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Review Article

Ubiquitination-mediated protein homeostasis in cardiovascular diseases: molecular mechanisms and therapeutic opportunities

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Abstract: Cardiovascular diseases (CVDs) remain one of the leading causes of death worldwide. Although the well-known risk factors include hypertension, hyperglycemia, dyslipidemia and obesity, the latest studies implicate involvement of pathological mechanisms at the molecular level. Various cellular processes, including oxidative stress, inflammatory response, mitochondrial dysfunction, and ferroptosis, are regarded as contributors to the initiation and progression of CVDs. Ubiquitination, a post-translational modification essential for the maintenance of protein homeostasis, influences the pathogenesis of CVD through regulating protein degradation, signal transduction and cellular functionality. The enzymes E1, E2 and several E3 ligases (e.g., TRAF6, TRIM21, TRIM35) participate in autophagy, inflammation and cardiac remodelling, while deubiquitinating enzymes (DUBs) (e.g., USP25, OTUB1) modulate cardiac function by stabilizing calcium pumps or regulating key signalling molecules. For example, ubiquitination of TRPC3 Ca^{2+} channels prevents them from functioning closely with phospholipase C; excessive accumulation of TRPC3 lowers cardiac contractility. On the other hand, new protein degradation technologies like Proteolysis-Targeting Chimera (PROTAC) are promising for precise selective down-regulation of disease-related proteins. This study will systematically summarize the molecular mechanisms of ubiquitination in CVDs and its potential therapeutics to provide theoretical support for mechanistic research and the development of new targeted drugs.

Keywords: Cardiovascular diseases, ubiquitination, E3 ligases, deubiquitinating enzymes, protein degradation, signaling pathways, targeted therapy

Introduction

CVDs, such as coronary artery disease (CAD), together with other forms of ischemic heart disease, stroke, cardiomyopathies as well as arrhythmias, remain among the leading causes of death (and a cause of significant disease burden) worldwide, as well as a major cause of loss of economic productivity. Between 1990 and 2021, the global number of CVD cases and deaths increased by nearly 92% and 58%, respectively. Over time, the age-standardized incidence and mortality rates have been declining as a whole. Markedly, improvements have been seen in high-sociodemographic index (SDI) regions while low-SDI regions are facing a burden disproportionately high [1-3]. Overall, younger people usually exhibit lower incidence compared to older ones. There are striking differences across SDI regions, sex, and disease subtype. Many cases can be prevented through primary prevention strategies [4, 5]. In middle-

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aged or older people, moderate to high CVD risk is closely related to cognitive decline. In contrast, escalating metabolic factors remain the main modifiable risk factors, such as hypertension, high fasting glucose, dyslipidaemia, obesity and impaired renal function [6-10].

Mechanistic studies reveal that oxidative stress, inflammatory responses, mitochondrial dysfunction, and ferroptosis are all main driving forces of CVD. Hypoxia-inducible factor-1α (HIF-1α) can activate cardiac fibroblasts (CFs) [11]; methylmalonic acid (MMA), uric acid (UA) makes ischemia/reperfusion (I/R) injury and inflammation worse through the generation of reactive oxygen species (ROS) [12, 13]; Long non-coding (lnc) RNAs and circular RNAs, natural products like tanshinone IIA, fucoxanthin and isorhamnetin have cardioprotective effects through ferroptosis [14-17]. Thus, CVD cannot be explained only by risk factors; rather pathogenic mechanisms operate through multiple levels of genes, molecules and cells or multiple mechanisms contribute to the same clinical phenotype.

Ubiquitination is a highly conserved post-translational modification (PTM) that is used by the protein degradation system. It is an ATP-dependent enzymatic cascade that follows E1 activating, E2 conjugating, and E3 ligating enzymes. This process begins with the formation of a thioester bond between a cysteine residue of E1 and the C-terminus of the ubiquitin (Ub) that takes place in the presence of ATP. An E2 ubiquitin-conjugating enzyme receives the activated Ub. In the end, an E3 ligase (such as MDM2) instructs the Ub molecule to attach to the target substrate's lysine residue (such as p53 or PDCD4) [18]. This modification determines whether a substrate is targeted for proteasomal degradation or participates in signal transduction. Ubiquitination plays a crucial role in key cellular functions such as metabolic stress response, energy homeostasis, and cell survival by precisely regulating the stability of important proteins such as PDCD4 [19, 20]. The small molecule AT III inhibits the E3 ligase MDM2 leading to stabilization of its substrate protein p53 and inhibiting disease progression, emphasizing the therapeutic potential of targeting that system [21]. Within the cardiovascular system, ubiquitination precisely regulates crucial biological processes such as cardiomyocyte survival, mitochondrial dynamics and inflammatory activation frequently via Ub ligase-mediated protein degradation. For example, the ubiquitin ligase FBXO32 promotes the degradation of ANXA1. Dysregulation of this system can impair important signaling pathways like the PI3K/AKT pathway, disrupt protein turnover, and cause faulty stress responses, collectively leading to pathological remodeling. This process is crucial in the development of cardiovascular diseases, like septic cardiomyopathy [22]. In fact, endotoxins mainly target NF-κB, which leads to increased levels of pro-inflammatory cytokines (such as TNF-α and IL-6) [23]. This worsens the systemic inflammatory situation and thus causes CVD. Moreover, we know that this situation is further supported by our team's own findings. Indeed, in patients with acute myocardial infarction (MI) complicated by high-altitude ventricular septal rupture, strong inflammatory activation reflected by a significant increase in IL-6 is closely associated with poor prognosis [24]. Meanwhile, microRNA (miRNA) networks are involved as well. For instance, miR-21 demonstrates a dual role; most studies indicate a cardioprotective function, while other studies report that elevated miR-21 upon concentration in patient serum or tissues promotes fibrosis and cardiac dysfunction [25]. These molecular signals offer new angle to understand the pathogenesis of CVD. The results suggest that the entire molecular basis of CVD development is ascribed to the ubiquitination system, inflammatory response network and miRNA regulation. Mechanistic studies further show that various enzymes related to Ub are involved in the precise regulation of the significant pathways of the cardiovascular system. E1 enzymes regulate ion channel stability; E3 ligases modulate inflammatory and hypertrophic signaling; and DUBs stabilize calcium-handling proteins and transcriptional regulators [26], thereby fine-tuning cell death processes. In alcoholic cardiomyopathy, the deubiquitinase USP53 removes K63-linked Ub chains from lysine 377 of RIPK1, thereby relieves the inhibition of its kinase activity. This directly induces the programmed death of cardiomyocytes as well as necroptosis. In particular, studies show that targeted intervention of this axis holds therapeutic potential [27]. Furthermore, MAPK pathways play a vital role in cell proliferation and apoptosis processes in eukaryotes. The modification

of SIRT1 via SUMO E3 ligase inhibits myocardial fibrosis through the AKT/GSK3β signalling pathway which depends on the stable regulation of transcription factor SP1. This further builds upon the universal regulatory principle of Ub-like modification systems within cardiovascular signaling networks [26]. In addition, the emergence of targeted protein degradation strategies including PROTACs opens up new therapeutic avenues with the selective elimination of pathogenic proteins. Research has demonstrated that using PROTAC technology to degrade TRAP1 protein in vascular smooth muscle cells (VSMCs) inhibits its mediated glycolysis-lactate-H4K12la epigenetic axis, thereby markedly delaying atherosclerosis (AS). This not only confirms the therapeutic potential of targeted protein degradation techniques but also reveals a new mechanism linking crosstalk between metabolism and epigenetics involved in CVD [28]. Fundamental role of ubiquitination in linking protein homeostasis and CVD is shown by these findings. Ubiquitination holds promise as a target for innovative diagnostics and therapies. Studies on acute MI with ventricular septal rupture (AMI-VSR) have found that its important inflammatory pathological processes are associated with ubiquitination regulation [29].

This review focuses on how ubiquitination affects the pathogenesis and progression of various common CVDs. We will aim to understand the specific role of ubiquitination in cardiomyocyte survival, endothelial dysfunction, vascular inflammation, smooth muscle cells phenotypic switch, cardiac and vascular remodelling through incorporation of cell type specific mechanisms and disease-related progresses.

Basic mechanisms of ubiquitination

Major steps of the ubiquitination process: enzymatic actions and regulation

Ubiquitination is a conserved posttranslational modification that covalently attaches the 76-amino acid Ub molecule to substrates. Furthermore, it plays a vital role in degradation, regulation, and signalling. This three-enzyme cascade works with the 26S proteasome in ubiquitination: E1 activating enzyme, E2 conjugating enzyme, and E3 ligase. E1 activates Ub and creates a high-energy thioester bond in an ATP-dependent manner, thus establishing the transfer. Studies with a structural framework have shown the Uba7-UBE2L6-ISG15 complex undergoes conformational switching to regulate the reaction process [30, 31]. UBA5-UFC1 binding is reliant on short linear motifs, uncovering the unique mechanism of UFM1 conjugation [32]. Following activation, Ub is transferred to the catalytic cysteine residue of an E2 enzyme, forming an E2~Ub intermediate. Beyond acting as a carrier, E2 determines chain elongation patterns and linkage specificity; for instance, the UBA domain of UBE2K modulates chain conformation, conferring distinct assembly capabilities [33]. In certain substrates, mono-ubiquitination enhances affinity for E2-E3 complexes - for example, mono-ubiquitinated β-catenin promotes binding to CRL1, thereby accelerating polyubiquitination [34].

E3 ligases regulate substrate recognition and Ub transfer, which is the critical step of ubiquitination. The HECT, RING/U-box and RBR types are catalytic mechanism classifications. The atypical E3s, such as KCTD5 can act on the Gβγ complex for specific ubiquitination and fine-tuning of GPCR/cAMP signaling [35]. On the other hand, the NEDD8 modification of CRL-type E3s activates the RING domain and efficiently drives the polyubiquitin chain formation [36]. Dynamic homeostasis is achieved in cells through various DUBs that cleave or remove Ub tags. For example, Ataxin-3 employs both its Josephin catalytic domain and its UIM motifs for chain editing and substrate-specific regulation [37].

The specificity of E1-E2-E3-DUB activities in the cardiovascular system and regulation are determined by expression levels of enzymes, conformation, other PTM crosstalk, and pathological signals such as oxidative stress, inflammation and hypoxia. Research has shown that specific E3s (CHIP, MDM2, FBXO32) and DUBs (members of USP family) regulate cardiac contractile proteins, ion channels and important signaling molecules, thereby contributing to the development of CH, HF, and AS. Most studies focus mainly on structural evidence or mainly on functional evidence of ubiquitination. Thus, combining both evidence will not only give us a better idea about the molecular mechanisms of ubiquitination but also the rational basis of CVD pathology for better therapeutic development. The central mechanism of ubiquitination relies on the stepwise cascade of E1, E2 and E3

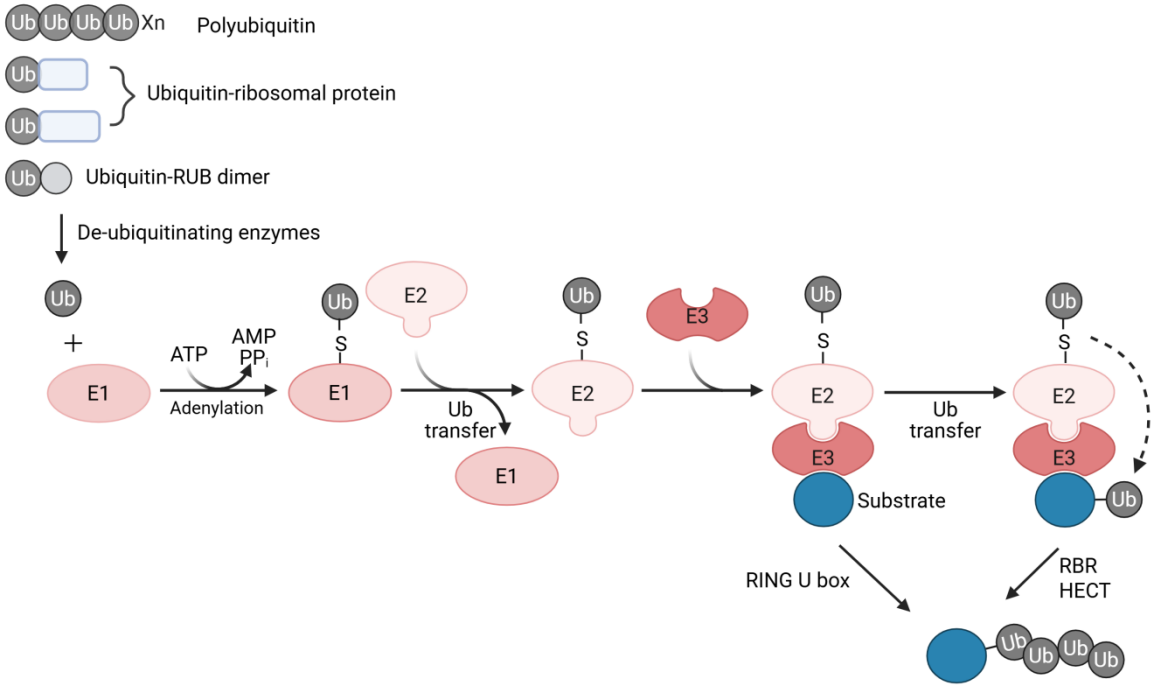

Figure 1. Basic process of ubiquitination and the enzymatic cascade of E1-E2-E3: In an ATP-dependent manner, E1 activates Ub and transfers it to the E2 conjugating enzyme. E3 ligases recognize specific substrate proteins and catalyze the covalent attachment of Ub to lysine residues, thereby forming either mono-Ub or polyubiquitin chains. Substrate specificity and the method of Ub chain elongation are determined by different E3 types RING, HECT, RBR. Proteins may be degraded via the 26S proteasome pathway or have non-proteolytic regulatory functions upon ubiquitination. These functions include signal transduction, subcellular localization and protein-protein interactions. DUBs can reverse ubiquitination by hydrolysing Ubiquitin chains. In doing so they are important for maintaining cellular homeostasis and modulation of signaling networks.

enzymes. Different classes of E3 are responsible for determining not only substrate specificity, but also functional output. To make the modification more clear, we present a schematic diagram of the fundamental ubiquitination mechanism (**Figure 1**).

