its phosphorylation and modulating histopathological abnormalities manifested by cardiomyopathy[72]. In Aph2-deficient mice, the absence of PLN provides some protection against cardiac dysfunction but does not correct ocular anomalies or improve postnatal survival, suggesting alternative substrates or pathways may play compensatory roles[72]. Furthermore, deletion of TGR5, a G-protein-coupled receptor 5, elevates CD36 palmitoylation *via* palmitoyl transferase DHHC4, enhancing CD36 plasma membrane localization, fatty acid uptake, and lipid accumulation in cardiomyocytes, making TGR5 a therapeutic target for diabetic cardiomyopathy[73]. In septic cardiomyopathy, suppression of NLRP3 palmitoylation and its interaction with zDHHC12 is observed. Vaccarin promotes NLRP3 palmitoylation and inactivation, reducing pro-inflammatory cytokine release and providing cardioprotection[74]. And recent research reveals that fatty acid synthase (FASN) induces palmitoylation at NLRP3-Cys898, leading to NLRP3's translocation to the inflammasome assembly site within the *trans*-Golgi network vesicles, thus promoting NLRP3 inflammasome assembly and activation[75]. Targeting FASN can thus modulate inflammatory responses in infectious, inflammatory, and metabolic diseases characterized by NLRP3 signaling dysregulation[75].

2.4.2. Other substances in myocardiopathy

Palmitoylation of desmoglein-2, a desmosomal cadherin, is essential for its trafficking to the plasma membrane, contributing to desmosome stability and preventing ventricular cardiomyopathy[76].

Palmitoylation primarily affects inflammation and desmosome stability by altering substrate localization, thus impacting heart structure and function and ultimately influencing cardiomyopathy progression.

2.5. Palmitoylation in other cardiac abnormalities

K channel interacting protein 2 (KChIP2), the sole cardiac-expressed member of the KChIP family[77-81], which has functions in channel modulation and miRNA transcriptional regulation[78,82], shows dynamic distribution based on its palmitoylation state[83]. Palmitoylated KChIP2 is cytoplasmic, whereas the depalmitoylated form is nuclear. During cardiac arrests in rats, KChIP2 translocates from the periphery to the nucleus[83]. The palmitoylation state of KChIP2 is mutable under varying conditions, with cardiac arrest/resuscitation causing KChIP2 depalmitoylation, leading to increased cytoplasmic mobility, expedited nuclear translocation, and a nuclear retention mechanism[83]. Yang et al.[84] demonstrated that palmitoylation of the Kir6.2 subunit of the ATP-sensitive K^+ channel at Cys166 amino acid alters its gating properties, compromising its closed state and enhancing PIP2 interaction. This site is also implicated in clinical conditions like developmental delays, epilepsy, and neonatal diabetes,

suggesting therapeutic potential in cardiac diseases[84]. Additionally, palmitoylation of cysteine 341 on β2-AR is linked to the arrestin/phosphodiesterase 4D signaling cascade, affecting cAMP−PKA signaling and the contractile response of cardiomyocytes[85]. These insights are pivotal for understanding and treating cardiac pathologies (Fig. 2).

3. Palmitoylation in vascular diseases

Vascular diseases occur due to abnormal intravascular stability and paracrine signaling. Palmitoylation affects membrane protein localization and cell membrane stability, potentially inducing vascular abnormalities or diseases by impacting the surface receptor function of ECs, pericytes, and other cell types, as well as signal transduction pathways.

3.1. Palmitoylation in angiogenesis

3.1.1. PATs in angiogenesis

KAI1 (CD82) in pericytes, palmitoylated by the zDHHC4 enzyme and localized on the membrane surface, induces leukemia inhibitory factor *via* the Src/p53 pathway, inhibiting angiogenic factors in ECs and pericytes, thereby suppressing angiogenesis[86].

3.1.2. Depalmitoylases in angiogenesis

A deficiency in endothelial APT1 disrupts endothelial palmitoylation cycling, reducing membrane movement of constitutive palmitoylation R-Ras, altering the cytoskeleton, and damaging vascular stability, adversely affecting angiogenesis[87]. Moreover, targeted inhibition of PPT1 to enhance palmitoylation of GPX1 at cysteine-76 and -113 can enhance its protein stability and effectively inhibit angiogenesis, presenting a potential therapeutic strategy against angiogenesis[88].

3.1.3. Other substances in angiogenesis

Fatty-acid synthase (FAS), upregulated by insulin, is crucial for the palmitoylation of endothelial eNOS, essential for its proper localization on the endothelial plasma membrane and NO production[89]. In FASTie mice, the absence of FAS in ECs prevents FAS-derived palmitate from modifying eNOS, leading to its disconnection from caveolae, which preferentially produce NO, resulting in superoxide production, oxidative stress, endothelial dysfunction, inflammation, and impaired angiogenesis, underscoring the enzyme's importance in vascular function[89]. Similarly, APT1-mediated regulation of eNOS depalmitoylation can prompt eNOS translocation[90]. DHHC-21 palmitoyltransferase also regulates eNOS palmitoylation, with its inhibition reducing eNOS palmitoylation, eNOS targeting, and stimulating NO production, thereby affecting eNOS localization and function[91]. ENOS activation and deactivation are linked to cyclic depalmitoylation and repalmitoylation of specific cysteine residues, influencing eNOS activity rather than its expression levels[92]. Insulin also modulates EC function through the palmitoylation at cysteines 56 and 206 of PAFAH1b3 (platelet-activating factor acetylhydrolase IB subunit gamma), contributing to cell migration and angiogenesis[93]. Studies by Boucher et al.[94] have shown that palmitoylation of membrane-localized vascular endothelial growth factor receptor-1 (mVEGFR1) is essential for its stability and trafficking, influencing angiogenesis and vascular development. Additionally, the GTPase Rab27a is crucial in regulating mVEGFR1 palmitoylation, acting as a pivotal upstream element in this angiogenic pathway. Its absence may reduce mVEGFR1 palmitoylation, increase mVEGFR1 transport to lysosomes for degradation, decrease stability, and ultimately interfere with vascular morphogenesis *in vitro* and *in vivo*[94]. Glutamine synthetase (GS), encoded by the *GLUL* gene, modulates EC motility and migration through its self-palmitoylation and thereafter transfers the palmitoyl group to the GTPase RHOJ[95]. Knockdown of *GLUL* impairs RHOJ activity and EC movement, highlighting the therapeutic potential of GS in pathologic angiogenesis[95].

Palmitoylation can modify cell migration abilities and affect the stability and localization of angiogenic substances. These alterations influence angiogenesis and vascular development, presenting potential therapeutic interventions for the future.

