Roles of TRIM proteins in cardiovascular diseases: From pathogenesis to therapeutic targeting (Review)

FENGMEI WANG[1], ZHIBO XING[2], YUJUAN GAO[3] and YANHONG GAI[3]

[1]Department of Cardiac Function, Qingdao Central Hospital, University of Health and Rehabilitation Sciences, Qingdao, Shandong 266000, P.R. China; [2]Department of Breast Surgery, Qingdao Central Hospital, University of Health and Rehabilitation Sciences, Qingdao, Shandong 266000, P.R. China; [3]Department of Cardiology, Qingdao Central Hospital, University of Health and Rehabilitation Sciences, Qingdao, Shandong 266000, P.R. China

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Abstract. Cardiovascular diseases are driven by sustained mechanical stress, metabolic derangement, inflammation and oxidative injury, which progressively disrupt cellular homeostasis within the heart and vasculature. Although current therapeutic strategies have substantially improved clinical outcomes, most interventions primarily target downstream pathological manifestations rather than upstream regulatory mechanisms that determine stress adaptation and tissue remodeling. Tripartite motif (TRIM) proteins constitute a large family of E3 ubiquitin ligases characterized by a highly conserved RBCC domain architecture and diversified C-terminal regions. By catalyzing distinct ubiquitin chain topologies and functioning as molecular scaffolds, TRIM proteins broadly regulate protein turnover, inflammatory signaling, metabolic adaptation and cell fate determination. Emerging evidence identifies TRIM proteins as context-dependent regulators whose biological effects are shaped by cell type, disease stage and microenvironmental conditions. Multiple TRIM family members have been linked to a wide spectrum of cardiovascular diseases, including atherosclerosis, vascular calcification, myocardial infarction, cardiac hypertrophy and metabolic cardiomyopathy. At the cellular level, TRIM proteins influence disease initiation and progression by modulating endothelial dysfunction, vascular smooth muscle cell phenotypic remodeling, cardiomyocyte survival and metabolic homeostasis, fibroblast activation and immune-inflammatory responses. The present review summarized the biochemical characteristics and cell-specific functions of TRIM proteins and delineates their mechanistic roles in cardiovascular pathogenesis. In addition, it discussed their emerging potential as diagnostic biomarkers and therapeutic targets, highlighting both translational opportunities and context-dependent challenges.

Correspondence to: Professor Yanhong Gai, Department of Cardiology, Qingdao Central Hospital, University of Health and Rehabilitation Sciences, 127 Siliu South Road, Shibei, Qingdao, Shandong 266000, P.R. China
E-mail: m13953256850@163.com

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1. Introduction

Cardiovascular diseases (CVDs) remain the leading cause of mortality and disability worldwide (1). According to the 2021 Global Burden of Disease Study, CVD-related mortalities have continued to rise, reaching ~19.4 million in 2021 and accounting for more than one quarter of all global mortalities (2). Despite substantial advances in prevention and therapeutic strategies, CVDs continue to impose a major health burden. This persistent impact is attributable, in part, to limitations in precise risk stratification and to ongoing adverse clinical sequelae, including plaque rupture, myocardial infarction (MI) and heart failure (HF) (3). Moreover, a central challenge in contemporary cardiology lies in the limited regenerative capacity of the adult heart and the progressive nature of pathological remodeling once initiated (4). Accordingly, there is an urgent need to identify molecular regulators that coordinate stress responses, preserve proteostasis and integrate immune and metabolic signaling within the cardiovascular system.

Post-translational modifications (PTMs) directly or indirectly influence cellular metabolism and function by modulating protein activity, thereby contributing to the pathogenesis of numerous diseases (5). To date, >400 types of PTMs have been identified, including phosphorylation, acetylation,

ubiquitination, lactylation and methylation. Among these, ubiquitin-dependent signaling has garnered increasing attention due to its dynamic regulation of protein stability, signal transduction, transcriptional programs and organelle quality control (6). The Tripartite motif (TRIM) protein family comprises multifunctional regulatory proteins characterized by three conserved domains, collectively referred to as the RBCC motif: An N-terminal RING finger domain conferring E3 ubiquitin ligase activity; one or two B-box zinc-finger domains; and a coiled-coil (CC) domain mediating dimerization and higher-order assembly. The C-terminal region is highly variable and contains motifs that determine substrate specificity and functional diversity, such as PRY/SPRY domains, NHL repeats or PHD-bromodomains (7). Collectively, TRIM proteins constitute one of the largest families of E3 ligases, with >80 members identified in humans, the vast majority of which exhibit E3 ubiquitin ligase activity. These proteins participate in a broad spectrum of biological processes, including inflammation, cell death, energy metabolism and tumorigenesis.

The structural diversity and multifunctionality of TRIM proteins enable them to exert pivotal regulatory roles in both cellular physiology and pathology (8). TRIM proteins were initially characterized for their roles in antiviral immunity and cancer (9-11). For example, TRIM25 mediates K63-linked ubiquitination of RIG-I, thereby enhancing cytosolic RIG-I activation and downstream signaling to initiate host antiviral innate immune responses (12). In addition, TRIM41 promotes innate antiviral responses by ubiquitinating B-cell lymphoma 10 (Bcl) 10, leading to activation of the nuclear factor-κB (NF-κB) and TANK-binding kinase 1 (TBK1)-interferon regulatory factor 3 (IRF3) signaling pathways (13). Furthermore, TRIM8 facilitates K48-linked ubiquitination of myoferlin, promoting its proteasomal degradation, thereby suppressing matrix metalloproteinase (MMP) secretion and ultimately inhibiting the progression of non-small cell lung cancer (14).

Emerging evidence indicates that TRIM family members are expressed and functionally active in nearly all cardiovascular cell types, including cardiomyocytes, endothelial cells (ECs), vascular smooth muscle cells (VSMCs), fibroblasts and immune cells (15,16). However, the cell type-specific functions of individual TRIM isoforms within the cardiovascular system remain incompletely characterized. Moreover, the intricate interaction networks between TRIM proteins and other signaling pathways or cytokines in the context of cardiovascular homeostasis are poorly defined, limiting a comprehensive understanding of their regulatory mechanisms in cardiac and vascular diseases.

The present review summarized the emerging links between TRIM family proteins and cardiovascular diseases, delineating the mechanisms and signaling pathways regulating TRIM expression and activity and discussed their potential implications for the diagnosis and therapeutic targeting of cardiovascular disorders.

2. Structural features and classification of TRIM proteins

Domain architecture and subfamily classification. TRIM proteins constitute a large family of E3 ubiquitin ligases defined by a conserved N-terminal RBCC motif, composed of a RING domain, one or two B-box domains and a CC domain (7). This shared architecture establishes TRIM proteins as a coherent biochemical family, whereas diversification of the C-terminal region underlies their functional heterogeneity. The RING domain confers E3 ubiquitin ligase activity through recruitment of E2 ubiquitin-conjugating enzymes. The B-box domains modulate protein-protein interactions and fine-tune ligase activity. The CC domain mediates homo- or hetero-oligomerization, enabling TRIM proteins to assemble into higher-order complexes that function as signaling hubs (8). By contrast, the C-terminal domains are highly variable and determine substrate recognition, subcellular localization and pathway specificity. These domains include PRY/SPRY motifs involved in substrate binding; PHD-bromodomain modules that link TRIM proteins to chromatin regulation; and other motifs such as fibronectin type III, NHL repeats, or meprin and tumor necrosis factor receptor-associated factor (TRAF) homology domains. Based on differences in C-terminal domain composition, TRIM proteins are generally classified into 11 subfamilies (17). Although this structural classification provides a useful organizational framework, functional outcomes remain highly context-dependent, reflecting the integration of TRIM activity with cell type-specific signaling programs and disease stage.

E3 ubiquitin ligase activity. A defining biochemical feature of TRIM proteins is their capacity to catalyze distinct forms of ubiquitination. TRIM-mediated K48-linked polyubiquitination typically targets substrates for proteasomal degradation, thereby contributing to protein quality control and signal termination (14,18). By contrast, K63-linked ubiquitination and other non-degradative modifications promote the assembly of signaling complexes and activation of signaling pathways such as NF-κB and β-catenin (19-21). As well as canonical linkages, certain TRIM proteins catalyze atypical ubiquitin chains, including K27-, K29- and K33-linked modifications, which regulate protein-protein interactions, vesicular trafficking and transcriptional control (22-24). Importantly, TRIM proteins frequently couple enzymatic ubiquitination with scaffolding functions, enabling fine-tuning of signaling amplitude and duration rather than binary on/off regulation. This versatility provides a biochemical basis for the context-dependent roles of TRIM proteins in cardiovascular cells and disease states.

As well as ubiquitin-chain topology, another important determinant of TRIM function is substrate specificity. Substrate specificity of TRIM proteins is primarily determined by their structurally diverse C-terminal domains, whereas the RING domain mainly mediates E2 recruitment and ubiquitin transfer (25,26). Among these recognition modules, the PRY/SPRY domain is particularly well characterized and recognizes specific linear or conformational epitopes on target proteins, while CC-mediated oligomerization can further regulate substrate engagement. In cardiovascular cells, substrate selection is additionally shaped by cell-specific protein expression, subcellular localization, interacting cofactors and stress-dependent changes in substrate accessibility, providing a potential explanation for the context-dependent actions of individual TRIM proteins. Notably, the SPRY domain of TRIM16 directly interacts with the proline-rich domain of disabled-2 (DAB2) and subsequently mediates K63-linked ubiquitination

of DAB2 at K656 in VSMCs facilitate vascular calcification, providing direct evidence for domain-dependent substrate recognition in the cardiovascular system (27). Nevertheless, the precise recognition interfaces remain unresolved for most cardiovascular TRIM-substrate pairs, highlighting the need for structural studies, domain-specific mutagenesis, interactomics and quantitative ubiquitinomics (28).

Notably, TRIM-mediated ubiquitination is not a unidirectional process but is dynamically counterbalanced by deubiquitinating enzymes, which can remove specific ubiquitin chains from TRIM proteins or their substrates and thereby reshape protein stability and signaling output. For example, in cardiomyocytes, ubiquitin specific peptidase 28 (USP28) deubiquitinates and stabilizes TRIM21 through removal of K48-linked ubiquitin chains, thereby enhancing TRIM21-dependent suppression of the nuclear factor erythroid 2-related factor 2 (Nrf2) antioxidant response (29). Similarly, Myb-like, SWIRM and MPN domains 1 (MYSM1) directly interacts with TRIM21 and modulates its deubiquitination and stability in doxorubicin-treated cardiomyocytes, thereby potentiating TRIM21-associated ferroptosis (30).