Types of ubiquitination and their biological significance

Ubiquitination displays diversity mainly because of how the Ub binds to target proteins and how Ub chains are assembled. The differences help to meticulously regulate the destiny of proteins and cellular functions. According to their modification patterns, ubiquitination can be classified into three main types.

Mono-ubiquitin is generally located at one lysine and associated with non-degradative function like endocytosis of membrane proteins, transcriptional regulation, and chromatin re-organization. In the cardiovascular system, site-specific mono-ubiquitination of Rab proteins regulates membrane trafficking [38], whereas mono-ubiquitination of MxIRT1 at K165/K196 mediates endocytosis and iron homeostasis [39]. In DNA damage repair, RAD18 recruits the SMC5/6 complex via mono-ubiquitination to promote homologous recombination [40], while RNF168 modifies histone H2A at K13/15 through mono- or di-monoubiquitination to regulate chromatin accessibility [41]. Notably, histone H2B K120 mono-ubiquitination (H2BK120ub1) plays a pivotal role in transcriptional regulation; TRIM35-mediated H2BK120ub1 enhances p53 activity and contributes to HF, a mechanism validated in dilated cardiomyopathy (DCM) [42].

Polyubiquitination involves the attachment of Ub chains to lysine residues on substrates. The resulting functional outcomes are controlled by the type of chain linkage used. K48-linked chains act as the main signal for degradation via the proteasome. For instance, TRIM31 enhances the K48-linked polyubiquitination of

MAP3K7, preventing TGF-β1 pathway activation and alleviating Ang II-induced ventricular remodeling [43]. K63-linked chains, on the other hand, mainly mediate signal transduction, DNA repair and inflammation. TRIM67 inhibits the K48-linked polyubiquitination of IκBα, resulting in the stabilization of IκBα and inhibition of NF-κB activity, thereby reducing inflammation and apoptosis in cerebral ischemia [44]. In addition, mixed or branched chains (such as K63 hybrid chains) promote UBQLN2 phase separation, which allows formation of proteasome condensates that simultaneously enhance substrate recruitment and inhibit degradation, manifesting the spatiotemporal specificity of substrate fate control [45].

DUBs play a key role in regulating the dynamic balance of ubiquitination. The UAF1 complex directs the deubiquitination of NLRP3 and p65, thereby regulating inflammation and the activity of pro-inflammatory factors [46], as well as the ZnF4 region of A20 participates in the regulation of Nrdp1 polyubiquitination in an anti-inflammatory manner [47]. Collectively, the different type and chain architectures of ubiquitination can all control the substrate's stability, location, and interaction network, having extensive regulatory effect on the signal transduction, metabolism, inflammatory responses and stresses adaptation in CVD. Gaining a deeper understanding of these mechanisms will help us in elucidating pathogenesis of diseases.

Relationship between ubiquitination and protein degradation: the contribution of the ubiquitin-proteasome system (UPS)

Ubiquitination is a key PTM that maintains cellular protein homeostasis. Its classical function is targeted degradation. The E1-E2-E3 enzyme system and the 26S proteasome together form the UPS. In this case, Ub chains usually joined through K48 are conjugated to lysine residues of substrate proteins as markers for degradation. Following substrate recognition by the 26S proteasome, the substrate is deubiquitinated and unfolded. Further substrates are hydrolyzed to short peptides and amino acids ensuring protein quality control and metabolic balance [48]. In the cardiovascular system, the UPS not only sustains protein turnover in cardiomyocytes but also plays critical roles in pathological processes such as ischemia-reperfusion injury (IRI), CH, and HF. Dysfunction of this system causes abnormal protein accumulation and subsequently endoplasmic reticulum stress, mitochondrial dysfunction and apoptosis.

Recent studies have revealed that UPS activity in the heart is regulated by multiple factors. They explain how the DUBs Ubp2 and NEDD4 family E3 ligase Rsp5 coordinately affect monoubiquitination of Rpn10. Moreover, they point out that decrease of this modification during stress suggests dynamic limitation of receptor availability [48]. The binding of Rpn11 to Ub induces conformational changes in Rpn10 and accelerates substrate translocation [49]. Also, ZFAND5 binds to 19S regulatory particle. In addition, this particular binding case makes the ATPase channel entrance broader to help substrate loading efficiency [50]. Interestingly, M1-linked ubiquitin hexamers (M1-Ub6) which are non-substrate conjugated hexamers interacts with hRpn11 to regulate the proteasome core particle conformation. This demonstrates that Ub binding itself can allosterically regulate proteasome structure [51].

Autophagy also works with UPS to keep proteostasis. When proteasomes are inhibited, NRF1 helps trigger the actions of genes like p62/SQSTM1 or GABARAPL1. This, in turn, helps spur protein degradation that relies on p62 (aggrephagy) and helps get rid of proteins that have been tagged with ubiquitin [52]. The loss of HGS leads to an imbalance of lysosomes as well as pathology that resembles restrictive cardiomyopathy. Doxycline helps reduce cardiac dysfunction and suppresses protein aggregation [53]. In various types of models of cardiac proteinopathy, the phosphorylation of Rpn6 at Ser14 (pS14-Rpn6) helps to facilitate PKA-dependent activation of 26S proteasomes. This suggests that proteotoxicity impairs this modification, and restoring it may represent a novel therapeutic strategy [54]. Collectively, this evidence shows that the UPS, through its structural regulation, substrate recognition, and crosstalk with autophagy, is crucial for protein degradation and CVD pathology, presenting important molecular targets for future therapies.

Taken together, the biochemical properties and regulatory complexity of the UPS represent the

molecular basis by which ubiquitination modifies cardiovascular pathology. The UPS is the main proteolytic system that makes use of E3 Ub ligases for the accurate recognition of degradation signals present on substrates which helps in clearing aberrant and regulatory proteins to maintain proteostasis. The fundamental mechanism directly underlies performing key processes including cardiomyocyte contractile function, endothelium inflammatory responses, and vascular smooth muscle remodeling. Thus, it creates a vital link of ubiquitination with diverse phenotypes of CVD [55].

Ubiquitination in cardiovascular cells

In cardiac muscle cells, ubiquitination controls the turnover of proteins. For example, the Xbp1s-STUB1 axis mediates FoxO1 transcription factor ubiquitination and degradation. This axis is instrumental in pressures overload-induced heart diastolic dysfunction, HFpEF. Ubiquitination is involved in other biological processes such as regulating mitochondrial dynamics, contractile protein quality control and cell death pathways. All these processes contribute to cardiac remodeling and the development of HF [56]. The interaction between energy metabolism and cell death regulation is an important aspect of HF. Based on studies, ATP-induced cell death (AICD) is a novel mode of regulated cell death that largely contributes to HF due to MI and IRI [57]. In endothelial cells, ubiquitination involves greatly in the regulation of the stability of key proteins that maintain the integrity of the endothelial barrier and also modulates Nitric oxide (NO) signalling, inhibits inflammatory activation, and influences the formation of early atherogenic lesions. Research shows that ginsenoside Rb1 recruits the E3 Ub ligase SYVN1 to drive Keap1 degradation via ubiquitination to activate the Nrf2 signaling pathway. The expression of inflammatory factors, such as IL-1β, ICAM-1, IL-6, VCAM-1, induced by ox-LDL/high glucose, is significantly inhibited, thus ultimately leading to a reduction in aortic atherosclerotic plaque formation in diabetic ApoE$^{-/-}$ mouse models, thereby mechanistically explaining the vital role of ubiquitination in regulating inflammatory activation and AS progression [58]. Ubiquitination regulates phenotypic switching, proliferation, migration, and ECM remodeling in VSMCs by modulating the stability of important signaling proteins, such as the G protein signaling negative regulator RGS2. The UPS tightly controls the protein levels of RGS2. RGS2 deficiency or down-regulation causes vasoconstriction and hypertension and further lead to pathological changes including vascular stiffening and plaque progression. Ubiquitination plays an important role in pathogenesis by regulating factors such as RGS2, whose dysregulation causes hypertension and vascular remodeling diseases [59].

Ubiquitination in cardiomyocytes and its relationship with cell death

The fate of cardiomyocytes, whether they live or die, determines how CVDs happen and develop. Ubiquitination is a reversible and dynamic PTM that regulates different types of cell death.

While Mdm2 attaches Ub to p53 and causes its degradation, whereas USP7 removes the Ub and stabilizes it. As a member of the CRL5 complex, RBX2 regulates mitophagy and cardiac homeostasis via the Parkin/PINK1 pathway [60]. Also, MARCH5, which promotes MIC60 degradation, induces mitochondrial dysfunction and apoptosis in diabetic cardiomyocytes, and TRAP1 protects against this by competitive binding to MIC60 [61].

Necrosis and programmed necrosis; the UPS is equally crucial. The ubiquitination status of RIPK1/RIPK3 dictates whether they are degraded or activate downstream MLKL signalling. WWP1 promotes the degradation of KLF15, thus activating MAPK inflammatory pathway while its inhibitor indole-3-carbinol (I3C) improves cardiac function after MI [62]. AM404 enhances RIPK1/3 which inhibits necroptosis during IRI [63]. Cops8/COP9 signalosome dysfunction directly causes necroptotic death, indicating its critical cardioprotective role [64]. Meanwhile, RIPK3 also regulates HF progression through the AMPK/Parkin-mitophagy-mPTP axis and is a drug target for post-MI cardiac insufficiency [65]. In autophagy-related cell death, the antagonism between Parkin and USP30 determines mitophagy efficiency, while PFKFB3 stabilizes OPA1 via NEDD4L-mediated K6-linked polyubiquitination, thereby maintaining mitochondrial homeostasis and preventing excessive autophagic death [66].

Ferroptosis has also been increasingly linked to the UPS. Significantly, increasing TRIM16 levels

can attenuate doxorubicin-induced cardiotoxicity by modulating the signaling of specific proteins [67]. In all, the UPS has two sides to its role. Under normal conditions, it regulates heart cell death by maintaining cellular health. But abnormal conditions would cause cell injury and death. As a result, the targeting of specific E3 ligases or DUBs (e.g., WWP1, MARCH5, TRIM16, RBX2) is a valuable therapeutic option in MI, diabetic cardiomyopathy and HF.