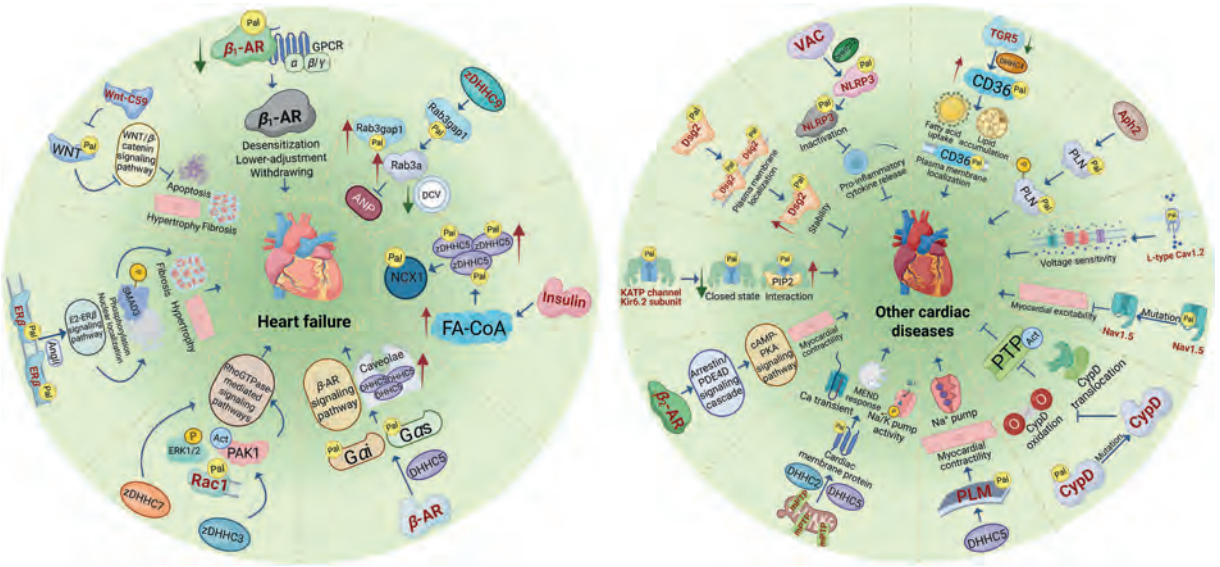

Figure 2 Palmitoylation in heart failure and other cardiac diseases. Palmitoylation influences the heart *via* several enzymes, inducing pathological alterations like fibrosis and apoptosis, which ultimately lead to heart failure. Pal, palmitoylation; P, phosphorylation; Act, activation.

3.2. Palmitoylation in abnormal blood pressure

3.2.1. PATs in abnormal blood pressure

Protein acyltransferase zDHHC21 forms a complex with α1D−AR, enhancing its palmitoylation and regulating vascular constriction by targeting α1D AR[96]. The absence of zDHHC21 disrupts α1 AR function, resulting in vascular anomalies that may present as hypotension and tachycardia[96]. Previously, using acyl biotin exchange, the substrate cell adhesion protein platelet EC adhesion molecule-1 (PECAM-1) of ZDHHC21 was also identified in ECs[97]. ZDHHC21 knockout reduced PECAM-1 levels on the cell surface. Mass spectrometry combined with acyl biotin exchange identified over 150 putative palmitoyl proteins in EC, highlighting the significance of palmitoyl modification in EC function[97].

3.2.2. Other substances in abnormal blood pressure

Palmitoylation of ERβ and its subsequent localization to the cell membrane are implicated in mitigating cardiac cell pathology and preventing hypertension[49]. Estrogen receptor α (ERα) also plays a pivotal role in the relationship between palmitoylation and cardiovascular protection. Mice harboring the cysteine 451 mutation in ERα (ERα C451A) abolished membrane localization of ERα, resulting in the eNOS phosphorylation and expedited re-endothelialization in response to 17β-E2[98]. This mutation can also mitigate hypertension by selectively activating nuclear ERα with estrogen and activating membrane-initiated steroid signaling through palmitoylation of ERα at cysteine 451, thereby aiding in the prevention of atheroma formation and offering a novel therapeutic strategy for cardiovascular diseases[98]. Recent findings suggest selective nuclear ERα agonists as potential therapeutic agents for managing hypertension. Palmitoylation often influences blood pressure by changing the content and localization of substances within vascular constriction pathways.

3.3. Palmitoylation in thromboembolism

As early as the 1990s, a study identified that P-selectin in human platelets undergoes palmitoylation at Cys766 *via* thioester bonding, influencing its intracellular transport and functions[99]. Later research demonstrated that depalmitoylation of platelet proteins using APT1 inhibits protease-activated receptor-1 mediated alpha granule secretion, resulting in the cytoplasmic relocation of palmitoylated G(αq) and SNAP-23, thereby suppressing platelet granule secretion and aggregation[100]. In mice models, inhibiting protein palmitoylation significantly reduced platelet accumulation and thrombus formation at vascular injury sites[100]. Subsequent proteomic analysis using liquid chromatography−tandem mass spectrometry identified 215 palmitoylated proteins in platelets, underscoring the significant role of palmitoylation in platelet function[101]. Among these, TREM-like transcript-1, exclusive to platelets and megakaryocytes, was specifically validated with a palmitoylation site at Cys196[101]. Identifying this novel palmitoylated platelet protein aids in elucidating the role of palmitoylation in platelet biology.

And the critical interplay between palmitoylation and platelets contributes to thrombosis-related vascular diseases. Mutating the palmitoylation site at Cys451 of ERα to alanine, thereby disrupting membrane ERα function, affects tail bleeding time and E2-induced collagen/adrenaline thromboembolism in mice[102]. Conversion of Cys245 to Ser increases tissue factor procoagulant activity through depalmitoylation, likely due to enhanced fXa production and altered transmembrane domain length as well as orientation, facilitating tissue factor association with thicker lipid raft domains that support its activity, thus elevating procoagulant function[103]. Additionally, inhibition of STING palmitoylation under sepsis-derived cGAMP stimulation mitigates excessive thrombin-induced platelet activation, indicating that STING palmitoylation promotes platelet activation in septic thrombosis[104].

3.4. Palmitoylation in atherosclerosis

3.4.1. PATs in atherosclerosis

Deletion of zDHHC1 in mice markedly decreased macrophage uptake of oxidized low-density lipoprotein (oxLDL), thereby inhibiting foam cell formation and atherosclerosis progression[105]. This effect may be due to zDHHC1 deficiency reducing the palmitoylation of the PI3K subunit p110α, which promotes its nuclear translocation and affects the PI3K−Akt−mTOR signaling pathway, leading to reduced downstream phosphorylation and modulation of the disease[105]. Similarly, selenoprotein K (Selk) is essential for the palmitoylation of CD36 in macrophages, which is critical for foam cell formation and atherosclerosis[106]. The absence of Selk reduces modified LDL uptake and foam cell formation, indicating a potential treatment for atherosclerosis[106]. Further studies demonstrated that CD36 palmitoylation relies on DHHC6 acyltransferase and its cofactor Selk[107]. Concurrently, oxidized high-density lipoprotein (oxHDL) enhances CD36 incorporation into plasma lipid rafts by increasing the palmitoylation of CD36, thereby activating downstream signaling and promoting oxHDL uptake and foam cell formation. Reducing CD36 palmitoylation can decrease lipid uptake *in vivo*, providing strategies to mitigate atherosclerosis[107]. CD36, serving as a substrate, is also present in diabetic cardiomyopathy[73]. Despite different palmitoylation catalytic enzymes in the two diseases, their mechanisms are related to fatty acid uptake, offering new insights into the etiology of other lipid-related cardiovascular diseases.