Crosstalk with other PTMs. The functional activity of most proteins is mediated through interactions with other proteins and is frequently modulated by PTMs. A substantial proportion of proteins undergo at least one PTM and numerous proteins are subject to multiple modifications, underscoring the prevalence of crosstalk among distinct PTMs (31). TRIM proteins both regulate and are regulated by other PTMs, including SUMOylation, acetylation, phosphorylation, S-nitrosylation, palmitoylation and lactylation. For example, TRIM28 functions as a scaffold linking SUMOylation to transcriptional repression. TRIM28-mediated SUMOylation modulates the transcriptional activity of the methyl-DNA-binding protein Kaiso (32). SUMOylation of TRIM28 promotes stabilization of NLR family pyrin domain containing 3 (NLRP3), thereby facilitating inflammasome activation (33). TRIM28-mediated SUMOylation of viral nucleocapsid proteins enhances the virulence of severe acute respiratory syndrome coronavirus 2 (34). In addition, TRIM28-dependent SUMOylation of G3BP1/2 regulates stress granule dynamics (35). Endogenous TRIM5α activity in dendritic cells is modulated by SUMOylation and nuclear sequestration to ensure efficient innate immune sensing (36). Muscle RING finger protein-1 (MuRF1) undergoes SUMO1 modification that regulates its function and subcellular localization (37).

TRIM66 recognizes unmodified H3R2K4 and H3K56ac to coordinate DNA damage responses in embryonic stem cells (38). Histone deacetylase 6 (HDAC6) deacetylates TRIM56, thereby negatively regulating cyclic GMP-AMP synthase-stimulator of interferon genes-mediated type I interferon responses and also mediates acetylation of TRIM50 (39,40). TRIM65 has been identified as a key regulator of lactate-driven tubular injury, ferroptosis and glycolysis in diabetic nephropathy (41). Crosstalk between chromatin acetylation and SUMOylation of TRIM24 influences cell adhesion (42). TRIM21-mediated ubiquitination of SQSTM1/p62 eliminates its Ser403 phosphorylation and enhances palmitate-induced cytotoxicity (43). Cyclin-dependent kinase 2-activated phosphorylation and nuclear translocation of TRIM32 promote radioresistance in triple-negative breast cancer (44).

Additional redox- and lipid-related modifications further expand TRIM functional regulation. S-nitrosylation of TRIM72 at cysteine 144 is essential for preventing oxidative stress-induced protein degradation and cell death, and knock-in mutation at this residue confers cardioprotection while reducing myocardial TRIM72 release (45). Moreover, ZDHHC palmitoyltransferase 20-mediated S-palmitoylation of KRAB-associated protein-1/TRIM28 enhances DNA damage repair (46). Collectively, these findings underscore that TRIM proteins operate within an intricate PTM network, in which ubiquitination is dynamically coordinated with other modifications to shape protein stability, localization and signaling specificity. This multilayered regulatory landscape is likely to be particularly relevant in cardiovascular pathophysiology, where precise integration of stress, metabolic and inflammatory cues is required for maintaining tissue homeostasis.

3. Roles of TRIM proteins in cardiovascular cell types

Vascular pathology arises from coordinated dysfunction of multiple cellular types within the vessel wall, including VSMCs, ECs and infiltrating immune cells. These cellular populations do not operate in isolation but instead engage in continuous bidirectional communication that governs vascular tone, inflammatory activation, remodeling and lesion stability. TRIM proteins have emerged as critical regulators within this multicellular vascular ecosystem, integrating ubiquitin-dependent signaling with inflammatory, metabolic and stress-responsive pathways to shape the progression of vascular disease.

ECs. ECs constitute the first line of defense against hemodynamic stress and circulating inflammatory stimuli. Endothelial dysfunction, characterized by impaired barrier integrity, aberrant angiogenesis and enhanced inflammatory activation, represents a central pathological mechanism in vascular disease. TRIM proteins have emerged as key modulators of endothelial signaling networks, controlling angiogenic balance and inflammatory responses. In patients undergoing percutaneous coronary intervention, TRIM27 promotes endothelial progenitor cell apoptosis by ubiquitinating TBK1, thereby exacerbating in-stent restenosis (47). Wang *et al* (48) identified TRIM28 as a nuclear regulator in ECs that controls endothelial inflammation and angiogenic activity by maintaining the expression of tumor necrosis factor receptor (TNFR)-1, TNFR2 and VEGFR2. Another study further demonstrated that TRIM28 regulates sprouting angiogenesis via the VEGFR-delta-like protein 4-Notch signaling axis (49). Similarly, Huang *et al* (50) reported that TRIM14 is highly expressed in human vascular ECs and enhances monocyte-endothelial adhesion by activating NF-κB signaling, thereby upregulating adhesion molecules vascular cell adhesion molecule-1 and intercellular adhesion molecule-1, as well as cytokines CCL2, interleukin-8 and tumor necrosis factor-α. Recombinant high-density lipoprotein (rHDL) has been shown to upregulate TRIM2 expression, and TRIM2 deficiency attenuates rHDL-induced angiogenesis under hypoxic and

inflammatory conditions (51). Notably, TRIM2 selectively regulates inflammation-driven pathological angiogenesis without affecting physiological hypoxia-mediated angiogenesis (52). Collectively, this evidence indicates that TRIM proteins are essential for maintaining endothelial homeostasis by coordinating inflammatory signaling and angiogenic responses.

VSMCs. VSMCs exhibit remarkable phenotypic plasticity. In response to injury and inflammatory stimuli, they transition from a contractile phenotype that preserves vascular structural integrity to a synthetic phenotype characterized by enhanced proliferative and migratory capacity. This phenotypic switch is a hallmark of atherosclerosis, restenosis and neointimal hyperplasia. Accumulating evidence suggests that TRIM proteins function as molecular gatekeepers that determine VSMC identity by regulating growth factor signaling, redox homeostasis and metabolic reprogramming. Several TRIM proteins have been implicated in promoting pathological VSMC activation. Liu *et al* (53) demonstrated that TRIM28 expression is markedly upregulated in atherosclerotic tissues and in platelet-derived growth factor-BB (PDGF-BB)-stimulated human aortic smooth muscle cells (HASMCs). TRIM28 knockdown suppresses VSMC proliferation and migration and inhibits phenotypic switching. Notably, another study reported that TRIM28 cooperates with TRIM27 to maintain endogenous PDGFR-β expression and preserve the contractile phenotype of HASMCs (54).

More recently, TRIM5 was identified as a novel transcriptional target of Nrf3 and was shown to serve a pivotal role in VSMC dysfunction and neointimal hyperplasia (55). In addition, TRIM21 mediates ubiquitination of phosphofructokinase platelet type (PFKP) and muscle type, thereby influencing PFKP protein stability. The mitochondrial protein mitofusin 2 reduces PFK1 ubiquitination by disrupting its interaction with TRIM21, ultimately suppressing neointimal formation in vein grafts (56). Taken together, these findings position TRIM proteins as central regulators of VSMC phenotypic plasticity. Rather than functioning as simple binary switches, TRIM proteins fine-tune signaling thresholds that determine whether VSMCs maintain a contractile state or enter a program of pathological vascular remodeling.

Cardiomyocytes. In cardiomyocytes, TRIM proteins are critical for maintaining proteostasis, sarcomeric integrity, mitochondrial quality control and regulation of cell death. Members of the MuRF subfamily, including TRIM63 (MuRF1) and TRIM54 (MuRF3), govern the turnover of contractile proteins and metabolic enzymes, thereby preserving sarcomeric function under physiological conditions. Dysregulation of these pathways leads to pathological remodeling and progression to HF. Other TRIM proteins modulate cardiomyocyte survival during stress. Several TRIM proteins regulate apoptosis, ferroptosis and pyroptosis by controlling key signaling nodes, including p53, mitogen-activated protein kinases (MAPKs), the NLRP3 inflammasome and antioxidant pathways. TRIM72 (MG53), a membrane repair protein, enhances sarcolemmal integrity and mitochondrial protection during ischemic stress, although species-specific expression differences complicate translational interpretation in humans. In MI murine models, TRIM11 expression is downregulated and has been shown to attenuate Dusp6-mediated cardiomyocyte ferroptosis in acute MI (AMI) (57). TRIM13 reduces oxygen-glucose deprivation-induced apoptosis by ubiquitinating CD3D and decreasing its expression (58). Liu *et al* (59) demonstrated that TRIM21 promotes atrial inflammation and post-MI remodeling by activating NF-κB signaling and inducing NADPH oxidase 2 expression. More recently, TRIM55 was shown to exacerbate cardiomyocyte apoptosis after MI by promoting ubiquitin-mediated degradation of Nrf2 (60).

Cardiac fibroblasts (CFs). CFs are key mediators of extracellular matrix remodeling. TRIM proteins regulate fibroblast activation, proliferation, senescence and autophagic flux through pathways involving transforming growth factor-β (TGF-β)/Smad signaling, mechanistic target of rapamycin (mTOR) activation and inflammatory cascades. Depending on disease context, TRIM-mediated modulation of fibroblast behavior may support reparative scar formation or drive maladaptive fibrosis that impairs cardiac compliance and electrical conduction. TRIM35 promotes fibroblast proliferation, migration and myofibroblast differentiation by regulating solute carrier family 7 member 5-mediated amino acid transport and activating mTOR complex 1, thereby exacerbating cardiac fibrosis and structural remodeling (61). Qian *et al* (62) reported that TRIM44 aggravates post-MI cardiac fibrosis by inhibiting ubiquitin-mediated degradation of TGF-β-activated kinase 1 (TAK1), leading to increased TAK1 phosphorylation and activation of MAPK signaling. Conversely, TRIM38 attenuates post-MI fibrosis by promoting degradation of TAK1-binding proteins 2/3 (TAB2/3), thereby suppressing TAK1 activation (63). Epigenetic regulation further intersects with TRIM signaling. Histone demethylase Kdm4a suppresses TRIM44 expression by increasing H3K9me3 enrichment at its promoter in CFs, thereby enhancing autophagy in prematurely senescent fibroblasts and mitigating post-MI fibrosis (64). TRIM72 regulates CF proliferation and migration via TGF-β signaling (65). In transverse aortic constriction (TAC)-induced cardiac hypertrophy, TRIM72 promotes fibroblast-to-myofibroblast transition and cardiac fibrosis by enhancing signal transducer and activator of transcription 3 (STAT3) phosphorylation and activating downstream Notch-1 signaling (66). TRIM72 also exacerbates atrial fibrosis through modulation of the TGF-β/Smad pathway (67).