Importance of ubiquitination in endothelial cells (ECs) and vascular function

ECs are the key barriers that maintain blood vessel homeostasis; thus, their dysfunction is an early pathological sign of CVD. Accumulating evidence suggests the importance of ubiquitination on the regulation of endothelial function. On one hand, E3 ligases like Mdm2 affect NO output and adjust vascular tone through E3 ligase-mediated ubiquitination and degradation of endothelial nitric oxide synthase (eNOS). Conversely, the degradation of IκB caused by ubiquitination activates the nuclear factor-κB (NF-κB) signalling pathway, which keeps ECs in a pro-inflammatory condition, promotes the progression of AS, and weakens the integrity of the endothelial barrier [68, 69]. In addition, the UPS aids in the clearance of oxidatively damaged proteins and the maintenance of cellular homeostasis, which helps to protect the endothelium from oxidative stress. L-carnitine, for example, stabilizes the PHB2-PARL interaction, thereby increasing PINK1/Parkin-dependent mitophagy, which mitigates mitochondrial dysfunction and microvascular damage in diabetic cardiomyopathy [70]. Exosome-mediated THBS1-OTUD5-GPX4 signalling axis orchestrates endothelial ferroptosis in cerebral ischaemia-reperfusion injury (CIRI), establishing that it could be modulated to ameliorate secondary injury [71]. Moreover, inhibition of DUBs like USP9X, CYLD, and USP20 is crucial to inflammatory attack as well as endothelial protection, and their dysfunction creates a pro-inflammatory situation, disrupting vascular homeostasis, which further accelerates the inflammatory injury [69].

Angiogenesis and vascular repair both rely on Ubiquitination. Ubiquitination facilitates the activity of the vascular endothelial growth factor (VEGF)/VEGFR2-PI3K/Akt pathway, which regulates new vessel formation and maturation. Research indicates that circUCK2 interacts with FUS which positively influences the expression of HECTD1. This then leads to a reduction in endothelial-to-mesenchymal transition (EndMT) and improvement in damage caused to blood-brain barrier (BBB) following an ischemic stroke [72]. MEF2A transcriptionally activates E3 ligase WWP2 on the other hand promotes the degradation of SH2B3. This in turn boosts microglial activation states along with a reduction in injury caused to the brain microvascular endothelial cells (BMECs) [73]. In addition, TIMP1 protects against early brain injury after subarachnoid hemorrhage by inhibiting the interaction between β1-integrin and TRIM21, restoring astrocyte-endothelial communication [74].

The impact of ubiquitination in VSMCs on AS

VSMCs are crucial to the initiation and development of AS. They directly determine plaque formation and stability with their phenotypic switching, proliferation, migration, and apoptosis. Recent research reveals that the actions of ubiquitination on critical signalling cascade and transcription factors in VSMC control their degradation or stabilization which has profound effects on AS pathogenesis. Under normal conditions, VSMCs maintain their contractile characteristics to help maintain vascular tone but under pathological conditions, they switch to a synthetic phenotype which exhibit an enhanced capacity to proliferate and migrate. This switch is tightly associated with the UPS-mediated degradation of transcription factors like KLF4 and SRF.

Numerous E3 ligases and deubiquitination regulators have been identified as key modulators of VSMC phenotype and pathological behaviour at the molecular level. TRIM35 promotes SUMOylation and ubiquitination of vimentin to enhance its degradation, which maintains the contractile phenotype and inhibits PDGF-BB-induced VSMC proliferation and migration to slow plaque progression [75]. Members of the TRIM family also perform important functions. TRIM65 activates the PI3K/Akt/mTOR pathway to accelerate phenotypic switching, which promotes plaque development [76]. In contrast, TRIM7 is upregulated in diseased tissues, and its knockdown blocks c-Jun/AP-1 signaling,

which suppresses aberrant VSMC proliferation and migration to slow plaque development [77]. In addition, Tudor-SN deficiency decreases NEDD4-1-dependent polyubiquitination of PTEN and reduces pathological vascular remodeling, indicating potential value for the prevention and treatment of vascular diseases [78].

Ubiquitination displays both beneficial and detrimental effects in inflammation and calcification. Circ-UBR4 governs the apoptosis and inflammation of VSMCs driven by ox-LDL, along with plaque evolution, via miR-515-5p/IGF2 axis [79]. Nesfatin-1 controls the E3 ligase SYTL4 to enhance BMP-2/SMAD1/5/9 signalling. RUNX2 and MSX2 are activated, which aggravates the vascular calcification [80]. Kynurenine, a metabolic product of IDO1, promotes RUNX2 ubiquitination/degradation through the proteasome, restricting the osteogenic reprogramming of VSMCs. Kynurenine depletion accelerates vascular calcification [81]. Moreover, Canagliflozin (CANA) alleviates vascular calcification by inhibition of NLRP3 inflammasome activation, thus it may have clinical significance [82]. Most importantly, the DUB OTUB1 limits the K48-linked Ub modification of PDGFRβ at K707. This prevents the proteasomal degradation of PDGFRβ and promotes VSMC phenotypic switching. Inhibition of OTUB1, however, delays pathological VSMC transformation and attenuates AS progression, underscoring its translational potential as a therapeutic target [83].

In all, ubiquitination acts as a central regulatory mechanism in CVD influencing inflammation, energy metabolism, apoptosis and hypertrophy signaling. To make this regulatory network more intuitive, we summarize the molecular interactions and signaling pathways in a schematic diagram (**Figure 2**).

Ubiquitination and CVDs

CAD

CAD is the most common cardiovascular disorder in the world and the top cause of death. AS causes vascular stenosis and hemodynamic disturbance and is its main pathology. In the advancement of CAD, numerous studies have indicated that the ubiquitination process is also involved. The UPS regulates EC and VSMC functions and is also involved in inflammatory responses, lipid metabolism, plaque stability, vascular calcification, and the like. It is a critical link connecting molecular events to clinical phenotypes.

Endothelial dysfunction is regarded as the initial trigger of CAD at an early stage of disease. The process of Mdm2-mediated ubiquitination and degradation of eNOS reduces the production of NO which impairs vascular relaxation. The NF-κB pathway gets activated with IκB's ubiquitination-driven degradation, helping promote inflammatory responses and monocyte adhesion thus accelerating plaque formation. In addition, coup jarenlang blood flow pricks endothelial MAPK6 UPS-dependent degradation (via TRIM21 binding), whereas MAPK6 plays an anti - inflammatory role with EGR1/CXCL12 axis [84, 85]. circ_USP36 can alleviate oxLDL induced endothelial injury via targeting miR-197-3p/ROBO1 axis [86]; overexpression of USP14 inhibits NF-κB activation and plaque burden [87]; HCP1 and Grp94 exhibit plaque stabilization [88].

As the disease progresses, atherogenesis is driven by VSMC phenotypic switching and the activation of inflammation. The TRIM family E3 ligases cause the phenotypic conversion of VSMCs from contractile to synthetic via either PI3K/AKT/mTOR or AP-1 pathways, enhancing VSMC proliferation, migration, and plaque growth. On the other hand, DUBs like USP20 and CYLD decrease the TRAF6/NF-κB pathway and lessen inflammation. Peli1 deficiency does not change the plaque burden, but it does enhance VSMC foam cell formation, increase necrotic core expansion, and diminish collagen deposition. All of these factors boost Th1/Th17/Tfh cell expansion and cytokine storms, which ultimately, lowers plaque stability [89]. Further, circZBTB46 binds with hnRNPA2B1 to activate the PTEN/AKT/mTOR pathway, which thus worsens CAD progression [90].

Stability is a direct determinant of clinical event risk in advanced plaques. Ubiquitination is required for the for activation of the NLRP3 inflammasome in macrophages which leads to the release of IL-1β and enhances local inflammation. RNF128 promotes K63-linked ubiquitination to facilitate SRB1 recycling, enhancing oxLDL-induced foam cell formation and inflammatory responses [91]; circARCN1 activates

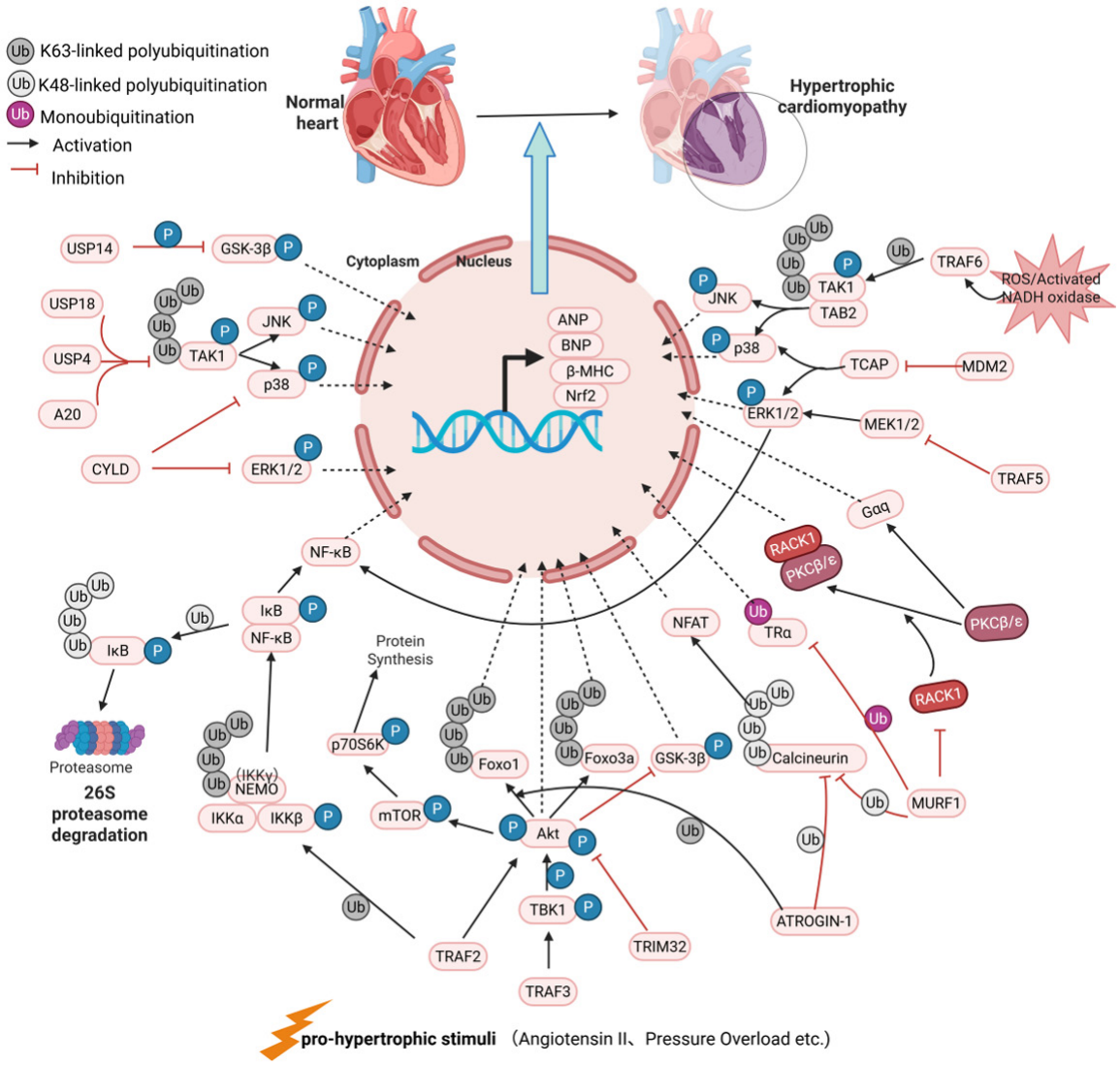

Figure 2. Mechanisms of ubiquitination in cardiomyocyte signaling networks and cardiovascular pathological remodeling: Ubiquitination plays essential roles in different signaling pathways during the transition of cardiomyocytes from normal to hypertrophic cardiomyopathy. Polyubiquitin chains linked to K48 mostly induce substrate proteins' degradation, whereas K63-linked chains, as well as mono-ubiquitination, have a non-degradative regulatory effect on signaling. Distinct E3 ligases (e.g., TRAFs, TRIMs, MuRFs) and DUBs (e.g., USP14, USP18) modulate pathways including NF-κB, Akt/mTOR, MAPK, and Calcineurin/NFAT, thereby influencing cardiomyocyte survival, proliferation, hypertrophy, and fibrosis. The scheme depicts activations by black arrows and inhibitions by red lines; this emphasizes the importance of ubiquitination in the regulation of cardiovascular pathology remodeling.

NF-κB signaling via HuR-mediated stabilization of USP31 mRNA, aggravating plaque inflammation [92]. Moreover, miR-30a-5p targets NEDD4L to inhibit PPAR-γ ubiquitination, thereby improving lipid metabolism and inflammatory status, reducing the M1/M2 macrophage ratio, and limiting lipid uptake [93]. With respect to stabilizing vulnerable plaques, DV-DMS-SDT suppresses matrix degradation by regulating the caspase-3-PEDF/HIF-1α-MMP-2/MMP-9 signaling axis, thereby enhancing plaque stability [84]. To provide a clearer understanding of the mechanisms of ubiquitination in CAD and the associated molecular players, recent findings are systematically summarized (see **Table 1**).