3.4.2. Depalmitoylases in atherosclerosis

MiR-138-5p, an upstream regulator of APT1, promotes H-Ras depalmitoylation, thereby translocating APT1 and H-Ras from the cytoplasm to the plasma membrane, regulating H-Ras localization and expression, and consequently affecting the MAPK signaling pathway and its downstream factors[108]. APT1 also traverses cellular and tissue barriers via BP, facilitating interactions between ECs, macrophages, and influencing atherosclerosis progression[108]. Additionally, the deficiency of carcinoembryonic antigen-related cell adhesion molecule-1 (CEACAM1), critical for angiogenesis, may result in aortic plaque-like lesions through eNOS depalmitoylation, leading to EC subcellular redistribution of eNOS and increased leukocyte-EC interactions, underscoring CEACAM1's role in vascular endothelial homeostasis[109].

3.4.3. Other substances in atherosclerosis

Triglyceride accumulation in vascular ECs promotes lipid droplet formation, disrupts the balance between saturated and monounsaturated fatty acids, reduces PA availability, and inhibits protein *S*-palmitoylation, potentially resulting in cilia loss and atherosclerosis[110].

3.5. Palmitoylation in other vascular diseases

Palmitoylation also plays a role in other vascular abnormalities. Under hypoxic conditions, palmitoylation of Gαq is increased,

strengthening its interaction with thromboxane prostanoid receptors and enhancing thromboxane prostanoid α-mediated vasoconstrictive responses, such as thromboxane-induced calcium response, which are crucial in the context of persistent pulmonary hypertension in neonates[111,112]. Several studies have reported cardiovascular damage without specifying the underlying disease. Pyruvate kinase M2 (PKM2), under the influence of palmitoyltransferase zDHHC13, undergoes palmitoylation at the primary site Cys31[44]. This process disrupts PKM2 tetramerization, inhibiting its pyruvate kinase activity and endothelial glycolysis. These findings indicate that PA-induced palmitoylation of PKM2-C31 results in endothelial injury and cardiovascular dysfunction[44]. Furthermore, bioinformatics analysis by Dai et al.[113] identified *ABHD17A* as a pivotal gene mediating CAD and type 2 diabetes, suggesting its potential as a target for diagnostic and therapeutic interventions. These findings lay a significant groundwork for future vascular disease research (Fig. 3, Table 1[44,47,48,50-55,59,61,63,69,72-74,86-89,93-96,100,102−109,111−113]).

4. Clinical therapy and diagnosis

4.1. *Clinical therapy*

4.1.1. *Chemical drugs*

Currently, no direct therapeutic link has been established between palmitoylation and cardiovascular disease; however, exploring the therapeutic potential of palmitoylation in various conditions may provide valuable insights. Afrin et al.[114] demonstrated that simvastatin inhibits estrogen-responsive leiomyoma growth by reducing palmitoylation of ERα, thus decreasing its presence in the plasma membrane and nucleus. A phase II clinical trial (NCT03400826) supported the efficacy of simvastatin therapy. Further research by the same team indicated that simvastatin targets caveolae and caveolin-1 (CAV1) in both immortalized and primary leiomyoma cells, reducing CAV1 palmitoylation and subsequently ERα localization, potentially mitigating pathological mechanical signaling in uterine leiomyoma[115]. Previous research

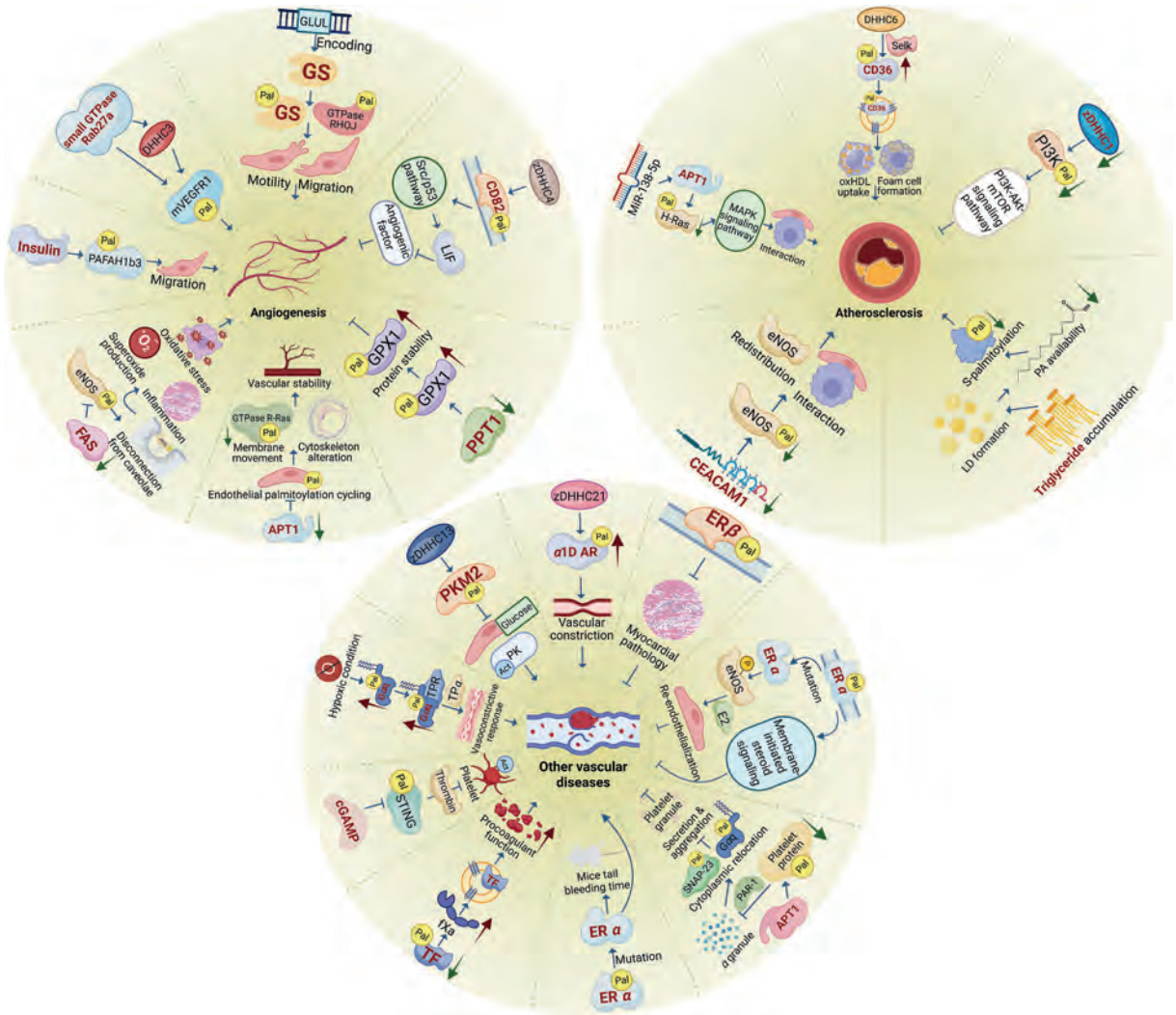

Figure 3 Palmitoylation in angiogenesis, atherosclerosis, and other vascular diseases. Palmitoylation affects blood vessels through several agents, resulting in pathological changes like inflammation and cell migration, which ultimately culminate in angiogenesis. Pal, palmitoylation; P, phosphorylation; Act, activation.