Immune cells. Immune cells infiltrating the vascular wall serve critical roles in plaque initiation, progression and stability. Macrophages, dendritic cells and T lymphocytes coordinate inflammatory cascades that determine whether vascular lesions progress toward rupture or adopt a stable phenotype (68-70). Increasing evidence indicates that TRIM proteins are key regulators of immune cell fate and function within the vascular microenvironment. In macrophages, TRIM proteins modulate polarization and inflammatory signaling. For example, Li *et al* (71) confirmed that TRIM21 exacerbates post-MI cardiac remodeling by promoting M1 macrophage polarization. Lipopolysaccharide suppresses TRIM65 expression in macrophages and in C57BL/6J mice via activation of extracellular signal-regulated kinase 1/2

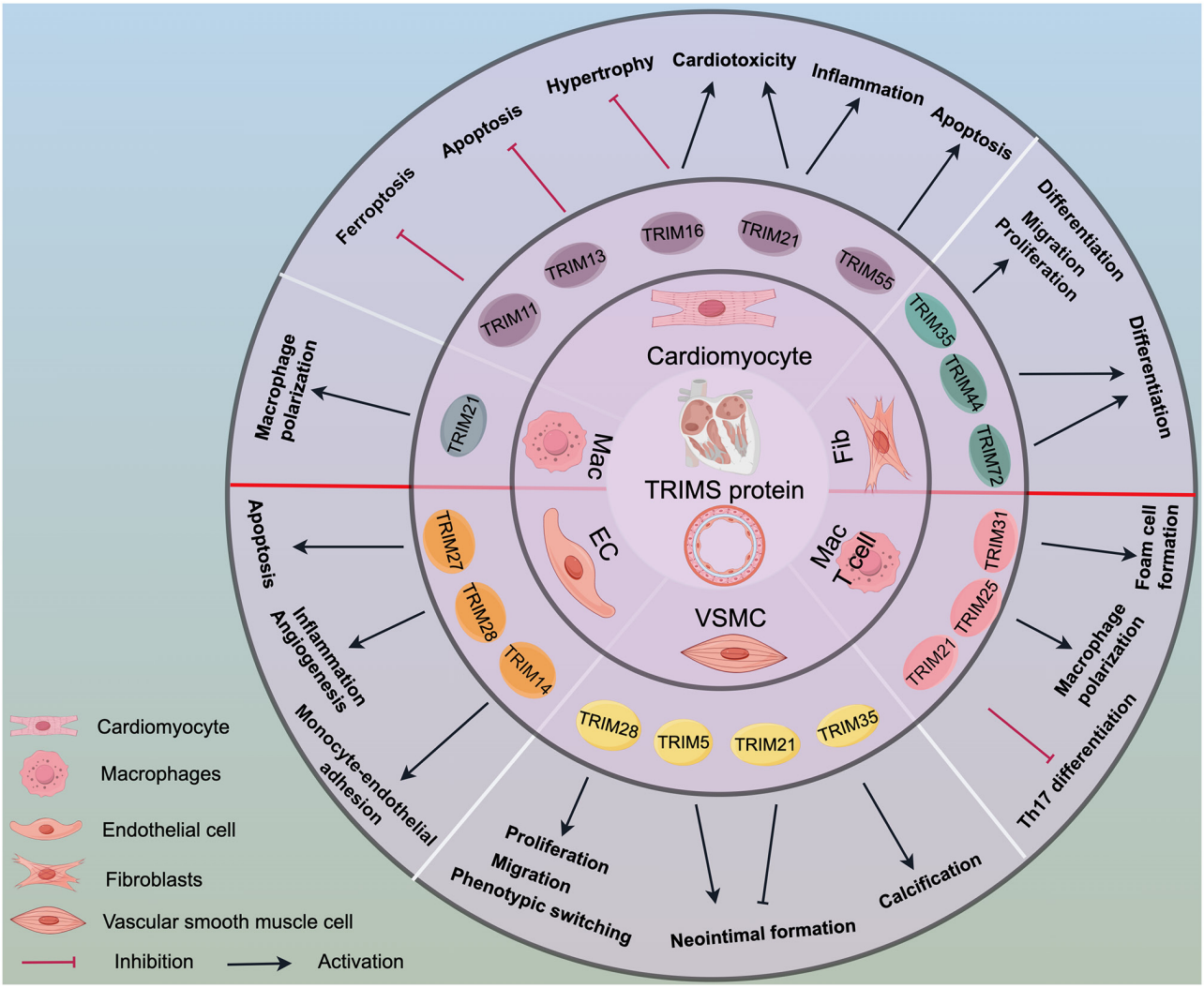


Figure 1. TRIM proteins functions in cardiovascular biology. TRIM proteins promote the migration and proliferation of VSMCs; facilitate inflammation, angiogenesis and adhesion of ECs and promote macrophages polarization and Th17 differentiation. TRIM proteins also regulate cardiomyocyte hypertrophy and apoptosis, ferroptosis, cardiotoxicity and activation of cardiac fibroblasts. TRIM, tripartite motif; VSMCs, vascular smooth muscle cells; ECs, endothelial cells; Fib, fibroblast; Mac, macrophage.

(ERK1/2) signaling (72). In monocytes, TRIM22-mediated apoptosis is closely associated with Bcl-2 homologous antagonist/killer oligomerization (73). Furthermore, TRIM proteins also modulate adaptive immune responses relevant to vascular disease. TRIM33 serves a pivotal role in dendritic cell differentiation and homeostasis by controlling transcription of interferon regulatory factor 8 and Bcl2-like 11 (74). Moreover, TRIM21 influences atherosclerosis by modulating T helper 17 (Th17) responses. TRIM21 deficiency enhances Th17 differentiation and promotes formation of collagen-rich, stable atherosclerotic plaques (75).

Across diverse vascular-associated cell types, converging evidence identifies TRIM proteins as integrative signaling nodes within the vascular-immune axis. By coordinating ubiquitin-dependent signaling among VSMCs, ECs, cardiomyocytes, fibroblasts and immune cells, TRIM proteins synchronize phenotypic plasticity, inflammatory activation and tissue remodeling (Fig. 1). Notably, the same TRIM protein may exert distinct, and occasionally opposing, effects depending on cell type, hemodynamic context and disease stage, underscoring the necessity of cell type and context-specific analyses. This integrative perspective provides a conceptual framework for understanding how dysregulated TRIM signaling drives cardiovascular pathology and suggests that therapeutic strategies targeting TRIM proteins will require precise modulation rather than indiscriminate inhibition. Advances in single-cell and spatial omics technologies are expected to further delineate TRIM-centered signaling networks within the cardiovascular microenvironment, thereby enabling cell-selective therapeutic interventions.

4. Roles of TRIM proteins in vascular diseases

Vascular diseases encompass a broad spectrum of pathological entities, including atherosclerosis, vascular calcification, aneurysm formation, pulmonary arterial hypertension (PAH) and microvascular dysfunction, which arise from chronic stress exposure and maladaptive remodeling of the vessel wall. Although these conditions differ in anatomical distribution and clinical presentation, they converge on shared pathogenic