HF

HF appears at the end stage of a number of CVDs. The pathological processes in HF include

Table 1. Summary of molecular mechanisms of ubiquitination modifications in CAD

Ubiquitination Pathways/ Mechanisms	Types of CAD	Key Proteins Involved	Functions of Ubiquitination	Relevant Signaling Pathways	Clinical and Experimental Data	References
TRIM25-mediated ubiquitination of XRCC1	Atherosclerotic CAD	TRIM25, XRCC1, PARP1, RIPK3	Inhibition of XRCC1 releases PARP1 and promotes macrophage necroptosis	Macrophage Pyroptosis and Necroptosis Signaling Pathways	Patient Serum Analysis, Mouse Models, Macrophage Experiments, and RNA-seq Analysis	[123]
CUL4B/AhR forms an E3 ligase complex to mediate RUNX2 ubiquitination	Atherosclerotic Calcification/Plaque Instability	IDO1, Kynurenine, AhR, CUL4B, RUNX2	Promotes proteasomal degradation of RUNX2 and inhibits osteogenic reprogramming of VSMCs	Kynurenine-AhR non-genomic pathway regulates RUNX2 ubiquitination	Gene knockout mouse model, kynurenine injection, and patient serum activity assay	[81]
USP7 removes K48-linked ubiquitin chains from SMAD2/3 to prevent degradation	Kawasaki Disease (KD)-associated Coronary Artery Aneurysms/Vasculopathy	USP7, SMAD2, SMAD3, TGF-β2	USP7 deubiquitinates and stabilizes SMAD2/3, enhancing their signaling	TGF-β2/SMAD2/SMAD3 signaling pathway	Serum from KD patients/mice, cell models, gene knockout, and inhibitor injection experiments	[124]
cIAP2 mediates IGF2BP2 ubiquitination and promotes proteasomal degradation	MI-related CAD	cIAP2, IGF2BP2, BAX	Promotes IGF2BP2 degradation and inhibits apoptosis	IGF2BP2/BAX-mediated apoptotic pathway	OGD-treated cardiomyocytes, MI mouse model, and inhibitor experiments	[125]
USP10 mediates the deubiquitination of Smad4	AMI, myocardial IRI	HSP47, USP10, Smad4, TGF-β1	USP10 stabilizes Smad4 through deubiquitination, promoting the fibrotic pathway	TGF-β1/Smad4 signaling pathway	Mouse myocardial IRI model; CF experiments; gene manipulation/ inhibitor experiments	[126]
Ubiquitin-proteasome pathway promotes SLC3A2 degradation	CAD and AS	circBTBD7-420aa, SLC3A2, osteopontin (targeted)	Promotes SLC3A2 degradation and inhibits abnormal cell proliferation and migration	Ubiquitin-proteasome degradation pathway	Human coronary artery smooth muscle cell experiments; engineered exosome construction	[127]
Exogenous Ub therapy ameliorates myocardial injury	Myocardial I/R injury	GSK3β, ERK1/2, AKT, MYH-7B, MMP-2/9	Attenuates fibrosis/apoptosis/ hypertrophy and reduces inflammatory factors	Activation of GSK3β, ERK1/2, and AKT signaling pathways	Mouse I/R model; 28-day UB treatment; cardiac function/biochemical assays	[128]
USP11 stabilizes TRAF3 through deubiquitination	Myocardial I/R injury	USP11, TRAF3, IKKβ/ NF-κB	Deubiquitination stabilizes TRAF3 and exacerbates injury	IKKβ/NF-κB signaling pathway	Rat I/R model and H9C2 cell experiments	[129]
USP25 mediates K63-linked deubiquitination of NLRP3	Myocardial I/R injury	USP25, NLRP3, ASC	USP25 deubiquitinates to inhibit NLRP3 activation and pyroptosis	NLRP3 inflammasome-pyroptosis pathway	USP25 knockout/overexpression mouse models and cardiomyocyte experiments	[130]
ILRUN contains a ubiquitin-associated domain and regulates lipid metabolism	AS (lesion/necrosis)	ILRUN, MerTK (macrophage receptor)	Domain involved in ubiquitination, promoting AS progression	Lipid metabolism (plasma cholesterol), macrophage efferocytosis	LdlrKO/ApoeKO DKO mice; AS phenotype	[131]
COP1 mediates p53 ubiquitination and degradation	Myocardial I/R injury	Fendrr, p53, COP1	Promotes p53 degradation and inhibits apoptosis	Fendrr/COP1/p53 apoptosis regulatory pathway	Rat I/R model and cardiomyocyte H/R experiments	[132]
SUMO2 mediates the SUMOylation of γ-actin	MI	SUMO2, γ-actin	Enhancing DNA repair to mitigate myocardial injury	SUMO2/γ-actin nuclear translocation pathway	MI mouse model and H9c2 cell H/R assay	[133]
IDOL-mediated LDLR ubiquitination and lysosomal degradation	CAD (lipid-related)	IDOL, LDLR	Lysosomal degradation of LDLR; plasma cholesterol reduction	IDOL-LDLR degradation pathway	Study on the protein structure and in vitro ubiquitination activity of IDOL	[134]
PIASy mediates SUMOylation of Cx43	Myocardial I/R injury	PIASy; Cx43; PKP2	SUMOylation suppresses Cx43 function and induces arrhythmia	PIASy/Cx43 SUMOylation-PKP2 pathway	Rat I/R model and rAAV9-mediated PIASy knockdown	[135]
USP5 mediates deubiquitination and stabilization of NFATC1	Coronary arteritis in KD	USP5, NFATC1, TLR4, NF-κB	Deubiquitination stabilizes NFATC1 and promotes inflammation	USP5/NFATC1/TLR4/NF-κB axis	Serum from KD patients and HCAEC cell model	[136]
RNF5 regulates ubiquitination of ASK1	MI	RNF5, ASK1	RNF5 may inhibit ASK1 activation and attenuate injury	RNF5/ASK1 apoptotic signaling pathway	RNF5-KO mouse MI model and NRCM OGD experiment	[117]
TRIM21 mediates ubiquitination and degradation of MAPK6	AtS	TRIM21; MAPK6; EGR1; CXCL12	Promotion of MAPK6 degradation leads to endothelial inflammation	MAPK6/EGR1/CXCL12 anti-inflammatory pathway	$ApoE^{-/-}$ mouse model and EC experiments	[85]

USP53 mediates deubiquitination and stabilization of SR-A	AS	DKK1; USP53; SR-A; CREB	Deubiquitination prevents SR-A degradation and promotes lipid uptake	DKK1/CREB/USP53/SR-A foam cell formation pathway	EC-specific conditional knockout/overexpression mice and co-culture model	[137]
Ubiquitination Regulation of USP10/p53	MI	PLIN5, USP10, p53, TfR	Promotion of p53 degradation inhibits TfR-mediated ferroptosis	PLIN5/USP10/p53/TfR ferroptosis pathway	Rat MI model and H9c2 cell experiments	[138]
USP9X mediates K63 deubiquitination of SR-A1	AS	USP9X, SR-A1	Deubiquitination inhibits SR-A1 internalization and suppresses lipid uptake	USP9X/SR-A1 lipid uptake pathway	$ApoE^{-/-}$ mouse model and macrophage experiments	[139]
MDM2 mediates polyubiquitination and degradation of RXRβ	AS	MDM2, RXRβ	Promotion of RXRβ degradation exacerbates endothelial injury	MDM2/RXRβ/TLR9/NF-κB/NLRP3 pathway	LDLr-/- mouse model and EC experiments	[140]
USP14 deficiency inhibits cGAS K48 polyubiquitination and degradation	AS	ALDH2, USP14, cGAS, STING, 4-HNE	Inadequate cGAS ubiquitination and degradation promote inflammation	ALDH2/USP14/cGAS/STING inflammatory pathway	ALDH2-KO mouse model and macrophage experiments	[141]
SYVN1 mediates Keap1 ubiquitination and degradation	Diabetic AS	Rb1, Keap1, SYVN1, Nrf2, p47phox	Promotion of Keap1 degradation activates Nrf2-mediated antioxidation	Rb1/Keap1/Nrf2/PGC-1α & p47phox/NOX2 pathway	$ApoE^{-/-}$ mouse model and EC experiments	[58]
Thrombin induces ABCA1 phosphorylation and CSN3 dissociation, leading to ubiquitin-mediated degradation	AS, particularly the formation of lipid-rich plaques	ABCA1, CSN3, Par1, Gα12, Pyk2, Gab1, PKCθ	This leads to ABCA1 degradation, inhibiting cholesterol efflux and promoting foam cell formation	The Par1-Gα 12-Pyk2-Gab1-PKCθ signaling cascade	Macrophage and smooth muscle cell experiments; $ApoE^{-/-}$ mouse model; human coronary artery samples observation	[142]
NLRC5 reduces STAT3 ubiquitination and enhances its stability	Acute coronary syndrome (AS-related)	NLRC5, STAT3, and M1/M2 macrophage-associated proteins	Reducing STAT3 ubiquitination to maintain its expression and promote the development of AS	STAT3 signaling pathway (NLRC5 regulates macrophages through STAT3)	Serum analysis of 30 AS patients; ApoE mouse model; in vitro macrophage experiments	[143]
MARCH2 mediates the K48 polyubiquitination of PGAM5, promoting its degradation	Myocardial Ischemia-Reperfusion (I/R) Injury	MARCH2, PGAM5, MAVS, NLRP3 inflammasome	Inhibition of PGAM5-MAVS co-condensation to block NLRP3 activation and pyroptosis	The PGAM5/MAVS/NLRP3 signaling axis regulates cardiomyocyte pyroptosis	Ischemic human/mouse heart samples; AAV-MARCH2 treatment mouse model	[144]
NEDD4L mediates the ubiquitin-mediated degradation of ACSL4, inhibiting ferroptosis	MIRI	YAP, NEDD4L, ACSL4 (ferroptosis-related proteins)	Promote the degradation of ACSL4, inhibiting ferroptosis in cardiomyocytes	YAP promotes the transcription of NEDD4L → ACSL4 ubiquitin-mediated degradation pathway	SD rat/H9C2 cell MIRI model; assessment of cardiac function/biochemical/ferroptosis markers	[145]
STUB1 mediates the ubiquitin-mediated degradation of LATS2	Myocardial IRI	KAT5, STUB1, LATS2, YAP, β-catenin	Promotion of LATS2 degradation activates the YAP/β-catenin pathway to inhibit necroptosis	STUB1/LATS2/YAP/β-catenin signaling axis	H9C2 cell/rat MIRI model; myocardial cell necroptosis detection	[146]
SMURF2 mediates ubiquitination and degradation of FOXA2	Myocardial IRI	UPF1, SMURF2, FOXA2, PAR4	Promotion of FOXA2 degradation enhances PAR4 expression and promotes apoptosis	UPF1-SMURF2-FOXA2-PAR4 signaling axis	H9C2 cell H/R model; rat myocardial I/R model; cell/molecular assays	[147]
TRIM38 mediates ubiquitination and degradation of TAB2/TAB3	MI and angiotensin II-induced cardiac fibrosis	TRIM38, TAB2, TAB3, TAK1, MAPK	Degradation of TAB2/TAB3 inhibits TAK1/MAPK signaling and alleviates fibrosis	TAK1/MAPK signaling pathway (TRIM38 negatively regulates)	Mouse MI/angiotensin II model; in vitro stimulation experiments with CFs	[148]

cardiomyocyte apoptosis, impaired energy metabolism; inflammatory responses, and fibrotic remodeling. Ubiquitination plays an essential role in the maintenance of protein homeostasis and is involved in the initiation and progress of HF. For example, the E3 ligases MuRF1 and MuRF2 mediate the degradation of myosin heavy chain and other sarcomeric proteins that lead to compromised contractile function. USP19, a deubiquitinase, could delay the degradation of abnormal proteins, demonstrating cardioprotective properties [94]. In cardiomyocytes, Xbp1 can transcriptionally activate STUB1 to mediate FoxO1 degradation to control cell survival [56]. Mettl13 prevents c-Cbl methylation to block SERCA2a degradation, leading to improved calcium homeostasis and contractile performance with the actual potential for ischemic HF [95].