Table 1 The relationship between palmitoylation modification and cardiovascular diseases.

Diseases	Tissue/Cell	Protein substrate	Enzyme	Modification site	Ref.
Cardiomyocyte function and heart diseases	HEK293 cell	β1-AR	N/A	Cysteines 392, 393, and 414	50,51
Heart failure	Cardiomyocyte	β-AR	DHHC5	C-terminal domain	52
Heart failure	Cardiac tissue	NCX1	zDHHC5	Cysteine 739	53
Heart failure	Cardiomyocyte	Rab3gap1	zDHHC9	N/A	54
Myocardial hypertrophy and heart failure	Cardiomyocyte	Rac1	zDHHC3	N/A	55
Myocardial hypertrophy	Cardiac tissue	N/A	Wnt-C59	N/A	59
Ischemia reperfusion	Cardiomyocyte	N/A	DHHC5	N/A	47
Ischemia reperfusion	Cardiac tissue	PLM	DHHC5	Cysteine 40	61
Ischemia reperfusion	Cardiac tissue	CypD	N/A	Cysteine 202	63
Arrhythmia	Cardiomyocyte	Nav1.5	N/A	Cysteine 981	48
Arrhythmia	Cardiac tissue	The α1C subunit of Ca(v)1.2 L-type Ca channels	N/A	The channel's amino terminus and I−II linker	69
Cardiomyopathy	Cardiomyocyte	PLN	Aph2	N/A	72
Diabetic cardiomyopathy	Cardiomyocyte	CD36	DHHC4	N/A	73
SCM	Cardiomyocyte	NLRP3	zDHHC12	N/A	74
Angiogenesis	Pericyte	KAI1	zDHHC4	N/A	86
Angiogenesis	Endothelial cell	R-Ras	APT1	N/A	87
Angiogenesis	Endothelial cell	Gpx1	PPT1	Cysteines 76 and 113	88
Angiogenesis	Endothelial cell	eNOS	FAS	N/A	89
Angiogenesis	Endothelial cell	PAFAH1b3	N/A	Cysteines 56 and 206	93
Angiogenesis	Endothelial cell	mVEGFR1	N/A	N/A	94
Angiogenesis	Endothelial cell	GS	N/A	N/A	95
Blood pressure	HEK293 cell	α1 AR	zDHHC21	N/A	96
Thrombus formation	Platelet	G(αq), SNAP-23	APT1	N/A	100
Thromboembolism	Vasculature	ERα	N/A	Cysteine 451	102
Thromboembolism	Endothelial cell	TF	N/A	Cysteine 245	103
Septic thrombosis	Vasculature	STING	N/A	N/A	104
Atherosclerosis	Macrophage	PI3K subunit p110α	zDHHC1	N/A	105
Atherosclerosis	Macrophage	CD36	Selk; DHHC6	N/A	106,107
Atherosclerosis	Endothelial cell	H-Ras	APT1	N/A	108
Aortic plaque-like lesion	Endothelial cell	eNOS	CEACAM1	N/A	109
PPHN	HEK293 cell	Gαq	N/A	N/A	111,112
Cardiovascular dysfunction	Endothelial cell	PKM2	zDHHC13	Cysteine 31	44
CAD	Peripheral blood	N/A	ABHD17A	N/A	113

N/A: not available; β1-AR: β1-adrenergic receptor; β-AR: β-adrenergic receptor; NCX1: sodium−calcium exchanger; PLM: phospholemman; CypD: Cyclophilin-D; Nav1.5: voltage-gated sodium channel; PLN: phospholamban; SCM: septic cardiomyopathy; APT1: acyl-protein thioesterase 1; FAS: fatty-acid synthase; eNOS: endothelial nitric-oxide synthase; mVEGFR1: membrane-localized vascular endothelial growth factor receptor-1; GS: glutamine synthetase; CEACAM1: carcinoembryonic antigen associated cell adhesion molecule-1; ERα: estrogen receptor α; TF: tissue factor; Selk: selenoprotein K; PPHN: persistent pulmonary hypertension in neonates; PKM2: pyruvate kinase M2; CAD: coronary artery disease.

indicated that oxidative stress regulates CAV1 palmitoylation in aortic ECs, impacting CAV1-dependent cellular activities such as signal protein concentration and cholesterol transport[116]. Simvastatin may also influence CAV1 palmitoylation in these cells, though the specific effects require further investigation. Studies have indicated that palmitoylation of CAV1 is essentially irreversible, likely due to the persistent retention of palmitate on CAV1, precluding subsequent repalmitoylation[117]. This could potentially create favorable conditions for simvastatin intervention in the future. Moreover, oxLDL and exogenous PA interact with CD36, leading to MYD88 palmitoylation and the subsequent activation of the CD36−TLR4−MYD88 nuclear factor kappa B innate immune signaling pathway[118,119]. This process enhances the capacity of acute myeloid leukemia (AML) cells to suppress T cell proliferation, adversely affecting disease prognosis. Statins that target the CD36 immunosuppressive pathway may enhance the effectiveness of decitabine in AML treatment[118,119]. This demonstrates significant antitumor activity and advances the development of novel therapies targeting palmitoylation for other systems.