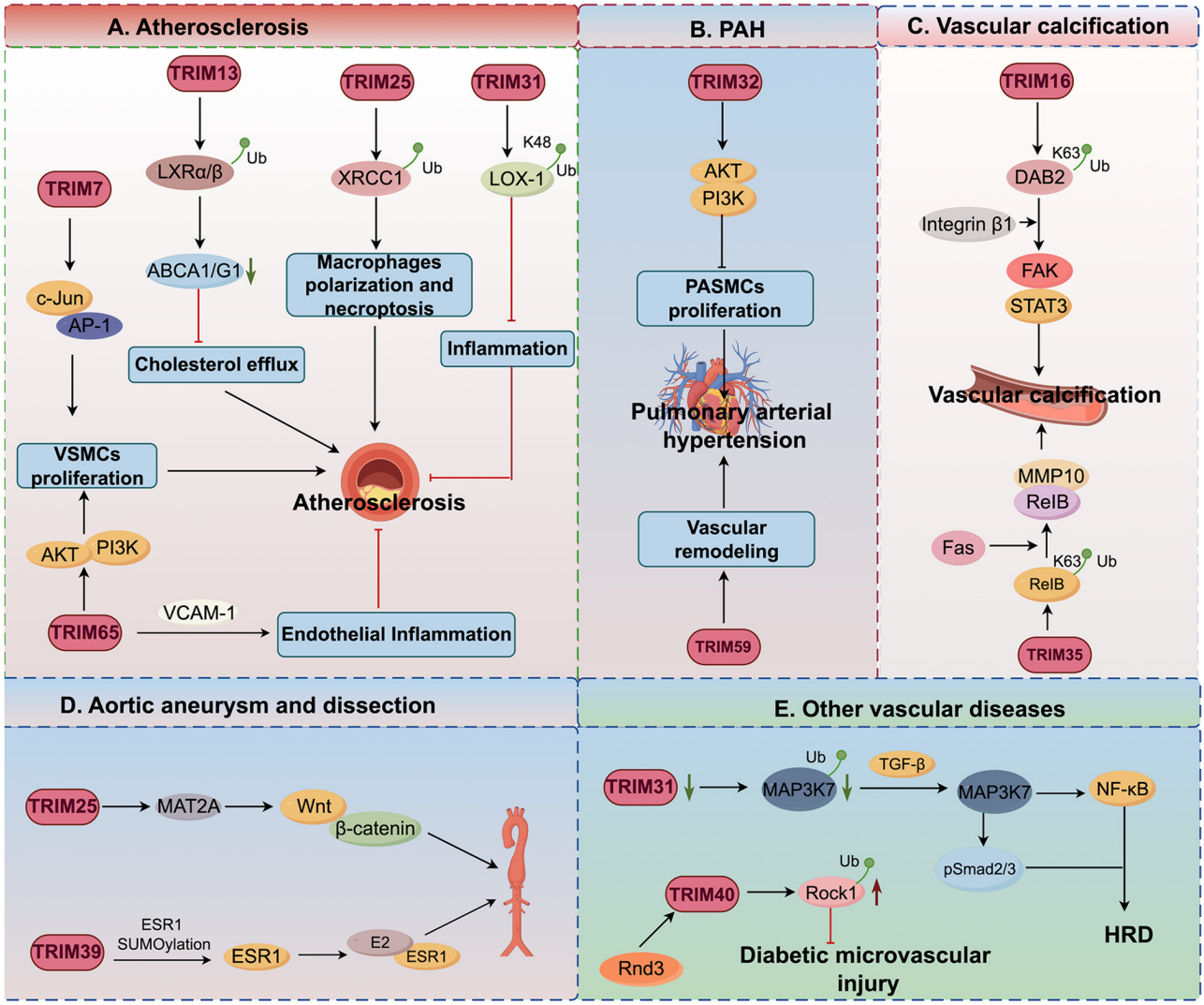


Figure 2. Roles of TRIM Proteins in Vascular Diseases. (A) In atherosclerosis, TRIM proteins could promote VSMC proliferation, endothelial inflammation, and macrophages polarization and necroptosis. TRIM13 promotes cholesterol efflux. TRIM31 inhibits inflammation. TRIM65 and TRIM7 promotes VSMCs proliferation. TRIM25 promotes macrophages polarization and necroptosis. (B) TRIM32 inhibits PASMCs proliferation and TRIM59 promotes vascular remodeling leading to PAH. (C) TRIM16 promotes VSMC calcification and aortic calcification. (D) In aortic aneurysm and dissection, TRIM25 promotes aortic aneurysm via regulating Wnt/β-catenin pathway. TRIM39 promote VSMC phenotypic transformation. (E) TRIM31 promote hypertensive nephropathy via regulating TGF-β1 signaling pathway. In diabetic microvascular injury, Rnd3 promotes the recruitment and interaction with TRIM40, facilitating endothelial integrity by ubiquitinating ROCK1. TRIM, tripartite motif; VSMC, vascular smooth muscle cell; ABCA1/G1, ATP-binding cassette transporters A1/G1; DAB2, disabled homolog 2; E2, 17β-estradiol; ESR1, estrogen receptor 1; FAK, focal adhesion kinase; LOX-1, lectin-like oxidized low-density lipoprotein receptor-1; LXR, liver X receptor; MAP3K7/TAK1, mitogen-activated protein kinase kinase kinase 7/transforming growth factor-β-activated kinase 1; MMP10, matrix metalloproteinase 10; PAH, pulmonary arterial hypertension; PASMC, pulmonary arterial smooth muscle cell; ROCK1, Rho-associated coiled-coil containing protein kinase 1; STAT3, signal transducer and activator of transcription 3; VCAM-1, vascular cell adhesion molecule-1; XRCC1, X-ray repair cross-complementing protein 1.

themes: Endothelial dysfunction, smooth muscle cell (SMC) phenotypic switching, immune activation, extracellular matrix remodeling and disruption of metabolic homeostasis. Increasing evidence places TRIM proteins at the intersection of these processes, acting as context-dependent regulators that shape the trajectory of vascular disease (Fig. 2).

Atherosclerosis. In recent years, TRIM proteins have been recognized as key regulators across multiple stages of atherogenesis, coordinating lipid metabolism, inflammatory signaling and cell death pathways through integrated actions in vascular and immune cells. TRIM7 promotes VSMC proliferation and migration through activation of c-Jun/AP-1 signaling, whereas TRIM7 knockdown disrupts this pathway, suppresses VSMC proliferation and attenuates atherosclerotic burden (76). In macrophages, several TRIM family members directly modulate foam cell formation and inflammatory activation. In Western diet-fed ApoE-deficient mice, TRIM13 promotes atherosclerosis by ubiquitinating liver X receptor α/β, downregulating ATP-binding cassette transporter A1/G1 expression, suppressing cholesterol efflux and enhancing oxidized low-density lipoprotein (ox-LDL) uptake, thereby accelerating foam cell formation and lesion progression (77). Under disturbed flow, endothelial TRIM21 promotes endothelial inflammation and atherogenesis by regulating the degradation of K48-linked MAPK6 (78). Loss of MAPK6

derepresses the EGR1/XXCL12 inflammatory axis and accelerates plaque formation. TRIM25-mediated ubiquitination of XRCC1 has been reported to accelerate atherosclerosis by promoting macrophage polarization toward an M1-like phenotype and triggering programmed cell death (79). More recently, macrophage-specific E3 ligase TRIM31 was shown to limit plaque development by promoting K48-linked ubiquitination of lectin-like oxidized LDL receptor-1 at lysine 12, thereby facilitating its degradation (80). Spectrin β nonerythrocytic 1 (SPTBN1), a key cytoskeletal component implicated in cell migration, apoptosis, adhesion and cell-cycle regulation, has also been linked to TRIM signaling in atherosclerosis. Overexpression of SPTBN1 attenuates oxidative stress and inflammation by engaging the TRIM37/TRAF2/NF-κB signaling axis, thereby mitigating atherosclerotic progression (81). TRIM64 enhances ox-LDL-induced foam cell formation, pyroptosis and inflammatory responses in THP-1-derived macrophages by promoting ubiquitination of IκBα at K67, thereby activating NF-κB signaling and establishing a positive feedback loop (82).

As well as immune cells, TRIM proteins also exert important functions in resident vascular wall cells. TRIM65 has been reported to promote atherosclerosis by activating the PI3K/Akt/mTOR pathway, thereby driving VSMC phenotypic switching from a contractile state toward a synthetic phenotype (83). By contrast, other evidence suggests that TRIM65 may exert protective effects by interacting with VCAM-1 to suppress ox-LDL-induced endothelial inflammatory activation, underscoring context-dependent actions of the same TRIM member (84). These opposing effects illustrate that the biological of TRIM65 is not fixed but is shaped by the cellular compartment and its accessible substrate repertoire and signaling architecture. Although VCAM-1 has been established as a direct ubiquitination substrate of TRIM65 in endothelial cells, the E3 substrate responsible for linking TRIM65 to PI3K/Akt/mTOR activation in VSMCs remains unresolved, representing an important mechanistic gap. Collectively, these findings position TRIM proteins as central coordinators of lipid-driven inflammation and intercellular crosstalk during atherogenesis, rather than isolated effectors acting within a single cell type.

Vascular calcification and aneurysm formation. Vascular calcification and aneurysm formation represent advanced manifestations of vascular remodeling, characterized by extracellular matrix degradation, altered mechanotransduction and impaired cell-matrix interactions. Emerging evidence suggests that TRIM proteins regulate these processes by controlling ubiquitin-dependent cytoskeletal dynamics, matrix turnover and signaling stability. The E3 ligase TRIM16 promotes vascular calcification in chronic kidney disease by catalyzing K63-linked ubiquitination of DAB2 at lysine 656, enhancing integrin β1 endocytosis and activating downstream focal adhesion kinase (FAK)-STAT3 signaling (27). Endothelial TRIM35 has been shown to regulate non-canonical NF-κB signaling via K63-linked polyubiquitination of RelB at lysines 242 and 327, thereby modulating the synthesis and secretion of MMP10 (85). Through endothelial paracrine signaling, this pathway drives aberrant osteogenic transdifferentiation of VSMCs and promotes graft vessel calcification. In the setting of diabetes-associated plaque microcalcification, recent work indicates that acetylation-ubiquitination crosstalk mediated by N-acetyltransferase 10 and TRIM32 promotes degradation of DJ-1, a multifunctional protein implicated in diabetic complications. DJ-1 depletion activates DJ-1/STAT1/receptor for advanced glycation end product signaling and facilitates microcalcification formation through collagen-matrix vesicle interactions (86).

TRIM proteins have also been implicated in aneurysmal disease. In a mouse model of thoracic aortic aneurysm, TRIM25 activates Wnt/β-catenin signaling by stabilizing methionine adenosyltransferase 2A (MAT2A) mRNA, thereby driving aneurysm development (87). TRIM25 deletion enhances VSMC viability, suppresses apoptosis and attenuates aneurysm formation, in part by binding MAT2A and limiting Wnt/β-catenin pathway activation. In intracranial aneurysm, tRF-AspGTC promotes VSMC phenotypic switching, increases MMP9 expression and induces oxidative stress and inflammation. Mechanistically, tRF-AspGTC binds galectin-3 and inhibits TRIM29-mediated ubiquitination of galectin-3, stabilizing galectin-3 and activating the Toll-like receptor 4 (TLR4)/myeloid differentiation primary response 88 (MyD88)/NF-κB axis, which further amplifies phenotypic switching and inflammation (88). Conversely, TRIM39 has been reported to enhance estrogen receptor 1 (ESR1) stability through SUMOylation, augmenting E2-ESR1 signaling and mitigating aortic dissection (89).

PAH. PAH is characterized by progressive pulmonary vascular remodeling driven by excessive SMC proliferation, endothelial dysfunction and metabolic dysregulation. TRIM proteins are increasingly recognized as regulators of these pathological processes. TRIM32 alleviates PAH by inhibiting pulmonary arterial SMC proliferation and migration through inactivation of the PI3K/Akt pathway (90). By contrast, TRIM59 overexpression promotes pulmonary vascular SMC proliferation and exacerbates PAH (91). TRIM29 has been reported to accumulate in the serum of patients with PAH and to promote proliferation and migration via activation of AKT/mTOR signaling. Overexpression of miR-637 or miR-661 reverses TRIM29-driven proliferation and migration in human pulmonary arterial SMCs, thereby improving hypoxia-induced PAH (92). Together, these observations suggest that TRIM proteins modulate the balance between pro-proliferative and anti-proliferative signaling within the pulmonary vasculature, positioning them as potential molecular determinants of PAH progression and therapeutic response.