Another major driver of HF progression is inflammatory response. When IκB is degraded by UPS, NF-κB is released in the nucleus that leads to an elicited expression of pro-inflammatory cytokines. E3 ligases known as TRAF family promote inflammatory signaling through a process called K63-linked polyubiquitination. However, not all is positive. There are some deubiquitinases like CYLD and A20 that control the activation of NF-κB. USP38 was found to stabilize p-TBK1 through the TBK1/AKT/CaMKII pathway. It was shown to promote CH, fibrosis, and enhanced vulnerability to ventricular arrhythmias [96-98]. Further, PGAM5 was seen to promote the Keap1 ubiquitination and stabilization of Nrf2. In doing so, it was able to alleviate ROS-induced oxidative stress and ferroptosis and confer cardioprotection in HF [99]. Interestingly, SGLT2 was found to promote the degradation of cyclic GMP-AMP synthase (cGAS). In turn, this enhanced the central inflammatory responses driving sympathetic excitation and cardiac remodeling. Thus, it suggests a role in neuro-cardiac regulation [100].

Fibrosis and remodeling are controlled by other ubiquitination mechanisms. Smurf2 has been implicated in the degradation of Smad7, which in turn results in the release of inhibition of the TGF-β/Smad pathway, and promotes fibroblast activation and collagen deposition. USP10 prevents the degradation of Smad4 and enhances the TGF-β signaling cascade, subsequently contributing to ventricular remodeling [101]. NGR1 disrupts the binding of β-arrestin2 to MDM2 which prevents the degradation of β2AR and ameliorates chronic HF [102]. Xinbao Pill improves cardiac function by inhibiting USP18 and the MDM2/β-arrestin2/Nedd4 pathway [103]. Similarly, a novel Shengmai powder downregulates MAFbx and MuRF1, suppressing UPS overactivation and the JNK pathway, thereby exerting anti-apoptotic effects [94]. In addition, Cereblon (CRBN) selectively degrades Cav1.2α, aggravating cardiac dysfunction, while CRBN inhibition has been proposed as a potential therapeutic strategy for HFrEF [104]. Collectively, the initiation and progression of HF are intimately associated with the UPS, involving multiple signaling pathways and post-translational modifications. To systematically summarize these mechanisms and their experimental evidence, recent studies are reviewed in **Table 2**.

Hypertension

Hypertension is one of the most common CVDs and is an important risk factor for AS, HF, and stroke. Vascular tone, inflammatory response, endothelial dysfunction and vascular remodelling are closely co-developed. Recent studies have shown that the UPS could play an important role in the initiation and development of hypertension. The UPS also plays a key role in the regulation of ECs and VSMCs, as well as in determining vascular tone and structural integrity through the modulation of inflammatory signalling, ion channel homeostasis, and fibrotic signalling.

To give an example, the E3 ligase Mdm2 mediates eNOS degradation in causing NO reduction and blood pressure elevation. Likewise, the breakdown of IκB leads to continued NF-κB activation, worsening inflammation and endothelial damage. Drugs also affect UPS modulation. For example, Atorvastatin activates the E3 ligase WWP2, which increases ATP5A degradation and maintains the Bcl-2/Bax balance, thus attenuating endothelial damage [105]. On the other hand, YOD1 protects against β-catenin degradation, thus alleviating Ang II (Ang II)-induced endothelial injury [106].

The UPS is in charge of the stability of transcription factors such as KLF4 and SRF during vascular remodeling, which are critical to the phenotypic switch of VSMCs from contractile to

Table 2. Molecular mechanisms and research progress of ubiquitination in HF

Ubiquitination Pathway/ Mechanism	Type of HF	Key Proteins Involved	Role of Ubiquitination	Signaling Pathways	Clinical/Experimental Evidence	References
Smurf1-mediated ubiquitination and degradation of TRIB2	DOX-induced and hypoxia/reoxygenation-induced experimental HF	The key proteins identified were Smurf1 and TRIB2	Promotes TRIB2 degradation and activates NF-κB pathway	The NF-κB signaling pathway is implicated in its regulation	Based on experimental models of HF rats and H9C2 cells	[149]
PINK1/Parkin-mediated mitophagy	Chronic heart failure (CHF) induced by MI	PINK1 and Parkin (key proteins regulating mitophagy)	Parkin mediates ubiquitination to facilitate the clearance of damaged mitochondria	The PINK1/Parkin-mediated mitophagy pathway	Mouse model of MI/Hypoxia-induced HL-1 cellular model, treated with NXK	[150]
Inhibition of the overactivated UPS	HF (rat model)	MAFbx, Murf-1, JNK, bcl-2, bax, caspase-3	Overactivation of UPS promotes apoptosis in cardiomyocytes/skeletal muscle cells	UPS, JNK signaling pathway	Studies in rat HF models involving traditional Chinese medicine intervention and exercise tolerance tests	[94]
FBXL8 mediates the ubiquitination and degradation of Snail1 via its C3 domain	HF associated with post-MI ventricular fibrosis	FBXL8, Snail1, RhoA	Degradation of Snail1 inhibits proliferation/differentiation of CFs and attenuates fibrosis	The FBXL8-Snail1-RhoA regulatory axis (inhibits myofibroblast differentiation)	AAV9-FBXL8 treatment in a mouse MI model; TGFβ-induced experiment in CFs	[151]
USP7 stabilizes SMAD3 through K63-linked deubiquitination	Heart failure with preserved ejection fraction (HFpEF)	USP7 and SMAD3 (dependent on the UBL domain and Cys223 site)	USP7-mediated deubiquitination prevents SMAD3 degradation, thereby promoting EndMT and fibrosis	The USP7-SMAD3 axis regulates the EndMT pathway	HFpEF mouse model; Endothelium-specific USP7 knockout; validated by LC-MS/MS and Co-IP	[152]
PINK1/Parkin-dependent ubiquitination promotes mitophagy	HF induced by MI	SIRT3, FOXO3a, Mfn2, OPA1, Drp1, PINK1, Parkin	Promotes mitophagy and improves mitochondrial quality	The SIRT3/FOXO3a signaling pathway and the PINK1/Parkin-mediated mitophagy pathway	Omentin-1 levels are reduced in HF patients; cardiac function is improved in the model	[153]
ASPP1-OTUB1 mediates the ubiquitination and degradation of p53	HF induced by MI	ASPP1, OTUB1, p53	Promotes p53 degradation, attenuating myofibroblast activation and fibrosis	The ASPP1-OTUB1-p53 signaling axis	ASPP1 knockout improves cardiac function and attenuates fibrosis in mice	[154]
Xbp1s activates STUB1 to mediate FoxO1 ubiquitination and degradation	Heart failure with preserved ejection fraction (HFpEF)	FoxO1, Xbp1s, and STUB1	Promotes FoxO1 degradation, reduces myocardial lipid accumulation, and ameliorates HFpEF	The Xbp1s-STUB1-FoxO1 signaling axis	Depletion of FoxO1 or overexpression of Xbp1s ameliorates the phenotype in HFpEF mice	[56]
WWP1 mediates K27-linked polyubiquitination of DVL2 and stabilizes it	Pressure overload-induced cardiac remodeling and HF	WWP1, DVL2, CaMKII, HDAC4, MEF2C	Stabilizes DVL2, exacerbating CH and HF	The DVL2/CaMKII/HDAC4/MEF2C signaling pathway	WWP1 is elevated in HF patients and TAC mice; its knockout or targeted inhibition improves cardiac function	[120]
TRIM16 mediates the ubiquitination and degradation of Src	HF associated with pathological CH	TRIM16, Src, Prdx1, Nrf2	Degrades Src to inhibit Prdx1 phosphorylation, thereby blocking CH	The TRIM16-Src-Prdx1-Nrf2 signaling axis	TRIM16 expression correlates in human/murine HF samples; genetic manipulation validates its anti-hypertrophic role	[155]
Silencing NAP1L1 promotes YAP1 ubiquitination and degradation	HF associated with ischemic cardiomyopathy	NAP1L1 and YAP1 proteins	Promotes YAP1 degradation and inhibits its expression	The YAP1 stability regulatory pathway	NAP1L1 is upregulated in patient hearts; its knockout improves cardiac function and reduces fibrosis in mice	[156]
UCHL1 acts as a deubiquitinase to promote autophagic flux	HF associated with DCM	UCHL1 protein	Maintains protein homeostasis and prevents UP accumulation	The autophagy signaling pathway	Cardiac-specific knockout (CKO) mice exhibit worsened cardiac function and reduced autophagy after MI	[157]
WWP2 promotes the ubiquitin-dependent degradation of FACL4	HF associated with sepsis	WWP2, FACL4	Promotes FACL4 degradation and inhibits ferroptosis	The ferroptosis signaling pathway	WWP2 overexpression confers cardiac protection, while its knockout exacerbates injury in mouse models	[158]

USP20 removes K63-linked Ub chains from STAT3	HF associated with CH	USP20, STAT3, CARM1	Deubiquitinates STAT3 and attenuates CH	The USP20/STAT3/CARM1 signaling axis	USP20 deficiency exacerbates hypertrophy, whereas its overexpression attenuates it	[159]
OTUD7B removes K48-linked Ub chains from HNF4α	HF associated with CH	OTUD7B, HNF4α	Stabilizes HNF4α protein and prevents its degradation	The fatty acid metabolism signaling pathway	OTUD7B deficiency exacerbates hypertrophy and cardiac dysfunction, whereas its overexpression attenuates these effects	[160]
HectD3 functions as an E3 Ub ligase regulating SUMO2 and Stat1	HF associated with CH	HectD3, SUMO2, Stat1	Attenuates cardiomyocyte hypertrophy and pro-inflammatory responses	The calcineurin-NFAT and inflammatory signaling pathways	HectD3 overexpression in mice attenuates hypertrophy and inflammation	[161]
USP10 functions as a deubiquitinase for Sirt6 and stabilizes it	HF associated with CH	USP10, Sirt6, Akt	Deubiquitinates and stabilizes Sirt6, thereby inhibiting cardiomyocyte hypertrophy	The Sirt6/Akt signaling pathway	USP10 knockout exacerbates cardiac dysfunction and hypertrophy in mice, whereas its overexpression ameliorates these effects	[162]
USP13 deubiquitinates STAT1 and reduces its degradation	HF associated with CH	USP13, STAT1	Deubiquitinates and stabilizes STAT1, promoting Nppb transcription and mitochondrial function	The USP13-STAT1 signaling axis	USP13 knockout exacerbates hypertrophy and dysfunction, while its overexpression produces therapeutic effects	[163]
HUWE1 mediates c-Myc ubiquitination, which is suppressed by EZH2	HF	EZH2, HUWE1, and c-Myc	Reduces c-Myc degradation and promotes CH	The EZH2/HUWE1/c-Myc signaling axis	EZH2 knockdown improves cardiac function and cardiomyocyte hypertrophy, which is partially reversed by c-Myc overexpression	[164]
USP10 mediates the deubiquitination of Smad4	HF associated with DCM	EDIL3, USP10, Smad4	Deubiquitinates and stabilizes Smad4, thereby promoting EndMT	The USP10/Smad4 signaling axis	EDIL3 deficiency alleviates cardiac dysfunction and remodeling in DCM mice; USP10 inhibition attenuates EndMT in vitro	[165]
TRIM26 functions as an E3 ubiquitin ligase to mediate protein ubiquitination	HF induced by pathological CH	TRIM26, TAK1, JNK/p38	Activates the TAK1-JNK/p38 pathway, promoting CH, inflammation, and fibrosis	The TRIM26-TAK1-JNK/p38 signaling axis	TAC mouse models and cellular experiments demonstrate that TRIM26 promotes pathological CH	[166]
The Parkin-mediated mitophagy-associated ubiquitination mechanism	Experimental HF	PINK1, Parkin, Bcl-2, Caspase-3, LC3	Regulates mitophagy, inhibits cardiomyocyte apoptosis, and promotes HF recovery	The PINK1-Parkin-mediated mitophagy pathway	ALDH2 activation improves cardiac function in HF rats by enhancing the PINK1-Parkin pathway	[167]
The USP47-mediated deubiquitination mechanism	HF associated with CH	USP47, PRMT5, O-GlcNAcase	Deubiquitinates and stabilizes PRMT5, inhibits O-GlcNAcylation, and attenuates CH	The USP47-PRMT5-O-GlcNAcase regulatory axis	Cellular and animal models demonstrate that USP47 overexpression attenuates angiotensin II-induced CH	[168]
The WWP1-mediated protein ubiquitination mechanism	Heart failure with preserved ejection fraction (HFpEF)	WWP1	Regulates protein turnover/stability and promotes extracellular matrix (ECM) accumulation	The WWP1 signaling pathway	Mouse models demonstrate that WWP1 overexpression induces left ventricular hypertrophy and diastolic dysfunction	[169]
The WWP2-mediated PARP1 ubiquitination and degradation mechanism	HF associated with CH	WWP2, PARP1	Promotes PARP1 degradation and attenuates cardiac remodeling injury	The WWP2-PARP1 signaling axis	Genetic knockout in mice and cellular models demonstrate that WWP2 regulates cardiac remodeling	[170]
The PINK1/Parkin pathway mediates the ubiquitination mechanism underlying mitophagy	HF associated with myocardial ischemia-reperfusion injury (MIRI)	PINK1, Parkin	Promotes the clearance of damaged mitochondria and attenuates myocardial injury	The PINK1/Parkin-mediated mitophagy pathway	Animal/cellular models and cardiac surgery patients confirm that GAS activates this pathway	[171]