Porcupine, an *O*-acyltransferase, and its substrate WNT ligands are also notable for their therapeutic potential. Porcupine palmitoylates WNT ligands, affecting their activity. Research focuses on using WNT pathway biomarkers for diagnostics and prognostics[18]. For instance, a clinical study (NCT04058496) investigates WNT signaling post-cardiac surgery to understand inflammatory processes and improve postoperative care. Another study (NCT02624934) aims to prognosticate left ventricular maladaptation in aortic stenosis patients by analyzing blood for WNT pathway regulators. Therapeutically, the novel porcupine inhibitor CGX1321, currently in a phase I clinical trial (NCT02675946) for solid tumors, has demonstrated efficacy in reducing infarct size and facilitating cardiac recovery post-myocardial infarction (MI) in mice by promoting cardiomyocyte

proliferation and regeneration[120]. CGX1321 also impedes WNT protein secretion, thereby obstructing both canonical and non-canonical WNT pathways[120]. It reduces myocardial hypertrophy and pathological cardiac remodeling while improving ventricular function in murine models[121]. This suggests CGX1321's potential in treating WNT-mediated cardiopathies. Additionally, the porcupine inhibitor LGK-974 has been shown to reduce inflammatory response and enhance cardiac performance post-myocardial I/R injury in mice by inhibiting WNT pathway activation in monocytes/macrophages, making it a potential immunomodulatory agent for MI recovery[122]. Moreover, innovative STING palmitoylation inhibitors like nitrofuran C-178 and the indole urea derivative H-151 have significantly improved cardiac function three weeks post-I/R and decreased collagen deposition and fibrosis in the infarcted area[123]. These inhibitors prevent cysteine palmitoylation and STING multimerization, which helps prevent infarct expansion and progression to ischemic cardiomyopathy and HF[123]. Blocking this pathway has shown efficacy in cardiac pathology, particularly by reducing palmitoylation in acute MI remodeling. Additionally, pre-treatment with the irreversible non-selective PATs inhibitor 2-bromopalmitate (2-BP) before doxorubicin-induced DNA damage in human vascular smooth muscle cells can alter aging phenotypes[43]. This suggests that overall inhibition of protein palmitoylation by 2-BP is linked to the attenuation of DNA damage-induced vascular smooth muscle cell aging, potentially by affecting the nuclear translocation of the aging marker p53, thus elucidating the relationship between palmitoylation and aging[43]. However, another inhibitor, cyanoacrylamide, exhibits similar efficacy to 2-BP, inhibiting protein *S*-acylation and disrupting DHHC-mediated cell signaling[124]. The role of cyanoacrylamide in cardiovascular disease palmitoylation warrants further investigation.

4.1.2. Biological products

Novel inhibitors of palmitoylases and depalmitoylases have been developed for cancer research, including selective short peptide conjugates that inhibit specific DHHCs, thereby blocking palmitoylation of key proteins[5]. For instance, combining FASN with taxane drugs disrupts tubulin palmitoylation and microtubule dynamics in cancer cells, enhancing tumor cell proliferation suppression *in vitro* and suggesting a promising therapeutic strategy for various cancers[125]. In parallel, palmitoyltransferase-zDHHC16 mediated palmitoylation of proprotein convertase subtilisin/kexin type 9 (PCSK9) is associated with increased PCSK9 levels and heightened resistance to sorafenib in hepatocellular carcinoma[126]. Sun and collaborators[127] have engineered a PCSK9-derived peptide that effectively curbs PCSK9 palmitoylation, thus augmenting the antineoplastic action of sorafenib in hepatocellular carcinoma. In YAP-dependent cancers, TEAD palmitoylation inhibitors can prevent TEAD autopalmitoylation, reducing therapeutic resistance by impairing cancer cell survival. In pancreatic cancer models, Wang et al.[128] identified Lomitapide as a ZDHHC5 inhibitor, reducing palmitoylation on the antiproliferative receptor SSTR5 and thereby decreasing pancreatic tumor cell growth and proliferation. Additionally, Mráziková et al.[119] reported that a palmitoylated anorexigenic prolactin-releasing peptide (palm11-PrRP) enhances leptin and insulin signaling and promotes hippocampal synaptogenesis in rat models, indicating neuroprotective benefits. A more stable palmitoylated PrRP31 analog (palm11-PrRP31) was engineered, showing multiple beneficial effects against obesity by improving glucose tolerance in rodent models[129]. Programmed cell death protein 1 (PD-1), a critical anti-cancer target, undergoes palmitoylation, influencing its stability[130]. Designing peptides that competitively inhibit PD-1 palmitoylation and expression offers new prospects for PD-1 inhibitors and combination immunotherapy[130]. While direct evidence for palmitoylation-based cardiovascular therapies is still lacking, insights from treatments for cancer and obesity may provide valuable strategies for developing targeted cardiovascular therapies through palmitoylation.

Extensive research has explored the interactions between palmitoyltransferases, their substrates, and their implications for cardiovascular therapies and diagnostics. These studies facilitate our understanding of palmitoylation's potential clinical utility in heart disease treatment. Sonic Hedgehog (Shh), a secreted morphogen, undergoes palmitoylation *via* Hhat[10]. In murine models, exogenous Shh administration boosts VEGFA synthesis in fibroblasts, promoting angiogenesis. Furthermore, disrupted Shh signaling in myocytes increases VEGFA-expressing macrophage recruitment, elevating VEGFA levels in ischemic muscle tissue[131]. Concurrently, Gupta et al.[132] found that Shh's angiogenic effects stem from stromal cell rather than endothelial Hedgehog signaling mediated by smoothened. Conditioned media from Shh-stimulated fibroblasts induce angiogenesis in ECs through the release of angiogenic proteins and growth factors[132]. Cardiac pathologies also benefit from these findings. Paulis et al. demonstrated that recombinant SHH protein (N-SHH) or microparticles derived from activated/apoptotic T lymphocytes harbor SHH (MPs^{SHH+}) protects against acute myocardial infarction and modulates cardiomyocyte electrophysiology in a rodent ischemia-reperfusion model[133]. Further studies in porcine models confirmed that SHH pathway activation with N-SHH or MPs^{SHH+} reduces reperfusion arrhythmias, infarct size, and myocardial damage biomarkers, offering protection from ischemia-reperfusion injuries[134]. These insights lay the groundwork for future clinical interventions to reduce cardiovascular disease and slow its progression. Palmitoylation of gasdermin D at cys192 by zDHHC14 exacerbates cardiomyocyte pyroptosis *in vitro*. Disulfiram, by antagonizing gasdermin D-N-terminal cys192 palmitoylation, mitigates myocardial pyroptosis, reduces infarct size, and preserves cardiac function in acute myocardial infarction[135]. Palmitoyl adrenomedullin and adrenomedullin/adrenomedullin 2 analogs self-assemble into liquid gels *in situ*[136]. These gels continuously lower blood pressure in hypertensive SHR rats and prolong local blood vessel relaxation by acting as calcitonin receptor-like receptor/receptor activity-modifying protein receptor agonists, presenting potential treatments for endothelial dysfunction-related diseases like refractory hypertension. These agents impact palmitoylation-dependent processes, altering cardiovascular structure and function, and show promise for disease intervention[136].

4.1.3. Traditional medicine

The current knowledge regarding palmitoylation's therapeutic potential, particularly in cardiovascular medicine and clinical trials, is limited. However, traditional medicine has provided more significant insights into treating palmitoylation-related cardiovascular diseases. Zhang et al.[137] showed that Baifuzi cerebrosides activate the BKCa channel through palmitoylation of the STREX domain, offering a molecular basis for Baifuzi's use in ischemic stroke therapy. Research on traditional medicines and palmitoylation extends to other diseases. Curcumin inhibits the autoacylation of DHHC3, reducing integrin β4-palmitoylation in invasive breast cancer cells, which correlates with cancer cell invasion potential, suggesting curcumin's therapeutic potential[138]. Green

tea polyphenols, especially 4″-alkyl ether lipophilic EGCG derivatives, significantly inhibit protein *S*-palmitoylation, reducing it to basal levels in DHHC3-overexpressing cells, highlighting their potential for clinical targeted therapy[139]. Studies have demonstrated the protective effects of curcumin and green tea polyphenols in cardiovascular disease[140-145], potentially linked to palmitoylation mechanisms, meriting further exploration.