Other vascular disorders. As well as large-vessel disease, TRIM proteins have been implicated in diverse vascular-related disorders. TRIM31 contributes to hypertensive nephropathy by promoting proteasomal degradation of MAP3K7 within the TGF-β1 signaling pathway (93). Recent evidence also implicates TRIM signaling in microvascular thrombosis during sepsis. NLRP6, a nucleotide-binding oligomerization domain-like receptor family member with cell type-specific pro- and anti-inflammatory functions, has been shown to protect against microvascular thrombosis in sepsis. Mechanistically, NLRP6 promotes the interaction between TRIM21 and TAB1 in activated platelets, leading

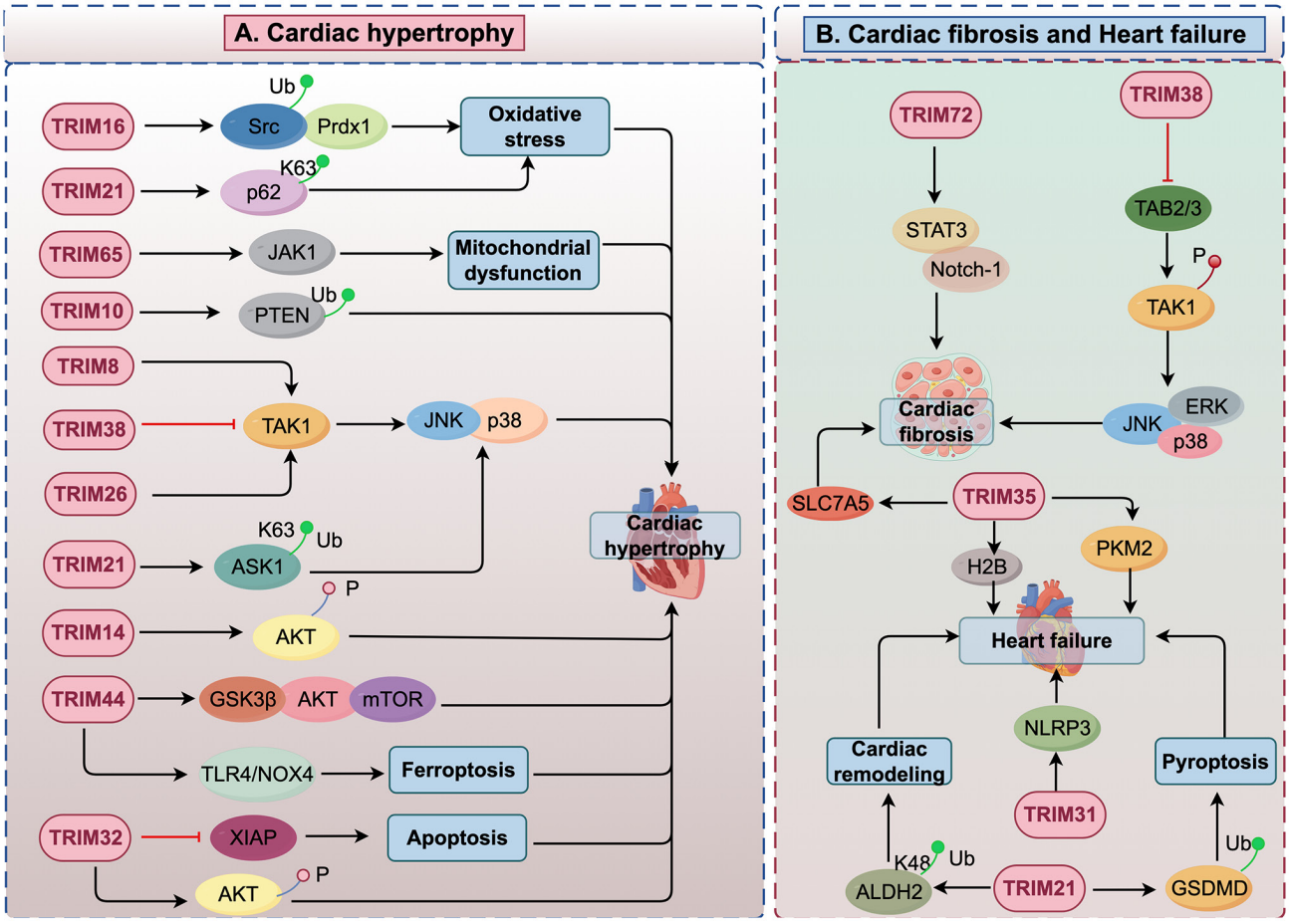


Figure 3. Role of TRIM proteins in cardiac hypertrophy, cardiac fibrosis and HF. (A) In cardiac hypertrophy, TRIM16 and TRIM21 promote oxidative stress, TRIM65 promotes mitochondrial dysfunction, TRIM8, TRIM26 and TRIM21 promote JNK/P38 pathway activation, TRIM44 promotes ferroptosis and TRIM32 inhibits apoptosis. (B) In terms of HF, TRIM21 promotes pyroptosis and cardiac remodeling, TRIM31 promotes inflammation. Furthermore, TRIM35 promotes HF and cardiac fibrosis. TRIM, tripartite motif; HF, heart failure; JNK, c-Jun N-terminal kinase; ALDH2, aldehyde dehydrogenase 2; ASK1, apoptosis signal-regulating kinase 1; GSDMD, gasdermin D; mTORC1, mechanistic target of rapamycin complex 1; NLRP3, NLR family pyrin domain containing 3; p62/SQSTM1, sequestosome 1; PKM2, pyruvate kinase M2; PTEN, phosphatase and tensin homolog; SLC7A5, solute carrier family 7 member 5; TAB2/3, TAK1-binding proteins 2/3; TAK1, transforming growth factor-β-activated kinase 1.

to K48-linked polyubiquitination and subsequent degradation of TAB1 (94). In addition, septic plasma can trigger NLRP6/TRIM21-mediated TAB1 degradation in healthy platelets through TLR4-MyD88 signaling (94). In diabetic microvascular injury, Rnd3 has been reported to protect endothelial function and vascular homeostasis by promoting TRIM40-mediated ubiquitination of ROCK1 (95). TRIM44 is highly expressed in diabetic rats and in high glucose-stimulated retinal microvascular ECs (RMECs); TRIM44 knockdown markedly reduces high glucose-induced RMEC viability, proliferative, migratory, invasive and angiogenic capacity, and TRIM44 has been identified as a transcriptional target of Krüppel-like factor 9 (96). In the context of cerebral ischemia-reperfusion (I/R) injury, TRIM45 exacerbates neuronal injury by amplifying microglia-mediated neuroinflammation (97) and TRIM56 aggravates I/R injury by enhancing KLF4-driven proapoptotic signaling (98). Although these disorders differ anatomically, they converge on common pathogenic themes, including chronic inflammation, aberrant ubiquitin signaling and maladaptive tissue remodeling, reinforcing the concept that TRIM proteins function as versatile regulators across vascular beds.

5. Roles of TRIM proteins in cardiac diseases

Cardiac diseases comprise a spectrum of pathological states driven by sustained biomechanical stress, ischemic injury, metabolic imbalance and inflammatory activation. Despite distinct etiologies, conditions such as cardiac hypertrophy, HF, MI and cardiomyopathies (Fig. 3) converge on shared cellular programs, including cardiomyocyte stress adaptation, regulated cell death, fibroblast activation, immune infiltration and metabolic reprogramming. Accumulating evidence identifies TRIM proteins as key regulators across this continuum, integrating ubiquitin-mediated signaling with redox control, inflammation and transcriptional programs to shape the trajectory of cardiac disease (Table I).

HF. HF reflects the progressive collapse of adaptive stress responses, ultimately resulting in impaired contractility, insufficient metabolic reserve and persistent inflammation. Increasing data suggest that TRIM proteins function as pivotal determinants of whether cardiomyocytes and non-myocyte populations mount compensatory adaptations or enter irreversible remodeling programs. In post-MI HF, TRIM21 was

Table I. Representative preclinical and clinical evidence linking TRIM proteins to cardiovascular diseases.

Authors, year	Disease/type of evidence	Member	Targets	Expression	Model/population	Condition/intervention	Molecular action	(Refs.)
Ji *et al*, 2020	Atherosclerosis (preclinical)	TRIM7	c-Jun/AP-1	Up	ApoE$^{-/-}$ mice; VSMCs	HFD diet feeding; PDGF-BB treatment *in vitro*	Pathway activation: activates c-Jun/AP-1 signaling, promoting VSMC proliferation/migration and atherosclerotic progression.	(76)
Govatati *et al*, 2024	Atherosclerosis (preclinical)	TRIM13	LXRα/β	Up	ApoE$^{-/-}$ mice; VSMCs; macrophages	WD feeding; interleukin-1β treatment *in vitro*	Direct ubiquitination: promotes ubiquitination and degradation of LXRα/β, suppressing ABCA1/G1-dependent cholesterol efflux and promoting foam-cell formation.	(77)
Wang *et al*, 2025	Atherosclerosis (preclinical)	TRIM 21	MAPK6	Up	ApoE$^{-/-}$ mice; HUVECs	WD feeding; disturbed shear stress treatment *in vitro*	Direct ubiquitination: TRIM21-dependent proteasomal degradation of MAPK6 enhances endothelial inflammatory signaling under disturbed shear stress.	(78)
Wu *et al*, 2024	Atherosclerosis (clinical and preclinical)	TRIM 25	XRCC1	Down	CTO patient (n=14) vs. non-CTO coronary stenosis (n=20); ApoE$^{-/-}$ mice; macrophages	Serum samples; HFD diet feeding; ox-LDL treatment *in vitro*	Direct ubiquitination: ubiquitinates XRCC1, promoting macrophage M1 polarization and programmed cell death; TRIM25 deficiency reduces plaque burden.	(79)
Zhang *et al*, 2026	Atherosclerosis (preclinical)	TRIM 31	LOX-1	Up	Macrophage-specific TRIM31 knockout ApoE$^{-/-}$ mice; macrophages	WD feeding; ox-LDL treatment *in vitro*	Direct ubiquitination: promotes K48-linked ubiquitination of LOX-1 at K12 and its proteasomal degradation, limiting foam-cell formation.	(80)
Zhu *et al*, 2023	Atherosclerosis (preclinical)	TRIM 64	IκBα/NF-κB	Up	ApoE$^{-/-}$ mice; THP-1-derived macrophages	Fat-rich diet feeding; ox-LDL treatment *in vitro*	Direct ubiquitination: promotes K48-linked IκBα ubiquitination and NF-κB activation, enhancing foam-cell formation, pyroptosis and inflammation.	(82)
Zhou *et al*, 2024	Atherosclerosis (clinical and preclinical)	TRIM 65	PI3K/AKT	Up	Human atherosclerotic lesions (paired specimens); ApoE$^{-/-}$ mice; VSMCs	Autopsy; Western diet feeding; PDGF-BB treatment *in vitro*	Pathway activation: activates PI3K/Akt/mTOR signaling and drives VSMC phenotypic switching toward a synthetic state.	(83)
Ma *et al*, 2024	Atherosclerosis (preclinical)	TRIM 65	VCAM-1	Up	TRIM65 knockout ApoE$^{-/-}$ mice; HUVECs	WD feeding; ox-LDL treatment *in vitro*	Protein interaction/protein stability: interacts with VCAM-1 and reduces VCAM-1-dependent endothelial inflammation and monocyte adhesion.	(84)

Table I. Continued.