CAND1 promotes the ubiquitination and degradation of calcineurin through mediating Cul1 complex assembly	HF induced by pathological CH	CAND1, calcineurin, and the Cul1/Atrogin-1 complex	Induces calcineurin ubiquitination and degradation, thereby suppressing CH and HF	The CAND1-Cul1/Atrogin-1-calcineurin degradation pathway	HF patients and TAC mouse models demonstrate that CAND1 regulates calcineurin degradation	[172]
RNF13 ubiquitinates p62 to activate the NRF2/HO-1 signaling pathway	HF resulting from CH	RNF13, p62, NRF2, HO-1	Activates the p62-NRF2 axis to prevent CH	The p62-NRF2 signaling axis regulates HO-1 expression	TAC mouse model, PE-induced cardiomyocyte experiments, genetic manipulation, and RNA sequencing	[173]
OTUD1 promotes STAT3 activation by removing K63-linked ubiquitin chains	HF associated with hypertension induced by angiotensin II or transverse aortic constriction (TAC)	OTUD1, STAT3	OTUD1 deubiquitinates STAT3 to enhance its activity, thereby inducing cardiac remodeling	The OTUD1-STAT3 signaling axis regulates inflammation and hypertrophy	Ang II infusion, TAC mouse model, OTUD1 genetic manipulation, and Co-IP analysis	[174]
USP28 stabilizes TRIM21 through deubiquitination, thereby suppressing the Nrf2-mediated antioxidant response	Hypertrophic heart failure induced by angiotensin II or transverse aortic constriction (TAC)	USP28, TRIM21, Nrf2	USP28 mediates the deubiquitination of TRIM21, promoting oxidative stress and exacerbating HF	The USP28-TRIM21 axis negatively regulates the Nrf2 antioxidant pathway	USP28 CKO mouse model, TAC/Ang II intervention, Co-IP/MS analysis, and pharmacological inhibition assays	[175]

synthetic, which ultimately leads to vascular wall thickening and lumen narrowing. The deubiquitinase JOSD2 stabilizes SMAD7, which further hinders excessive activation of the pathway of TGF-β/Smad. Moreover, this compound considerably slows down the vascular remodeling spurred on by Ang II [107]. Apart from JOSD2, there are also some deubiquitinases like USP20 and CYLD that are able to stop TRAF6-dependent NF-κB activation. This leads to reduced NF-κB activation and inflammation. All in all, the UPS has a double role as indicated by the effects of deubiquitinases on the pathology of the vascular system.

The UPS has a critical role in neurogenic hypertension. Nedd4-2 protein directs the degradation of ACE2. With loss of ACE2 in the γ-aminobutyric acid (GABA)-ergic neurons in the paraventricular nucleus (PVN) that modulate inhibitory tone as well as sympathetic activity to cause elevation of blood pressure [108]. The E3 ligase UBR1 also targets ACE2 and works together with Nedd4-2 to enhance ACE2 degradation. According to these findings, targeting Nedd4-1 and UBR1 could provide a novel therapeutic strategy for hypertension, namely, restoring ACE2 function and reducing sympathetic overactivation [109]. In summary, by regulating endothelial function, VSMC phenotypic switching, inflammatory signaling, and neurogenic control, the UPS plays a fundamental role in the initiation and progression of hypertension. **Table 3** summarizes representative findings to offer a more systematic perspective on the molecular mechanisms and experimental evidence.

Potential therapeutic targets and strategies

Current status of drug development targeting the ubiquitination pathway

In recent years, as the important role of UPS in the onset and development of CVDs is becoming clearer, drug development targeting ubiquitination pathway has gradually become a research hotspot. The UPS regulates protein degradation, signal transduction, and cellular homeostasis. It was deeply involved in processes such as endothelial function, VSMC phenotype switching, inflammatory response and myocardial remodelling. As a result, targeted therapy towards E3 ligases, DUBs, or proteasome activity is a promising approach. The first clinical drugs related to UPS were proteasome inhibitors, bortezomib and carfilzomib, mainly exert anti-inflammatory and anti-proliferative effects by inhibiting NF-κB signalling pathway. Nonetheless, their use in cardiovascular diseases has been limited by their cardiovascular toxicities, such as HF and hypertension. Research on regulatory molecules which are more selective has been on the rise due to this limitation. In particular, the MDM2 inhibitor Nutlin-3a restores p53 stability and improves cardiomyocyte survival; TRAF6 inhibitors have been shown to attenuate inflammatory injury, and Smurf2 inhibitors delay myocardial fibrosis by stabilising Smad7 and so restraining the TGF-β/Smad signalling pathway. On the other hand, the involvement of the DUBs USP7, USP14, and USP20 in inflammatory diseases and cancer suggests that these DUBs may also serve as therapeutic targets for CVDs [110-112].

New strategies like PROTAC and molecular glue technologies have entered cardiovascular research. These technologies can selectively degrade pathogenic proteins, serving as novel therapeutic and research tools. PROTACs employ E3 ligases to facilitate the ubiquitination and ultimate degradation of selected proteins. This leads to the precise removal of crucial inflammatory or fibrotic molecules. Additionally, proteomics studies have uncovered potential regulatory impacts of current drugs on the UPS. For instance, valsartan has been shown to modify multiple ubiquitination sites and improve energy metabolism and calcium homeostasis by regulating SERCA2a and the Akt/mTOR pathway, ultimately exerting cardioprotective effects against HF [111]. In addition, Trim65 alleviates DIC by mediating p53 degradation and inhibiting ferroptosis [110]. UCHL1 has been identified as a contributor to cardiac remodeling in spontaneously hypertensive rats, and its inhibition may represent a novel target for treating hypertensive heart disease [112]. While macrophage membrane-based MELT formulations, designed to mimic M2 macrophages, have been proposed as a new candidate therapy for AS by mitigating inflammation and plaque progression [113]. As mechanistic insights into the role of ubiquitination in CVDs continue to deepen, drug development is gradually shifting from non-specific interventions toward highly selective and precise modulation.

Table 3. Ubiquitin-regulated networks and experimental studies in hypertension and its complications

Ubiquitination pathways/ mechanisms	Types of hypertension	Key proteins involved	Functional roles of ubiquitination	Signaling Pathways	Involved Clinical Studies/Experimental Data	References
Gstp1 enhances the interaction between APLNR and Nedd4, promoting ubiquitination and degradation	Spontaneous hypertension and renovascular hypertension	Gstp1, APLNR, and Nedd4 (E3 ubiquitin ligase)	Induces APLNR protein degradation and regulates VSMC function	The Apelin/APLNR signaling pathway is involved in this regulatory process	Rat model experiments, blood pressure measurements, and in vitro VSMC studies	[176]
High salt reduces phosphorylation, decreases ubiquitination, and attenuates degradation	Salt-sensitive hypertension	WNK4	Reduces WNK4 degradation and increases its protein abundance	Phosphorylation-ubiquitination crosstalk	High salt treatment experiments in C57BL/6 mice and HEK293 cells	[177]
TRIM31 catalyzes K48-linked ubiquitination at Lys-72 of MAP3K7	Hypertensive renal disease (HRD)	TRIM31, MAP3K7	Promotes proteasomal degradation of MAP3K7 and inhibits its downstream signaling pathway	TGF-β1-mediated Smad and MAPK/NF-κB pathways	Human HRD kidney specimens and AngII-induced mouse models	[43]
Nesfatin-1 inhibits SYTL4 E3 ligase-mediated deubiquitination of BMP-2	Hypertension-associated vascular calcification	nesfatin-1, SYTL4, BMP-2	Stabilizes BMP-2 protein and enhances its signaling	The BMP-2/Smad and HDAC4/RUNX2 pathways	Calcified patient specimens, VSMC experiments, and mouse model studies	[80]
Nedd4-2 mediates the ubiquitination and degradation of ACE2	Neurogenic hypertension (Ang-II-mediated)	ACE2, Nedd4-2, and the ACE2-5R mutant	Downregulates ACE2 and impairs GABAergic inhibition in the PVN	The PVN GABAergic neuron regulatory pathway	Hypertensive mouse models (optogenetics/telemetric blood pressure monitoring)	[108]
UBR1 catalyzes ACE2 ubiquitination and synergizes with Nedd4-2	Ang-II-induced hypertension	ACE2, UBR1, Nedd4-2, SGK1	Degrades ACE2, impairs its function, and promotes hypertension	The SGK1-Nedd4-2 regulatory axis	Hypertensive mouse models, human samples, and UBR1 knockdown experiments	[109]
WWP2 catalyzes the ubiquitination of ATP5A and targets it for proteasomal degradation	AngII-induced hypertension	WWP2, ATP5A, Bcl-2/Bax	Degrades ATP5A, stabilizes the Bcl-2/Bax ratio, and inhibits apoptosis	The mitochondrial apoptosis pathway (Bcl-2/Bax)	AngII-induced hypertensive mouse model; endothelium-specific WWP2 knockout mice	[105]
WWP2 ubiquitinates Septin4 at Lys-174 and targets it for proteasomal degradation	Hypertensive vascular disease	WWP2, Septin4, PARP1	Degrades Septin4 and inhibits the Septin4-PARP1 damage complex	The Septin4-PARP1 endothelial injury pathway	AngII/oxidative stress-induced mouse model with endothelium-specific WWP2 knockout	[178]
USP25 removes K63-linked ubiquitin chains from FOXO3 at Lys-258	Ang II-induced hypertension	USP25, FOXO3	Deubiquitination promotes autophagic degradation of FOXO3	The autophagosome-lysosome degradation pathway	Ang II-challenged mouse models (knockout/overexpression)	[179]
JOSD2 removes K48-linked ubiquitin chains from SMAD7 at Lys-220	Ang II-induced hypertensive vascular remodeling	JOSD2, SMAD7	Maintains SMAD7 stability and suppresses TGF-β signaling	The TGF-β-SMAD signaling pathway	Ang II mouse models (whole-body knockout/VSMC-specific overexpression)	[107]
UCHL1 mediates deubiquitination to regulate protein stability	Spontaneous hypertension	Ubiquitin carboxyl-terminal hydrolase 1 (UCHL1)	Dysregulated ubiquitination promotes pathological CH and fibrosis	AKT, ERK, STAT3, calcineurin, TGF-β/Smad, and NF-κB pathways	Rat experiments demonstrate that UCHL1 inhibition improves cardiac remodeling and functional parameters	[112]
The CUL3-KLHL3 ubiquitin ligase complex mediates WNK4 degradation	Familial hyperkalemic hypertension (FHHt)	WNK4, SPAK, OSR1, CUL3, KLHL3	Modulates WNK4 stability and affects phosphorylation-dependent pathways	The WNK4-SPAK/OSR1 phosphorylation signaling pathway	Mouse models show mild alterations in NKCC2 phosphorylation	[180]
USP18 mediates deubiquitination to regulate protein stability	Metabolic hypertension (MHR)	Ubiquitin-specific protease 18 (USP18)	USP18 deubiquitination suppresses vascular injury and oxidative stress	The JAK/STAT signaling pathway	MHR rat models and HUVEC experiments confirm the protective role of USP18	[181]
CUL3 mutations impair the ubiquitination and degradation of WNK4	Familial hyperkalemic hypertension	CUL3, KLHL3, WNK4, SPAK, NCC, JAB1	Dysregulated WNK4 degradation leads to NCC overactivation and hypertension	The WNK4-SPAK-NCC signaling pathway	Mouse models investigating the impact of CUL3 mutations on the pathway	[182]
The CUL3-KLHL3 E3 ligase complex mediates ubiquitination of WNK isoforms	Gordon syndrome	CUL3, KLHL3, WNK1, WNK4	Modulates WNK degradation, affecting salt retention and blood pressure elevation	WNK-SPAK/OSR1 signaling pathway	Patient mutation analysis, in vitro ubiquitination assays, and cellular experiments confirm the mechanism	[183]
The KLHL3-CUL3 ubiquitin ligase specifically ubiquitinates the KS-WNK1 isoform	Familial hyperkalemic hypertension	KLHL3, CUL3, KS-WNK1, SPAK, NCC	Defective ubiquitination of KS-WNK1 activates SPAK-NCC, leading to hyperkalemia	SPAK-NCC phosphorylation cascade signaling pathway	Pedigree gene sequencing, Xenopus/HEK293T functional assays, and CRISPR mouse models	[184]