To expand our knowledge, we have gathered data on the palmitoylation substrates and enzymes within traditional medicinal practices. Berberine, an isoquinoline alkaloid derived from traditional herbs, diminishes hypertrophy in palmitate-treated H9C2 cells, offering a protective mechanism against diabetic cardiomyopathy[146]. Daucosterol palmitate, another herb-based compound, exhibits neuroprotective effects through the PI3K/Akt/mTOR signaling pathway, supporting its use in ischemic stroke management[147]. Continued research and refinement may establish the PI3K/Akt/mTOR pathway as a target for daucosterol palmitate to mitigate cerebral ischemia-reperfusion injury[147]. These preliminary findings are instrumental for advancing cardiovascular clinical therapies. Nonetheless, ongoing research into palmitoylation and cardiovascular diseases is imperative to devise novel and effective treatment strategies (Table 2[43,121-123,133,135-137,146,147]).

4.2. Diagnosis

Currently, definitive quantitative biomarkers for palmitoylation in cardiovascular pathology are lacking. Nonetheless, accumulating evidence underscores its significance in the pathogenesis of such diseases. Therefore, the exploration of palmitoylation's distinctive role in cardiovascular pathologies through biomarkers is meritorious. Recent studies have examined changes in protein palmitoylation dynamics in the circulatory system, identifying potential biomolecules as clinical diagnostic markers.

Porcupine acts as an *O*-acyltransferase, facilitating the palmitoylation of WNT proteins and activating the WNT/β-catenin signaling pathway, which is linked to cardiac hypertrophy and failure[59]. Upregulation of this enzyme may serve as an adjunctive biomarker for cardiovascular pathology. Palmitoyl acyltransferase DHHC5 modulates the β-AR signaling pathway *via* protein palmitoylation, though the impact of DHHC5 expression changes on cardiac pathology remains unclear, warranting further investigation[52]. Advancements in this area may position DHHC5 as a prospective biomarker for cardiac disorders. In murine models, diminished expression of zDHHC21 is associated with vascular anomalies, potentially leading to hypotension and tachycardia[96], positioning it as a candidate biomarker for vascular pathology. Additionally, zDHHC3-mediated *S*-palmitoylation of Rac1 in mice enhances hypertrophic signaling and cardiomyopathy, suggesting future research into zDHHC3 as a biomarker in human clinical assessments[55]. Concurrently, a noted decrement in zDHHC9 expression has been observed in the cardiac tissue of HF patients[54], indicating its potential role in the pathogenesis of cardiac dysfunction. At the genetic level, Aph2, a protein acyltransferase crucial for embryonic cardiac development and function, denotes the involvement of protein palmitoylation in cardiac development and performance[72], which may facilitate early genetic-based diagnosis of cardiovascular anomalies. The modulation of palmitoyltransferase levels can significantly impact the pathogenesis and progression of diseases, making its expression and activity valuable auxiliary diagnostic markers for early diagnosis or differentiation of cardiovascular conditions. A more direct diagnostic approach involves detecting palmitoylation levels, which can forecast disease trajectories based on variations in their levels and localization. Currently, prevalent techniques for detecting palmitoylation modifications include [^{3}H]-palmitate labeling, tracking, and Immunoprecipitation Acyl-Biotin Exchange,

Table 2 Drugs that affect palmitoylation and its substrates and enzymes.

Molecule	Target	Mechanism	Condition	Clinical trial	Ref.
N-SHH or MPsSHH+	N/A	Activate SHH pathway	Cardiac ischemia−reperfusion	N/A	133
CGX1321	Porcupine	Inhibit porcupine	Cardiac diseases	N/A	121
LGK-974	Porcupine	Inhibit porcupine			
Lomitapide	ZDHHC5	Inhibit palmitoylation on SSTR5	I/R injury	N/A	122
Disulfiram	GSDMD cys192	Antagonize GSDMD-N-terminal cys192 palmitoylation	AMI	N/A	135
2-BP	PATs	Inhibit protein palmitoylation and affect the nuclear translocation of p53	Aging	N/A	43
Palmitoyl ADM and ADM/ADM2 analogs	CLR/RAMP	Reduce the blood pressure and prolong the relaxation of local blood vessels	Refractory hypertension	N/A	136
Baifuzi cerebrosides	STREX domain	Activate BKCa channel through palmitoylation	Stroke	N/A	137
Berberine	N/A	Reduce palmitate-incubated hypertrophy	Diabetic cardiomyopathy	N/A	146
Daucosterol palmitate	N/A	Function through PI3K/Akt/mTOR signaling pathway	Ischemia stroke	N/A	147
Nitrofuran C-17; the indole urea derivative H-151	STING	Prevent cysteine palmitoylation and STING multimerization	MI	N/A	123

N/A: not available; N-SHH: recombinant sonic Hedgehog protein; MPs^{SHH+}: microparticles derived from activated/apoptotic T lymphocytes harbor SHH; I/R: ischemia/reperfusion; GSDMD: Gasdermin D; AMI: acute myocardial infarction; 2-BP: 2-bromopalmitate; PAT: protein acyltransferase; ADM: adrenomedullin; ADM2: adrenomedullin 2; CLR: calcitonin receptor-like recepto; RAMP: receptor activity-modifying protein; MI: myocardial infarction.

supplemented by bioinformatics analyses of specific modified proteins and regions, utilizing specialized software to predict palmitoylation sites within particular protein structures[32,73]. These methodologies establish a foundation for elucidating the diagnostic and therapeutic significance of palmitoylation in the future.