Authors, year	Disease/type of evidence	Member	Targets	Expression	Model/population	Condition/intervention	Molecular action	(Refs.)
Lan *et al*, 2025	Vascular Calcification (preclinical)	TRIM 16	DAB2	Up	SMC-specific TRIM16 knockout mice; rat; VSMCs	Adenine-induced CKD mouse; 5/6-nephrectomy rat; high-phosphates treatment *in vitro*	Direct ubiquitination/pathway activation: catalyzes K63-linked ubiquitination of DAB2 at K656, facilitating integrin β1 endocytosis and FAK-STAT3 signaling.	(27)
Leng *et al*, 2025	Vascular graft Calcification (preclinical)	TRIM 35	ReIB	Up	C57BL/6J mice; primary mice endothelial cells	Arterial isograft transplantation;	Direct ubiquitination: promotes K63-linked ubiquitination of RelB, maintains nuclear RelB and restrains MMP10 transcription/release; endothelial loss aggravates calcification	(85)
Li *et al*, 2024	Aortic aneurysm (preclinical)	TRIM 25	MAT2A	Up	C57BL/6J mice; VSMCs	β-aminopropionitrile-induced TAA; Ang II-treatment *in vitro*	Post-transcriptional regulation: binds MAT2A and destabilizes MAT2A mRNA, activating Wnt/β-catenin signaling and exacerbating TAA injury; direct ubiquitination was not established.	(87)
Hu *et al*, 2023	PAH (clinical and preclinical)	TRIM 32	PI3K/AKT	Down	PAH patient (n=35) and healthy volunteers (n=35) plasma; PASMCs	Hypoxia-treatment *in vitro*	Pathway regulation: inhibits PI3K/Akt activation, restraining PASMC proliferation/migration and promoting a contractile phenotype.	(90)
Lin *et al*, 2025	Heart failure (preclinical)	TRIM 21	GSDMD	Up	C57BL/6J mice; cardiomyocytes	LAD-ligation; hypoxia-treatment *in vitro*	Direct ubiquitination: promotes GSDMD ubiquitination and cardiomyocyte pyroptosis; myocardial TRIM21 knockdown reduces fibrosis and later dysfunction.	(99)
Han *et al*, 2026	Heart failure (preclinical)	TRIM21	ALDH2	Up	C57BL/6J mice; macrophage	LAD-ligation;	Direct ubiquitination: promotes K48-linked ubiquitination of ALDH2 at lysine 73, impair macrophage efferocytosis and accelerate post-MI fibrosis	(100)
Duan *et al*, 2025	Heart failure (preclinical)	TRIM 31	NLRP3	Down	TRIM31 knockout C57BL/6J mice	ISO induced HF	Pathway regulation: restrains NLRP3 inflammasome activation; TRIM31 deficiency worsens inflammation, hypertrophy, fibrosis and cardiac dysfunction.	(102)

Table I. Continued.

Authors, year	Disease/type of evidence	Member	Targets	Expression	Model/population	Condition/intervention	Molecular action	(Refs.)
Lorenzana *et al*, 2024	Heart failure (clinical and preclinical)	TRIM 35	H2B	Down	Human nonischemic DCM LV vs. nonfailing LV; cardiomyocyte-specific TRIM35-OE mouse; primary cardiomyocytes	Age-depended dilated cardiomyopathy	Direct ubiquitination: monoubiquitinates H2B at K120, increasing chromatin accessibility and p53 transcriptional activity; cardiomyocyte TRIM35 overexpression initiates HF.	(103)
Lorenzana *et al*, 2022	Heart failure (preclinical)	TRIM35	PKM2	Down	C57BL/6N mice; cardiomyocyte	TAC surgery;	Ubiquitin-mediated degradation: facilitates degradation of nuclear PKM2; promotes cardiomyocyte dysfunction.	(104)
Chen *et al*, 2017	Cardiac Hypertrophy (preclinical)	TRIM8	TAK1	Up	C57BL/6N mice; neonatal rat cardiomyocytes	TAC surgery; Ang II treatment *in vitro*	Direct ubiquitination: promotes TAK1 ubiquitination/activation and downstream p38/JNK signaling, driving pathological hypertrophy.	(107)
Yang *et al*, 2020	Cardiac Hypertrophy (preclinical)	TRIM10	PTEN	Up	TRIM10 knockout C57BL/6J mice; neonatal rat cardiomyocytes	TAC surgery; PE-treatment *in vitro*	Direct ubiquitination: binds PTEN and promotes its ubiquitination/degradation, activating Akt-dependent hypertrophic signaling.	(108)
Hou *et al*, 2023	Cardiac Hypertrophy (preclinical)	TRIM14	AKT	Up	TRIM14 knockout C57BL/6J mice; neonatal rat cardiomyocytes	TAC surgery; PE-treatment *in vitro*	Increases the phosphorylation levels of AKT	(109)
Liu *et al*, 2022	Cardiac Hypertrophy (preclinical)	TRIM16	Src, Prdx1	Up	C57BL/6J mouse; cardiomyocyte	TAC surgery; PE-treatment *in vitro*	Direct ubiquitination: promotes Src ubiquitin-dependent degradation, limits Prdx1 phosphorylation and activates Prdx1-Nrf2 antioxidant signaling.	(110)
Shi *et al*, 2025	Cardiac Hypertrophy (preclinical)	TRIM 21	ASK1	Up	C57BL/6J mouse; neonatal rat cardiomyocytes	TAC surgery; PE-treatment *in vitro*	Direct ubiquitination: catalyzes K63-linked polyubiquitination of ASK1 at K1064, activating ASK1-JNK/p38 signaling.	(111)
Xia *et al*, 2025	Cardiac Hypertrophy (preclinical)	TRIM26	TAK1	Up	C57BL/6J mouse; neonatal rat cardiomyocytes	TAC surgery; PE-treatment *in vitro*	Promotes the TAK1/Jun signaling pathway	(113)

Table I. Continued.

Authors, year	Disease/type of evidence	Member	Targets	Expression	Model/population	Condition/intervention	Molecular action	(Refs.)
Chen *et al*, 2016	Cardiac Hypertrophy (preclinical)	TRIM32	Not study yet	Down	Human DCM heart; C57BL/6J mouse; neonatal rat cardiomyocytes	TAC surgery; Ang II-treatment *in vitro*	Inhibits the AKT signaling pathways	(114)
Pang *et al*, 2025	Cardiac Hypertrophy (preclinical)	TRIM 38	TAK1	Down	C57BL/6J mouse; neonatal rat cardiomyocytes	TAC surgery; PE-treatment *in vitro*	Pathway regulation: suppresses TAK1/JNK/p38 signaling; loss of TRIM38 exacerbates pressure-overload hypertrophy.	(116)
Wu *et al*, 2023	Cardiac Hypertrophy (preclinical)	TRIM 44	TLR4	Up	C57BL/6J mouse; H9c2	TAC surgery; Ang II-treatment *in vitro*	Increases TLR4/NOX4-associated ferroptosis	(117)
Maejima *et al*, 2014	Cardiac Hypertrophy (preclinical)	TRIM 63	Calcineurin A	Down	C57BL/6J mouse	TAC surgery	Polyubiquitinates CnA	(119)
Liu *et al*, 2023	Cardiac Hypertrophy (preclinical)	TRIM 65	Jak1	Up	TRIM65-knockout C57BL/6J mouse	ISO treatment *in vivo*	Regulates the ubiquitination of Jak1	(120)
Guo *et al*, 2024	DIC (preclinical)	TRIM 16	TAK1	Up	C57BL/6J mouse; neonatal rat cardiomyocytes	DOX treatment *in vivo* and *in vitro*	Direct ubiquitination: enhances ubiquitination/degradation of p-TAK1, restrains JNK/p38 signaling and promotes YAP-Nrf2 antioxidant responses.	(121)
Hou *et al*, 2021	DIC (preclinical)	TRIM 21	P62	Up	TRIM65-knockout C57BL/6J mouse; H9c2 and AC16 cardiomyocytes	DOX treatment and LAD-ligation	Direct ubiquitination: interacts with and ubiquitinates p62, negatively regulating the p62-Keap1-Nrf2 antioxidant axis; TRIM21 loss reduces ferroptotic injury.	(122)
Shen *et al*, 2022	DIC (preclinical)	TRIM 25	p85α	Down	C57BL/6J mouse; neonatal mouse ventricular cardiomyocytes	DOX treatment *in vivo* and *in vitro*	Direct ubiquitination/protein stability: promotes p85α ubiquitination/degradation, facilitating XBP1s nuclear translocation and reducing ER stress/poptosis.	(123)
Wang *et al*, 2021	DIC (preclinical)	TRIM25	NLRP1	Down	C57BL/6J mouse; H9c2 cardiomyocytes	DOX treatment *in vivo* and *in vitro*	Promotes ubiquitination	(124)

Table I. Continued.