USP25 inhibits SMAD4 function through K63-linked deubiquitination	Angiotensin II-induced hypertensive renal disease (HRD)	USP25, SMAD4, TGF-β/SMAD2	USP25 removes K63-linked ubiquitin chains from SMAD4 to block the fibrotic pathway	TGF-β/SMAD signaling pathway	Human/mouse renal tissue analysis; knockout/AAV overexpression mouse models	[185]
HDAC6 mediates CSE deacetylation to promote its ubiquitination and degradation	Angiotensin II-induced hypertension model	CSE, HDAC6, HNK, Ang II	Ubiquitination of CSE at Lys-73 promotes its proteasomal degradation and exacerbates hypertension	HDAC6-CSE acetylation/ubiquitination regulatory axis	Ang II animal models + CSE mutant cell experiments	[186]
RNF34 mediates ubiquitin-dependent degradation of p22phox	Angiotensin II (AngII)-induced hypertension	RNF34, p22phox, p47phox, NOX2	Modulates p22phox protein stability	NADPH oxidase-associated signaling pathway	RNF34 knockout promotes vascular remodeling in mouse MCA	[187]
SGLT2 binds cGAS and prevents its ubiquitination and degradation	Angiotensin II infusion-induced HF model	SGLT2 and cGAS	Inhibits cGAS ubiquitination and degradation, leading to its accumulation and exacerbation of neuroinflammation	cGAS-driven neuroinflammatory pathway involves activation of pro-inflammatory cascades	Angiotensin II-induced HF mouse model utilized for evaluation	[100]
The CRL3 complex mediates substrate ubiquitination, while the CUL3-Δ9 mutant lacks ubiquitination activity	Familial hyperkalemic hypertension caused by CUL3 mutations	CUL3-Δ9, BTB adaptor proteins, COP9, and CAND1	Hyperneddylated CUL3-Δ9 mutant remains incapable of activating ubiquitination	CRL3 complex dynamic assembly cycle regulated by COP9 and CAND1	Mass spectrometry interactome analysis and SILAC experiments demonstrate the mechanism of mutant functional loss	[188]
The CUL3Δ474-477 mutant exhibits enhanced autoubiquitination leading to its degradation, while the surviving variants show increased NEDD8 modification	Familial hyperkalemic hypertension with congenital abnormalities	CUL3-KLHL3 complex, WNK4 kinase, and BTB substrate adaptors	Variants impair WNK4 ubiquitination, leading to uncontrolled activation of the NCC transporter	CUL3-KLHL3-WNK4-NCC thiazide-sensitive signaling axis	Patient-derived urothelial vesicles/fibroblasts validate CUL3 degradation and complex dysfunction	[189]
Hyperactivation of CRL3-mediated neddylation	Diabetes-associated secondary hypertension	CUL3, KLHL2/3, RhoBTB1, WNK3/4, and NEDD8	Hyperneddylation triggers KLHL2/3 degradation, impairing substrate stability	WNK3-RhoA/ROCK pathway; WNK4-regulated sodium reabsorption pathway	STZ/db/db mouse models exhibit aberrant CRL3 adaptor expression, with mechanistic validation	[190]
NEDD4L mediates T-bet ubiquitination via the PKA/p-Sp1 pathway	Age-related hypertension	DP1, T-bet, NEDD4L, PKA, p-Sp1	Promotes T-bet degradation, suppressing Th1 activation and hypertension	The PKA/p-Sp1/NEDD4L signaling pathway	This axis is downregulated in $CD4^+$ T cells of aged humans and mice; murine experiments demonstrate DP1 involvement and BW245C efficacy	[191]
AE promotes NLRP3 ubiquitination to suppress inflammasome activation	Hypertension-associated CVD	NLRP3, ZO-1/2, HMGB1	Inhibits NLRP3 inflammasome activation and reduces HMGB1 release	Ang II-NLRP3 inflammasome signaling pathway	In vivo and in vitro experiments demonstrate that AE restores ZO-1/2 and inhibits NLRP3	[192]
Ang II inhibits PIN ubiquitination (reducing conjugated species) via AT1R	Hypertension associated with elevated central Ang II levels	PIN, nNOS, AT1R, and Ub	Modulates PIN stability; its reduction leads to increased PIN expression	Ang II-AT1R signaling pathway	PIN, nNOS, and related measurements in rat and cell experiments	[193]
WWP2 functions as an E3 ligase and forms a complex with SIRT1-STAT3 to regulate signaling	Angiotensin II-induced hypertension	WWP2, SIRT1, STAT3	Inhibits SIRT1-mediated suppression of STAT3, thereby promoting its modification	SIRT1-STAT3 regulatory axis	Modulates VSMC function in vitro; knockout in vivo alleviates vascular pathology	[194]
Ubiquitination can be reversed by DUBs (e.g., UCHL1)	Angiotensin II-induced hypertension (associated with atrial fibrillation)	UCHL1, CX43, AKT, ERK1/2	DUBs regulate substrate degradation, activity, trafficking, and recycling	AKT, ERK1/2, HIF-1α, and TGF-β/Smad2/3 pathways	LDN attenuates Ang II-induced atrial fibrillation (AF) in mouse models	[195]
Cul3Δ9 impairs ubiquitin-dependent regulation of PP2A	Salt-sensitive hypertension	Cul3, Cul3Δ9, PP2A, eNOS	Modulates substrate ubiquitination, affecting eNOS activity and related functions	eNOS-NO signaling pathway (involving eNOS phosphorylation)	E-Cul3Δ9 mice exhibit abnormalities in blood pressure, endothelial function, and renal injury	[196]
WWP2 promotes non-degradative monoubiquitination of IRF7	Hypertension (inducing non-ischemic cardiomyopathy)	WWP2, IRF7, Ccl5, and Ly6c-high monocytes	Promotes IRF7 nuclear translocation and transcriptional activity, upregulating Ccl5	WWP2-IRF7-Ccl5/Ly6c-high monocyte axis	Myeloid WWP2 deficiency reduces hypertension-induced cardiac fibrosis; scRNA-seq defines Ly6c-high monocytes	[197]

To provide an overview of current progress and future directions, the research landscape of ubiquitination pathway-related drugs has been systematically summarized (see **Table 4**).

Prospects of RNA interference (RNAi) technology in the regulation of ubiquitination

RNAi technology is a highly efficient and specific gene-silencing approach that has shown broad potential in CVD research and therapy. By employing small interfering RNAs (siRNAs), short hairpin RNAs (shRNAs), or miRNA mimics to target specific mRNAs, RNAi enables precise suppression of post-transcriptional gene expression. In the regulation of the ubiquitination pathway, RNAi can selectively silence particular E3 ligases or DUBs, thereby avoiding the systemic toxicity associated with the global inhibition of the UPS caused by conventional drugs. Consequently, RNAi is regarded as an important strategy for achieving precision intervention in CVDs.

For example, siRNA-mediated knockdown of TRAF6 can attenuate the ubiquitination and degradation of IκB, thereby reducing the expression of adhesion molecules and inflammatory mediators in AS. In the same way, RNAi techniques aimed at Smurf2 focus on stabilizing Smad7, preventing activation of the TGF-β/Smad signalling pathway, and alleviating myocardial fibrosis and vascular remodelling. Furthermore, RNAi-mediated targeting of USP20, which exerts its deubiquitinating action on RIPK1 and associated signalling intermediates, reveals its vasculoprotective capability by decreasing inflammatory responses triggered by TNF-α and IL-1β [114]. Regarding myocardial injury, H_2O_2 stimulation induces RNF4 expression and PML SUMOylation. siRNA-mediated knockdown of RNF4 further enhances PML SUMOylation, promotes p53 recruitment and activation, and aggravates H_2O_2/arsenic trioxide (ATO)-induced cardiomyocyte apoptosis. siRNA-mediated p53 knockdown partially reverses this effect [115]. Notably, RIP1 siRNA silencing prevents necroptosis induction by 4-HNE since 4-HNE inhibits RIP1 K48-linked polyubiquitination to reduce degradation. The impact of RNAi intervention is a therapeutic blocking which results in cardioprotection against myocardial injury [116].

Gene editing technologies for the modification of ubiquitination-related genes

In the past few years, the rapid development of gene editing technologies such as CRISPR/Cas9 has opened new avenues for the prevention and treatment of CVDs through fine modulation of ubiquitination-related genes. Research has shown that the E3 ubiquitin ligase RNF5 (RING finger protein 5) regulates the kinase cascade activated by apoptosis signal-regulating kinase 1 (ASK1). Inhibiting the excessive activation of ASK1, RNF5 exerts cardioprotective effects against MI, thereby providing a new molecular player in MI-related signalings. According to these findings, gene editing to improve RNF5 function may represent a promising therapeutic strategy [117]. Overall, it is clear that gene editing of RNF5 may open new avenues for individualized treatment and precision intervention of CVDs.

Discussion

We are learning more about the complex networks of ubiquitination in CVDs thanks to multi-omics studies. Proteomics analyses have shed light on substrate profiles of the E1-E2-E3 cascade, for example, the cryo-EM-resolved structure of the Uba7-UBE2L6-ISG15 complex, which reveals the role of ISG15 modification in ischemic myocardial inflammation [30]. Integrated transcriptome-ubiquitome analyses have found that circSamd4, which maintains mitochondrial homeostasis by inhibiting VDAC1 ubiquitination, when lost leads to excessive ROS accumulation after MI, a process regulated epigenetically by H2BK120ub [118]. Metabolome studies further reveal metabolic drivers of ubiquitination: MMA activates the E3 ligase RNF128 to drive K63-linked polyubiquitination of SRB1, resulting in macrophage lipid accumulation and AS. On the contrary, enhanced fasting glucose inhibits NEDD4L-mediated OPA1 degradation, causing diabetic cardiomyopathy mitochondrial dysfunction.

In terms of clinical translation, the process of Dynamic changes of ubiquitination modifications are emerging as a novel entry point for early diagnosis and prognosis of CVDs. For example, USP25 enhances myocardial calcium handling by stabilizing SERCA2a, yet is signifi-

Table 4. Advances and therapeutic prospects of ubiquitination-targeted drugs in CVDs