5. Discussion and prospects

Recent advancements in palmitoylation research have enhanced our comprehension of this PTM's role in disease etiology and its therapeutic modalities within cardiovascular medicine. The primary research focus now is to integrate this knowledge into clinical practice for better treatment outcomes. It is crucial to recognize that the presence or absence of palmitoylation alone is insufficient to determine its definitive role in disease progression. Hence, it is imprudent to conclusively assess its promotive or inhibitory influence on cardiovascular pathologies. Palmitoylation shows specific changes related to particular disease categories. In cardiovascular disease, for instance, palmitoylation modifies proteins in heart disease pathways and affects cells involved in vascular abnormalities. This specificity might be linked to the types of substrates involved in palmitoylation across various diseases. However, the underlying mechanism of this modification appears consistent across different systems, typically affecting protein localization and stability, thereby influencing disease progression. Currently, no enzyme or substrate specific to cardiovascular palmitoylation has been identified, but certain palmitoylation-related enzymes exhibit tissue-specific functions crucial for cardiovascular health. DHHC5 regulates cardiac sodium channels and myocardial signaling[45,47,52,53,61], while APT1 modulates cardiac NCX1 and vascular homeostasis[58,87,90,100,108], marking them as potential therapeutic targets. Palmitoylation states of certain cardiac calcium and sodium channels affect electrophysiological properties[48,66-69], and eNOS palmitoylation influences membrane localization and endothelial function[39,89-92,98,109], making them novel targets for cardiovascular research. Contemporary studies have demonstrated that both palmitoylation and non-palmitoylation of the α1C subunit of the cardiac Ca(v)1.2 channel are necessary to elicit the aberrant effects that contribute to cardiac dysfunction and arrhythmogenesis[69]. Moreover, cardiovascular pathology is a chronic, dynamic process, illustrated by the remodeling that occurs after a myocardial infarction, showing distinct early and late pathological features. This indicates that the timing of targeting palmitoylation interventions can affect disease prognosis and progression. The role of palmitoylation at different stages of cardiovascular disease requires further investigation to understand its pathological and therapeutic implications. Techniques to quantify palmitoylation site occupancy are essential in exploring disease pathogenesis.

Palmitoylation, the covalent bonding between lipids and proteins, increases protein hydrophobicity and promotes interactions with lipid bilayers, distinguishing it from other post-translational modifications[148-154]. Unlike other lipid modifications such as pentanoyl and nutmeg acylation, palmitoylation is reversible and has a significant regulatory effect[96]. Predominantly, reversible *S*-palmitoylation affects cardiovascular-associated proteins, including ion channel subunits, receptors, and function-specific proteins. Investigating the localization and role of membrane receptors is crucial to understanding how extracellular proteins trigger signaling pathways or contribute to disease etiology. Continued research is necessary to reveal how bioactive molecules' expression and function correlate with and are regulated by cardiovascular pathways. In cardiovascular diseases, palmitoylation commonly affects the localization and transport of modified proteins, enriching them and subsequently influencing downstream pathways and pathological processes (Table 3[49,52,54,55,59,75,85,86,105,155]). Proteins such as ERβ, RAC1, and CD36 have been extensively studied in this context[55,73,155]. However, the effects of palmitoylation or depalmitoylation vary significantly, ranging from generating new bioactive substances to destabilizing existing structures and causing adverse pathological outcomes (Fig. 4). This complexity makes it challenging to categorize their functions uniformly. Nevertheless, in same cell types where modifiers aggregate, comparable functions can be observed despite differences in substrates and enzymes. For instance, in I/R, palmitoylation influences the activity of channels like the ion pump and transition pore in cardiomyocytes[47,62,63], whereas in atherosclerosis, it affects the enrichment and uptake of oxLDL in macrophages[105-107]. This indicates that targeting multiple palmitoylation sites could synergistically alter disease biomarker localization and distribution, enhancing therapeutic

Table 3 The signaling pathways involved in palmitoylation.

Signaling pathway	Type	Function	Diseases	Ref.
17β-E2/ERβsignaling pathway	*S*-Palmitoylation	SMAD3 phosphorylation and nuclear localization	Myocardial hypertrophy	49,155
β-AR signaling pathway	*S*-Palmitoylation	Membrane retention	Heart failure	52
Natriuretic peptide signaling pathway	*S*-Palmitoylation	The exocytosis effect of ANP release	Heart failure	54
RhoGTPase signaling pathway	*S*-Palmitoylation	Membrane localization	Myocardial hypertrophy	55
Wnt/β-catenin signaling pathway	*O*-Palmitoylation	Pathological myocardial hypertrophy, fibrosis, and myocyte apoptosis	Myocardial hypertrophy	59
NLRP3 signaling pathway	*S*-Palmitoylation	The translocation of NLRP3 and the assembly and activation of NLRP3 inflammasome	N/A	75
Src/p53 pathway	*S*-Palmitoylation	Inducing LIF	Angiogenesis	86
Arrestin/PDE4D signaling cascade; cAMP−PKA signaling pathway	*S*-Palmitoylation	The contractile response of cardiomyocytes	N/A	85
PI3K−Akt−mTOR signaling pathway	*S*-Palmitoylation	The downstream phosphorylation and the number of macrophages	Atherosclerosis	105

N/A: not available; E2: estradiol; ANP: atrial natriuretic peptide; LIF: leukemia inhibitory factor; PDE4D: phosphodiesterase 4D.

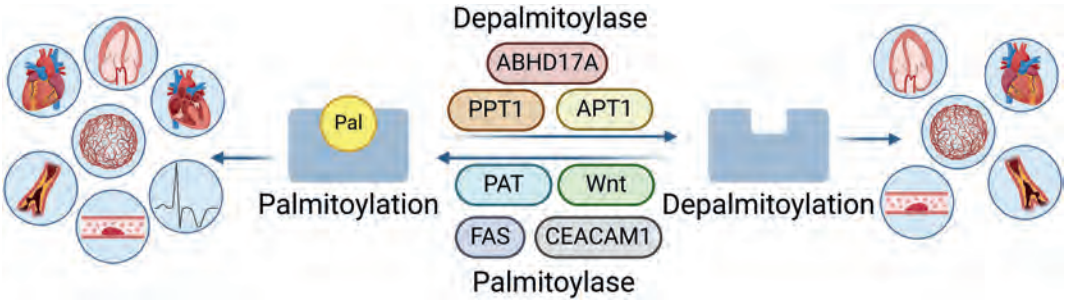

Figure 4 The relationship between protein palmitoylation and depalmitoylation processes and cardiovascular diseases. Pal, palmitoylation.

interventions for pathological processes. The reversible nature of *S*-palmitoylation suggests the presence of both stable modifications and dynamic, rapidly reversible modifications within the same pathological context[50]. This kinetic variability provides insights into predicting functional outcomes, with stable modifications likely ensuring protein repositioning following stimulation and dynamic modifications serving as a regulatory "switch". Prospective studies may investigate palmitoylation dynamics, the impact of palmitoylation ratios on cellular functions, and the subsequent alterations in downstream effectors and signaling pathways. Our current comprehension of palmitoylation involves initial auto-palmitoylation of zDHHC-PATs and subsequent palmitate transfer to target proteins[8,156,157]. To resolve prevailing ambiguities, improving palmitoylation detection methods and identifying new experimental areas are needed. By examining the subcellular localization of palmitoylating enzymes and determining the cellular compartments where palmitoylation occurs, we may clarify its relationship with disease pathogenesis and potentially apply these findings to a broader range of disorders.