Authors, year	Disease/type of evidence	Member	Targets	Expression	Model/population	Condition/intervention	Molecular action	(Refs.)
Ma *et al*, 2025	DIC (preclinical)	TRIM 65	P53	Down	C57BL/6J mouse; H9c2 cardiomyocytes	DOX treatment *in vivo* and *in vitro*	Inhibits the degradation of p53	(125)
Jiang *et al*, 2024	DIC (preclinical)	TRIM72	P53	Down	C57BL/6J mouse; neonatal rat cardiomyocytes	DOX treatment *in vivo* and *in vitro*	Increases p53 ubiquitination	(126)
Liu *et al*, 2015	DCM (Preclinical)	TRIM 72	PPAR-α	Down	C57BL/6J mouse; Neonatal rat ventricular myocytes	Palmitate treatment *in vitro*	Enhances the expression of PPAR-α	(145)
Liu *et al*, 2018	Viral myocarditis (preclinical)	TRIM21	MAVS	Up	BALB/c mouse; primary cardiomyocytes	CVB3-infection	Direct ubiquitination: promotes K27-linked polyubiquitination of MAVS, enhancing IRF3/type-I interferon signaling and antiviral defense.	(148)
Song *et al*, 2026	Autoimmune myocarditis (preclinical)	TRIM21	TRAF3	Up	TRIM21-defcient C57BL/6J mouse; IL-17A-stimulated cardiac fibroblasts	EAM mouse; IL-17A-stimulated *in vitro*	Direct ubiquitination: promotes K27-linked ubiquitination and lysosomal degradation of TRAF3, amplifying IL-17A signaling.	(149)
Wang *et al*, 2024	Viral myocarditis (preclinical)	TRIM29	PERK	Up	FLP-deleted mice; neonatal mouse cardiomyocytes; AC16	CVB3-infection	Promotes PERK SUMOylation	(151)
Xue *et al*, 2024	Viral myocarditis (preclinical)	TRIM72	NF-κB	Down	BALB/c mice; HL-1 cells	CVB3-infection	Pathway regulation: MG53 overexpression suppresses NF-κB/NLRP3 inflammasome signaling and pyroptosis, reducing myocardial injury.	(150)
Xiong *et al*, 2025	Myocarditis (preclinical)	TRIM28	NA	Down	$TRIM28^{iCKO}$ mice	Myocardial ischemia/reperfusion	Regulates TLR7/9-NF-κB signaling pathway	(152)
Zhang *et al*, 2020	Atrial fibrillation/fibrosis (preclinical)	TRIM72	CAV1	Up	Rat atrial fibroblast	Ang II-treatment *in vitro*	Protein interaction: interacts with CAV1 and enhances TGF-β1/SMAD signaling, promoting atrial fibrosis.	(153)
Tian *et al*, 2026	Septic cardiomyopathy (preclinical)	TRIM72	ATF2	Down	C57BL/6J mouse	LPS treatment *in vivo*	Direct ubiquitination: promotes ubiquitin-dependent degradation of ATF2, suppressing ATF2-driven TLR4 transcription and inflammatory/apoptotic injury.	(155)

Table I. Continued.

Authors, year	Disease/type of evidence	Member	Targets	Expression	Model/population	Condition/intervention	Molecular action	(Refs.)
Yang *et al*, 2024	Septic cardiomyopathy (preclinical)	TRIM10	NA	Up	SCM rat model	LPS treatment *in vivo*	NA	(156)

Up/down vs. normal control. ABCA1, ATP binding cassette subfamily A member 1; ATF2, activating transcription factor-2; ASK1, apoptosis signal-regulating kinase 1; AKT, protein kinase A; CAV1, caveolin-1; DAB2, disabled homolog 2; DCM, diabetic cardiomyopathy; DIC, doxorubicin-induced cardiotoxicity; EMA, experimental autoimmune myocarditis; FAK, focal adhesion kinase; LAD, left anterior descending coronary artery; LOX-1, lectin-like oxidized low-density lipoprotein receptor-1; LXR, liver X receptor; PASMC, pulmonary artery smooth muscle cells; PPAR-α, peroxisome proliferation-activated receptor alpha; WD, western diet; HFD, high fat diet; TAA, thoracic aortic aneurysm; TAC, transverse aortic constriction; TLR4, Toll-like receptor 4; TRAF3, Tumor necrosis factor (TNF) receptor-associated factor 3; LPS, lipopolysaccharide; LXRα/β, liver X receptor α/β; ISO, isoproterenol; NF-κB, nuclear factor-κB; SCM, Septic cardiomyopathy; SMAD, Small mothers against decapentaplegic; MAT2A, methionine adenosyltransferase 2A; NLRP1/3, NLR family pyrin domain containing 1/3; p-TAK1, phosphorylated transforming growth factor-β-activated kinase 1; PTEN, phosphatase and tensin homolog; PE, phenylephrine; PERK, protein kinase RNA-like endoplasmic reticulum kinase; PKM2, Pyruvate kinase M2; VCAM-1, vascular cell adhesion molecule-1; VSMC, vascular smooth muscle cell; XRCC1, X-ray repair cross-complementing protein 1; NA, No study yet.

shown to promote hypoxia-induced cardiomyocyte pyroptosis by mediating ubiquitination of gasdermin D, thereby accelerating functional deterioration. Further evidence indicates that HDAC6 modulates TRIM21 expression and amplifies pyroptotic signaling, highlighting the potential relevance of a TRIM-epigenetic regulatory axis in HF (99). TRIM21 directly binds the aldehyde dehydrogenase 2 (ALDH2) rs671 variant and catalyzes K48-linked polyubiquitination predominantly at ALDH2 K73, accelerating proteasomal degradation, impairing macrophage efferocytosis and worsening post-MI fibrosis and systolic dysfunction (100). TRIM24 has been implicated in the maintenance of contractile function and Ca^{2+} homeostasis through regulation of chromatin remodeling and Ca^{2+} handling pathways. TRIM24 overexpression markedly alters the expression of ryanodine receptor 2, sarco/endoplasmic reticulum (ER) Ca^{2+}-ATPase 2a and calsequestrin 1, thereby disrupting Ca^{2+} cycling and promoting decompensation (101). Duan *et al* (102) reported that TRIM31 deficiency aggravates cardiac remodeling in murine HF models by enhancing NLRP3 inflammasome activation, resulting in worsened cardiac function accompanied by increased hypertrophy and fibrosis. At the transcriptional and chromatin level, TRIM35 has emerged as an important regulator of HF progression. TRIM35 mediates monoubiquitination of histone H2B at lysine 120 in cardiac cells, thereby promoting chromatin remodeling and reshaping cardiomyocyte transcriptional programs (103). In addition, TRIM35 facilitates degradation of nuclear pyruvate kinase M2, destabilizes key cardiac transcription factors GATA4/6, and induces p53 activation, collectively promoting cardiomyocyte dysfunction and HF progression (104). Population-based studies have further suggested genetic and functional relevance of TRIM55 exon variants in HF, supporting a potential role for TRIM proteins in HF susceptibility and interindividual heterogeneity (105). In a rat model of HF with preserved ejection fraction (HFpEF), MuRF1 substantially improved diastolic function while concurrently enhancing skeletal muscle contractile performance, providing proof-of-concept for therapeutically targeting TRIM proteins. Inflammation and regulated cell death are major drivers of HF progression (106). Together, these findings establish TRIM proteins as central regulators of stress integration and maladaptive remodeling in HF, while the extent of human causal evidence remains limited.

Cardiac fibrosis. Cardiac fibrosis is a defining feature of chronic heart disease, driven by sustained fibroblast activation and excessive extracellular matrix deposition. TRIM proteins regulate fibrotic remodeling by controlling signaling pathways that govern fibroblast proliferation, differentiation, senescence and autophagic flux. For example, TRIM35 triggers cardiac remodeling by regulating solute carrier family 7 member 5-dependent amino acid transport and mTORC1 activation in fibroblasts (61). Another study showed that TRIM38 suppressed the proliferation and secretion of CFs after MI through promoting TAB2/3 degradation and suppressing TAK1 activation, ultimately alleviated cardiac fibrosis (63). In addition, a recent study identified a key modulator Kdm4a (histone demethylase) in cardiac fibrosis (64). A further study demonstrated that Kdm4a promotes interstitial fibrosis after MI by enhancing Trim44-mediated autophagy, ultimately resulting

in cardiac remodeling (64). TRIM72 regulates rat cardiac fibroblast proliferation and migration via regulating TGF-β signaling and promotes fibrosis through STAT3/Notch-1 signaling (66).

Cardiac hypertrophy. Pathological cardiac hypertrophy represents a key intermediate stage through which numerous cardiovascular diseases progress to HF. It reflects a transition from adaptive compensation to decompensated remodeling under sustained mechanical load and neurohumoral stimulation. Extensive evidence indicates that TRIM proteins act as core regulators of this transition by controlling ubiquitin-dependent signaling pathways. In TAC-induced murine hypertrophy, TRIM8 exacerbates hypertrophy by ubiquitinating TAK1 and enhancing TAK1-p38/JNK signaling (107). TRIM10 contributes to hypertrophic remodeling by ubiquitinating phosphatase and tensin homolog (PTEN) and modulating the PTEN/AKT axis (108). TRIM14 promotes hypertrophic responses in neonatal rat cardiomyocytes and transgenic mice through AKT activation (109). TRIM16 has been identified as a key inhibitor of pathological hypertrophy: By promoting K48-linked ubiquitination and proteasomal degradation of Src, TRIM16 reduces peroxiredoxin 1 phosphorylation, activates downstream Nrf2 antioxidant signaling, alleviates oxidative stress and suppresses cardiomyocyte hypertrophy (110). TRIM21 has been reported to enhance apoptosis signal-regulating kinase 1 (ASK1) activation via K63-linked polyubiquitination at ASK1 lysine 1064, thereby engaging JAK/p38 MAPK signaling and aggravating hypertrophy (111). In redox regulation, TRIM21 maintains intracellular redox balance by mediating K63-linked ubiquitination of p62/SQSTM1, suppressing protein aggregation (112). Consistently, the cardiomyocyte deubiquitinase USP28 promotes hypertrophy by deubiquitinating TRIM21, weakening antioxidant responses (29). TRIM26 similarly promotes pressure overload-induced hypertrophy via TAK1-related signaling (113). Conversely, several TRIM proteins exhibit antihypertrophic functions. TRIM32 suppresses and prevents pressure overload-induced hypertrophy by antagonizing AKT-dependent signaling (114) and further restrains hypertrophic growth through ubiquitination of dysbindin (115). Trim38 also attenuates pressure overload-induced hypertrophy by inhibiting TAK1/JNK/p38 signaling (116), further emphasizing TAK1 as a central hub in TRIM-mediated remodeling.