Drug Name/Candidate Drug	Target/Mechanism of Action	Drug Development Stage	Ubiquitination Pathway of the Target	Clinical/Experimental Research Progress	Associated Disease Types	References
Nicorandil (ATP-sensitive K^+ channel opener)	Activates AMPKα1 phosphorylation and promotes Parkin-dependent mitophagy	Experimental Research Stage	Pink1/Parkin-Mediated Mitophagy	Animal experiments demonstrate improved microvascular perfusion, suppressed ferroptosis, and attenuated myocardial injury	DCM with cardiac microvascular dysfunction	[198]
USP28 activator or AAV9-USP28 gene therapy (strategic candidate)	USP28 deubiquitinates and stabilizes PPARα, promoting Mfn2 transcription and improving mitochondrial function	Preclinical Research Stage	USP28 mediates deubiquitination of PPARα at Lys152	db/db mouse and hiPSC-cardiomyocyte experiments confirm improved cardiac function and attenuated mitochondrial damage	Type 2 DCM	[199]
YOD1 inhibitor	The YOD1-STAT3 axis; YOD1 deubiquitinates STAT3	Preclinical Research	K48-linked ubiquitination at Lys-97 of STAT3	YOD1 inhibition attenuates pathological ventricular remodeling in mice	Pathological CH (hypertrophic cardiomyopathy)	[200]
DOX and p53 inhibitor PFT-α	The AIG1-Pirh2-p53 axis inhibits cardiomyocyte ferroptosis	Experimental Research Stage	Pirh2 mediates ubiquitination and degradation of p53, facilitated by AIG1	Mouse experiments demonstrate that AIG1 overexpression and PFT-α ameliorate DIC	DIC	[201]
Luteolin	Directly targets PPARγ and inhibits its ubiquitination and degradation	FDA-approved compound under investigation for anti-hypertrophic applications	PPARγ ubiquitination and proteasomal degradation pathway	Demonstrates anti-hypertrophic effects in vitro and in mouse models	Pathological CH, HF and associated metabolic disorders	[202]
SUMOylation inhibitor Ginkgolic Acid	SUMOylation of FADD regulates its ubiquitination and complex formation	Animal Model Research Stage	Ubiquitination of FADD is competitively inhibited by its SUMOylation	In vivo and in vitro models confirm the role of FADD and the efficacy of GA	Hypoxia-related CVDs	[203]
Gastrodin (GAS)	Targets the CDT2-KAT2A axis to regulate ubiquitination-lactylation crosstalk	In Vivo/In Vitro Experimental Stage	The ubiquitin-mediated KAT2A degradation pathway	Completed in vivo and in vitro studies demonstrate efficacy in alleviating Sepsis-induced myocardial dysfunction (SIMD)	SIMD	[204]
Panax notoginseng saponins (PNS)	Inhibits USP2, promotes Keap1 degradation, activates Nrf2, and suppresses ferroptosis	In Vivo/In Vitro Experimental Stage	USP2-mediated deubiquitination pathway of Keap1	In vivo and in vitro studies demonstrate its anti-atherosclerotic effects and suppression of ferroptosis	AS	[205]
Notoginsenoside R1	Inhibits the interaction between β-arrestin2 and MDM2, reducing β2AR ubiquitination	Preclinical Stage	β-arrestin2- and MDM2-mediated ubiquitination process	Completed evaluations using mouse LAD ligation and H9c2 cell OGD/R models	Chronic HF	[102]
20S-O-Glc-DM (C20DM) ginsenoside precursor molecule	Modulates PGC-1α activity and the AMPK-mTOR-ULK1 pathway to enhance mitochondrial quality control and autophagic balance	Preclinical Research	PINK1-Parkin-mediated ubiquitination in mitophagy	Completed assessments of cardiac function in animals and validation of mitochondrial/autophagy mechanisms in cells	Left ventricular diastolic dysfunction (LVDD)	[206]
Qishen Yiqi Pills	Inhibits TTC39B-mediated LXR ubiquitination, upregulating LXR-α/ABCG5 to promote cholesterol reverse transport	Preclinical Research	TTC39B-E3 ligase-mediated LXR ubiquitination and degradation pathway (inhibited by QSYQ)	Completed validation of cardiac and hepatic function, along with molecular mechanisms, in high-fat diet mouse models	AS	[207]
Rapamycin	Inhibits mTOR to induce PHB1 ubiquitination and degradation, activating the OMA1-OPA1 pathway and leading to mitochondrial fragmentation	Mechanism Research	Ubiquitin-proteasome degradation pathway of PHB1	Completed mechanistic validation in cardiomyocyte models and inducible mTOR knockout animals	Cardiomyocyte mitochondrial dysfunction	[208]
USP20-targeting siRNA lipid nanoparticles	Silencing hepatic USP20 reduces HMG-CoA reductase stability and decreases lipid synthesis	Preclinical Research Stage	USP20-mediated deubiquitination pathway stabilizes HMG-CoA reductase	Completed validation of lipid-lowering and anti-atherosclerotic effects in Ldlr-/- mouse models	Atherosclerotic cardiovascular disease (ASCVD)	[209]

Calcitriol/Eldecalcitol (VDR ligands) and Carfilzomib (proteasome inhibitor)	Activates VDR or inhibits the proteasome to block E3 ligase MuRF1-mediated protein ubiquitination and degradation	New Indication Exploration for Marketed Drugs	MuRF1 E3 ligase-mediated proteasomal degradation pathway	Completed functional and structural validation in GC-induced injury mouse models and ex vivo organ culture	Multi-tissue damage (bone/muscle/heart) induced by long-term glucocorticoid therapy	[210]
Xinbao Pills	Upregulates USP18 to inhibit β1-AR ubiquitination; disrupts MDM2/β-arrestin2/Nedd4-mediated β2-AR ubiquitination	Preclinical Research	① β1-AR: USP18 deubiquitination pathway (activated by XBP) ② β2-AR: Nedd4 E3 ligase/MDM2-β-arrestin2-mediated ubiquitination pathway (inhibited by XBP)	Completed cardiac function assessment in LAD-ligated rats and validation of protective effects against OGD injury in AC16/H9c2 cells	Chronic HF	[103]
Adeno-associated virus (AAV)-mediated AMBP overexpression gene therapy	AMBP competitively binds to the FHL3 zinc finger domain, promoting ubiquitination and degradation of P-ERK1/2 and P-JNK	Preclinical Research	Loss of FHL3 protective function leads to ubiquitin-proteasome degradation of phosphorylated ERK/JNK proteins	Completed cardiac function assessment in Calcific aortic valve disease (CAVD) mouse models and validation of the FHL3-AMBP interaction mechanism	CAVD	[211]
Salvia miltiorrhiza-derived exosome-like nanoparticles (SM-ELNs)	Inhibits NEDD4-mediated ubiquitination and degradation of SGK1, blocking NLRP3 inflammasome activation	Preclinical Research	NEDD4 E3 ligase-mediated ubiquitin-proteasome degradation pathway of SGK1	Completed assessment of cardiac function/fibrosis and validation of macrophage pyroptosis mechanisms in mice	DCM	[212]
Gramine	Inhibits NF-κB p105 ubiquitination, blocking its processing into the p50 subunit	Preclinical Research	NF-κB p105 ubiquitination and degradation pathway	Completed assessment of cardiac function/mortality in septic mice and validation of NF-κB p105 ubiquitination mechanisms	Sepsis-induced myocardial dysfunction	[213]
Yimai Granules (YMG)	YMG activates mitophagy via miRNA-125a-5p and regulates the Pink1-Mfn2-Parkin pathway	Preclinical Research	Parkin-mediated ubiquitination for mitochondrial quality control	Therapeutic efficacy validated in HFD rat models and AngII-injured HUVECs	CVDs, particularly AS	[214]
Shengmai Yin	Inhibits K27-linked ubiquitination of AIM2, blocking AIM2 inflammasome activation	Preclinical Research	K27-linked ubiquitination-mediated AIM2 inflammasome activation pathway	Completed assessment of cardiac function/infarct size in I/R rats and validation of AIM2 ubiquitination mechanisms	Myocardial IRI	[215]
lncDACH1 inhibitor	Inhibits lncDACH1, blocking its mediated ubiquitination and degradation of SIRT3	Preclinical Research	lncDACH1 promotes the ubiquitination and degradation of SIRT3	① Animal models: lncDACH1 knockout improves cardiac function in DCM mice ② Cellular models: lncDACH1 silencing attenuates high glucose-induced cardiomyocyte injury	Diabetic cardiomyopathy	[216]
Xinyin Tablets (compound herbal formulation)	Activates the HDAC3-mediated PINK1/Parkin pathway to enhance mitophagy	Preclinical Research	Parkin mediates mitochondrial ubiquitination to initiate autophagy	① In vivo: Improves cardiac function and inhibits apoptosis in HF mice ② In vitro: Reduces hypoxic injury and promotes autophagy in cardiomyocytes	Chronic HF	[217]
Carvedilol	Activates βarrestin2 via β1AR to enhance SERCA2a activity	Preclinical Research	SUMOylation pathway of SERCA2a	Demonstrates pro-contractile effects in cardiomyocyte models	HF, particularly post-MI type	[218]
Pitavastatin (PTV), a statin drug	Activates the calcium-CAMK1-PINK1 phosphorylation cascade to promote mitophagy	Marketed Drug (Novel Mechanism Investigation)	PINK1 phosphorylates Parkin at Ser65 to initiate mitochondrial ubiquitination	① Animal models: PTV improves EPC proliferation and mitochondrial function in ApoE$^{-/-}$ mice ② Mechanism: Pink1 knockout abolishes the therapeutic effects of PTV	AS CAD	[219]

Tabersonine (Tab), an indole alkaloid candidate drug isolated from Catharanthus roseus	Inhibits TAK1 to suppress ubiquitination and phosphorylation, blocking NF-κB/JNK/P38 signaling pathways	Preclinical Research	TAK1 ubiquitination modification pathway, inhibited by Tab	Demonstrates cardioprotective effects in Ang II-induced mouse and cell models	Hypertensive heart failure associated with Ang II-induced cardiac injury	[220]
Remdesivir	Restoring TAL1-TRAF6 interaction inhibits ubiquitination and NF-κB signaling	Preclinical Research	Total ubiquitination and K63-linked ubiquitination pathways of TRAF6	Demonstrates anti-atherosclerotic effects in ApoE$^{-/-}$ mice and HUVEC models	AS	[221]
Baicalin (BAI)	Promotes SIRT3 deSUMOylation via SENP1 to restore mitochondrial homeostasis	Preclinical Research	SUMOylation pathway	① In vivo: Ameliorates myocardial injury in db/db mice ② In vitro: SENP1 silencing abolishes BAI's protective effects, while SENP1 overexpression mimics BAI's efficacy	Diabetic cardiomyopathy	[222]
TAK-243 (UBA1 inhibitor)	Inhibits UBA1 to suppress NF-κB signaling and attenuate macrophage activation	Preclinical Research	Inhibits the E1 ubiquitin-activating enzyme UBA1, blocking the initiation of the ubiquitination cascade	① Animal models: Prevents aortic dissection formation and attenuates vascular pathology in mice ② Cellular models: Inhibits AngII-induced inflammatory activation of macrophages	Aortic dissection	[223]
Tongxinluo Capsule (TXL), a traditional Chinese herbal compound formulation	Activates Parkin-mediated mitophagy and downregulates the UPS	Preclinical Research	Downregulation of the UPS reduces ubiquitination	Protective effects demonstrated in rat models; mechanisms validated by Western blotting	Myocardial IRI	[224]
Irisin, a cleavage product of FNDC5	Upregulates MITOL/MARCH5 to suppress endoplasmic reticulum stress and ROS production	Preclinical Research	MITOL (MARCH5) mediates mitochondrial ubiquitination to maintain homeostasis	① Animal models: Reduces MI size, apoptosis, and oxidative damage in mice ② Cellular models: Protects H9c2 cells against simulated IRI	Myocardial I/R injury	[225]

cantly downregulated in patients with HF, suggesting its potential as a biomarker [119]. Hyperactivation of the E3 ligase WWP1 promotes K27-linked polyubiquitination of DVL2, driving CH; notably, elevated WWP1 expression in clinical samples correlates with the severity of ventricular remodeling [120]. Similarly, TRIM family protein-mediated H2BK120ub is abnormally elevated in DCM, associated with chromatin remodeling and activation of the p53 pathway, thereby providing a basis for epigenetic subtyping [42]. However, clinical application remains constrained by the transient and tissue-specific nature of ubiquitination, the instability of ubiquitinated proteins in body fluids, and the functional heterogeneity of distinct Ub chain conformations, all of which pose higher demands on detection technologies [121, 122]. Looking ahead, translational advances are more likely to rely on integrated "ubiquitination-signaling pathway-phenotype" analyses, combined with single-cell omics to identify highly specific biomarkers within defined cellular subpopulations.

The ubiquitination pathway is emerging as an important therapeutic target for drugs. Cardioprotection through Inhibition of the MDM2-p53 Axis. Inhibitors of the MDM2-p53 axis have been shown to attenuate cardiomyocyte apoptosis in experimental MI models. Thus, targeted modulation of ubiquitination may have cardioprotective efficacy. Small-molecule ubiquitination regulators and E3 ligase inhibitors have been well studied in the fields of oncology and neurodegenerative disease, thus they provide valuable references for CVD therapy, although translation to cardiology still seems early. The dual role of DUBs in modulating inflammation and fibrosis is also noteworthy. This functional duality reveals new aspects of CVD pathogenesis and offers new opportunities for intervention. As we move forward, it is imperative to establish a systematic framework for Ub research, strengthening the link between basic science and clinical application, in order to drive innovation in the diagnostic and treatment of CVDs.

Conclusion

To sum up, protein degradation through ubiquitination is a critical regulatory mechanism of protein homeostasis. It is a critical regulator in the pathogenesis and progression of CVDs through modulating stability, activity and localization of key proteins. The ubiquitination modification network is widely involved in the pathological process of major CVDs, including CAD, HF, and hypertension, from the fine-tuning of cardiomyocyte survival and death, endothelial function, and inflammation, to phenotypic switching and remodeling of VSMCs. With the advent of emerging technologies like PROTACs and the gradual elucidation of key regulatory components such as E3 ligases and DUBs, therapies targeting the ubiquitination pathway appear highly promising. With the combination of multi-omics data, highly selective modulators, deepening knowledge of cell-type-specific functions, future research is poised to improve our understanding of cardiovascular pathological mechanisms and provide a solid theoretical basis for the development of new diagnostic biomarkers and precision therapeutics.

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Disclosure of conflict of interest

None.

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