Despite extensive research on palmitoylation, a deeper investigation into its complex mechanisms is necessary. Research has indicated varied roles of palmitoylation in cardiovascular physiology and pathologies. For instance, palmitoylation inhibition diminishes calcium mobilization and thromboxane-induced contractility in hypoxic persistent pulmonary hypertension in neonates, but not in normal pulmonary arteries. This phenomenon may arise from increased Gαq palmitoylation under hypoxic conditions, which potentially enhances its interaction with vasoconstrictor GPCRs, thus elevating the reactivity of hypoxic Gαq-coupled receptors[111,112]. Additionally, GS inhibition reduces Rhoj palmitoylation and EC motility, thereby impairing EC migration in pathological angiogenesis, with no significant impact on the vascular systems of healthy adult mice[95]. This lack of migration in stationary EC in healthy adults suggests that GS and its palmitoylation targets are relevant therapeutic targets for disease management[95]. Evidence indicates that alterations in zDHHC5 expression and palmitoylation occur in cardiac diseases, yet changes in substrate NCX1 and PLM palmitoylation do not directly correspond. Nonetheless, the impact of NCX1 and PLM palmitoylation on cardiac function, particularly myocardial contractility, cannot be dismissed[45]. Further exploration of pathway interactions or cascade events affecting substrate concentrations is needed. These uncertainties could provide new avenues for palmitoylation research. Databases constructed for the nervous system delineate the regional and cell type-specific expression of known palmitoylating and depalmitoylating enzymes and their associated proteins within the brain[158]. Finer differentiation of enzyme gene expression within narrow neuronal populations aids in characterizing enzyme functions in neuropathology. Such predictive pathways offer a model for cardiovascular palmitoylation studies, advancing our understanding of action modes based on substrate expression across different cell types and regions in the cardiovascular system. Additionally, palmitoyl acyltransferase Aph2 has been shown to modulate cardiac activity by phosphorylating the substrate PLN[72]. The potential crosstalk between palmitoylation, ubiquitination, and sumoylation pathways in modulating huntingtin protein localization and functionality warrants further investigation[7]. Understanding which PTMs depend on palmitoylation, their synergistic effects in producing aberrant phenotypes, and their ability to modulate palmitoylation through interference with other PTMs remains an open research area. Additionally, discrepancies in zDHHC5 expression and NCX1 palmitoylation between animal models and human subjects may stem from the human body's heightened state of decompensation or pharmacological interventions[45]. This highlights the limitations of animal models in accurately replicating human pathophysiology, hindering the translation of findings to human disease contexts.

Given the significant energy demands of cardiac function and its close link to mitochondrial health, identifying palmitoylation targets associated with mitochondrial regulation has become a key research focus. Understanding palmitoylation's role in various diseases can be advanced by investigating shared pathways and therapeutic responses among palmitoylation-related disorders. For instance, modulating mitochondrial function through calcium regulation has been shown to affect palmitoylation, underscoring the need to identify specific palmitoyltransferases that influence mitochondrial dynamics or composition and their precise targets in cardiovascular diseases[159]. Future studies are expected to clarify the connection between protein palmitoylation and mitochondrial function, potentially slowing cardiovascular disease progression by modulating senescence pathways. Additionally, while the role of zDHHC9 in ANP production is known[54], the exact downstream mechanisms, particularly whether it impacts Rab3a-mediated transport pathways or the exocytosis of dense-core vesicles containing ANP in atrial myocytes, require further exploration. Future research should focus on elucidating the roles of zDHHC9, Rab3gap1 palmitoylation, and Rab3a in ANP release and their implications for cardiovascular health. Future multiphase clinical trials will not only revalidate the practicality of this mechanism in human subjects but also confirm the accuracy of the underlying mechanistic investigations.

Currently, there is a lack of pharmacological agents for clinically modulating protein palmitoylation. The development of single-entity cardiovascular therapeutics and efficient screening methodologies for their mechanisms of action needs further

consideration. The scientific community is increasingly identifying novel depalmitoylases and creating palmitoylation inhibitors. Insights from advanced palmitoyl therapeutics in oncology trials may shift the focus towards cardiovascular applications, beyond enzyme inhibition or substrate mimicry, necessitating an interdisciplinary approach across various pathologies. Concurrent investigations in oncology, diabetology, endocrinology, and metabolic diseases could enhance the understanding of cardiovascular palmitoylation. Repeated studies highlight the protective influence of ERs during palmitoylation on cardiovascular pathologies, with the cardioprotective properties of estrogen, potentially through membrane-initiated steroid signaling, well-documented[52,96,98]. These findings advocate for future estrogen-centric research to develop pharmacotherapies for palmitoylation-associated cardiovascular conditions and emphasize the importance of gender-specific considerations in research, particularly ensuring gender parity in animal models for scientific rigor and result precision. Additionally, the role of Selk in cellular development and atherogenesis extends beyond pharmacological interventions, with dietary selenium offering alternative therapeutic avenues for cardiovascular health[106]. Furthermore, recent studies indicate that palmitoylation exerts a regulatory influence on cellular senescence, potentially attributable to the substantial effects of diet and fasting on PA availability and the extent to which this fatty acid covalent modification regulates proteins, thereby affecting cardiovascular aging and longevity[43]. Similarly, by modulating dietary intake and supplementing with palm oil, PA availability can be restored, presenting an efficacious strategy for the prevention and treatment of atherosclerosis[110]. This underscores the significance of diet and lifestyle in disease prevention and management, necessitating further investigation into the effects of dietary components on palmitoylation-linked disorders.

Notably, the therapeutic potential of traditional medicine in modulating palmitoylation is emerging, suggesting possible cardiovascular benefits through targeted pathways or compounds, potentially leading to novel therapeutic concepts that combine traditional medicine and Western pharmacology in PTM treatments. The clinical relevance of PTMs is increasingly acknowledged[160]. Exemplified by Imatinib, an ABL tyrosine kinase inhibitor and pioneering targeted therapy for chronic myeloid leukemia, approved in 2001[161]. This breakthrough has catapulted protein kinases as prime drug targets and intensified focus on protein phosphorylation[148]. Recent phase III trials featuring Sirtuin agonists like resveratrol and nicotinamide ribose for peripheral cardiovascular disorders, and completed phase IV trials with the SIRT3 agonist silybin for hypertension, highlight the therapeutic benefits of acetylation regulation in cardiovascular pathologies[162]. There is also a consideration that pharmacological interventions targeting certain PTMs may have adverse effects on other bodily tissues and organs. The potential for similar ramifications from palmitoylation therapies necessitates a prolonged period of research and exploration. Thus, potential similar ramifications from palmitoylation therapies necessitate extensive research. Currently, palmitoylation treatment methods in clinical trials are rare, with no reports related to cardiovascular diseases, so the prognostic effects still require time and more trials to substantiate.

These insights necessitate exploring and advancing palmitoylation as a therapeutic target, driving the discovery of new methods to elucidate its impact on the cardiovascular system. This broadens research directions and enhances the practical application of identifying palmitoylation targets, signal regulation, and the targeted management of related cardiovascular conditions. Recognizing the importance of targeting palmitoylation modifications has significant implications for medical interventions, enabling more precise and effective treatments. Unraveling palmitoylation promises to improve our approach to cardiovascular health and disease, paving the way for groundbreaking therapies that could transform patient outcomes.

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Author contributions

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Conflicts of interest

The authors have no conflicts of interest to declare.

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