As well as growth signaling, TRIM proteins modulate hypertrophy through control of regulated cell death and metabolic homeostasis. TRIM44 aggravates hypertrophy via activation of a TLR4/NADPH oxidase 4-dependent ferroptosis pathway (117), whereas cardiomyocyte-specific Trim44 deletion mitigates isoproterenol-induced remodeling through suppression of AKT/mTOR signaling (118). MuRF1 negatively regulates pathological hypertrophy by downregulating calcineurin A (119). Notably, studies of muscle atrophy indicate that myofibrillar degradation is a delayed event dependent on transcription factor paired box 4 activation and desmin depolymerization, suggesting temporal specificity in TRIM-mediated regulation of muscle structural homeostasis (114). Trim65 attenuates isoproterenol-induced hypertrophy by promoting autophagy and improving mitochondrial function through Jak1/Stat1 signaling (120). Overall, TRIM proteins exert bidirectional regulation of pathological hypertrophy by integrating growth signaling, oxidative stress, regulated cell death and proteostasis. Their context-dependent functions underscore the importance of precise and temporally controlled modulation of specific TRIM-centered pathways, rather than global inhibition, as a promising strategy to prevent hypertrophy and halt progression to HF.

Doxorubicin (DOX)-induced cardiotoxicity. DOX-induced cardiotoxicity (DIC) is a major limitation to its clinical antineoplastic use. Its pathobiology involves oxidative stress imbalance, ferroptosis, mitochondrial dysfunction and coordinated activation of multiple forms of regulated cell death, including apoptosis and pyroptosis. Studies indicate that TRIM family proteins integrate these stress responses through ubiquitin-dependent control of key signaling nodes and thereby influence cardiomyocyte fate (Fig. 4) (30,121,122).

In murine DOX cardiotoxicity models, TRIM16 mitigates injury by ubiquitinating phosphorylated TAK1, restraining excessive activation of JNK and p38/MAPK pathways, while increasing Yes-associated protein (YAP) abundance and nuclear translocation to enhance Nrf2 transcriptional activity, ultimately reducing oxidative stress and inflammation (121). This work delineates a TRIM16/TAK1/YAP/Nrf2 axis as a key protective pathway in DOX-induced myocardial injury. Hou *et al* (122) reported that TRIM21 negatively regulates the p62/Keap1/Nrf2 antioxidant axis via p62 ubiquitination, thereby suppressing DOX-induced cardiomyocyte ferroptosis and alleviating cardiotoxicity. By contrast, the deubiquitinase MYSM1 interacts with TRIM21 via its MPN domain to promote TRIM21 deubiquitination, augment ferroptotic signaling and exacerbate DOX-induced cardiac injury, underscoring the importance of dynamic TRIM-deubiquitinase balance in ferroptosis control (30).

TRIM25 exerts cardioprotection by ubiquitinating the PI3K regulatory subunit p85α, promoting nuclear translocation of XBP-1s and thereby attenuating DOX-induced ER stress and apoptosis (123). Mutational analysis implicated p85α K506 and K511 as ubiquitination-sensitive residues, although the study did not definitively assign a single ubiquitin-chain topology. Consistently, TRIM25 also suppresses cardiomyocyte pyroptosis through ubiquitination of NLRP1, conferring protection in DOX-related myocardial injury (124). TRIM65 has been reported to inhibit cardiomyocyte ferroptosis by ubiquitinating p53, thereby mitigating DOX-induced injury (125). Jiang *et al* (126) observed that DOX markedly reduces myocardial MG53 expression in murine DIC models, whereas MG53 overexpression suppresses ferroptosis via the p53/SLC7A11/glutathione peroxidase 4 axis and alleviates cardiotoxicity. Notably, other work reported that MG53 may aggravate DOX-induced cardiomyocyte apoptosis by reducing AKT phosphorylation (127), further highlighting the context dependence of TRIM function. Overall, these studies support a central role for TRIM proteins in DOX-induced cardiotoxicity by integrating oxidative stress, ferroptosis, inflammation and multiple regulated cell death pathways. This highly plastic and microenvironment-dependent regulation suggests that selective targeting of specific TRIM-centered signaling axes

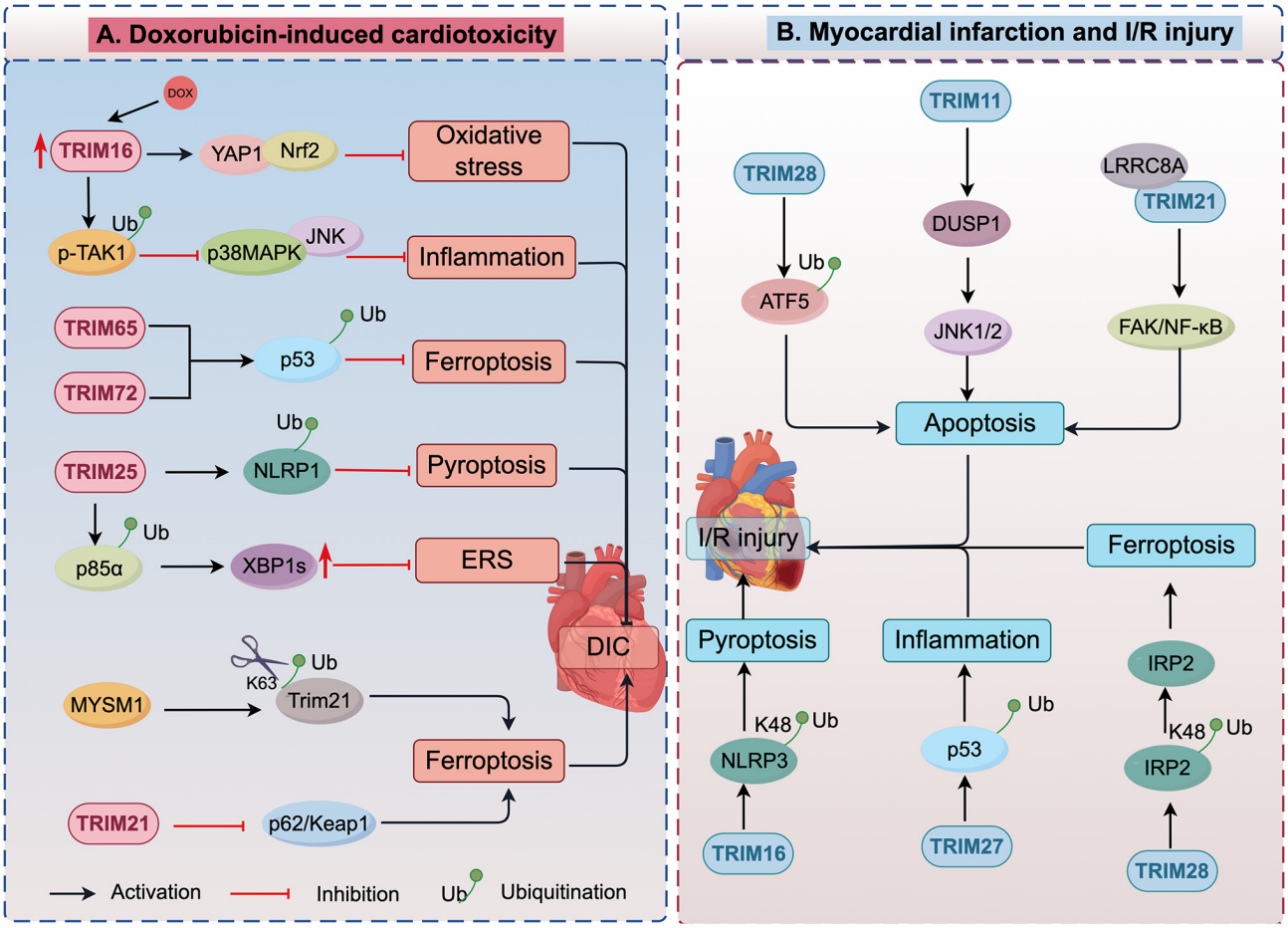


Figure 4. Role of TRIM proteins in DOX-induced cardiotoxicity and myocardial I/R injury. (A) In doxorubicin-induced cardiotoxicity, TRIM16 is protective by promoting ubiquitination of phosphorylated TAK1, restraining JNK/p38-associated oxidative and inflammatory signaling, and enhancing YAP/Nrf2 signaling. TRIM25 attenuates endoplasmic reticulum stress and apoptosis through p85α ubiquitination and suppresses pyroptosis through NLRP1 ubiquitination. TRIM65 and MG53/TRIM72 have been reported to suppress ferroptotic injury through p53-associated mechanisms, whereas TRIM21 promotes ferroptosis by suppressing the p62-Keap1-Nrf2 antioxidant pathway; MYSM1 stabilizes TRIM21 and potentiates this axis. The reported effect of MG53 in DOX injury is model and endpoint-dependent because a separate study reported increased apoptosis. (B) During myocardial I/R injury, TRIM16 promotes K48-linked ubiquitination and degradation of NLRP3 to reduce pyroptosis and inflammation; TRIM27 has been reported to suppress p53-associated apoptosis and inflammation; TRIM28 promotes K48-linked ubiquitination of IRP2 and suppresses ferroptosis; and the LRRC8A/TRIM21 axis promotes apoptosis through inhibition of FAK/NF-κB signaling. A previously reported TRIM11-DUSP1-JNK1/2 pro-injury mechanism has been retracted and is not used as supporting evidence. TRIM, tripartite motif; DOX, doxorubicin; I/R, ischemia/reperfusion; p-TAK1, phosphorylated transforming growth factor-β-activated kinase 1; YAP, Yes-associated protein; Nrf2, nuclear factor erythroid 2-related factor 2; NLRP1/3, NLR family pyrin domain containing 1/3; MG53, mitsugumin 53; MYSM1, Myb-like, SWIRM and MPN domains 1; DUB, deubiquitinase; FAK, focal adhesion kinase; IRP2, iron regulatory protein 2; JNK, c-Jun N-terminal kinase; LRRC8A, leucine-rich repeat-containing protein 8A; NF-κB, nuclear factor-κB; XBP1s, spliced X-box binding protein 1.

may provide a mechanistically grounded strategy to prevent and treat DOX-related cardiotoxicity.

MI. Multiple TRIM proteins have been implicated in MI and post-MI remodeling. TRIM11 downregulation has been reported to protect against Dusp6-driven cardiomyocyte ferroptosis in AMI (57). TRIM13 influences apoptosis in MI through interaction with CD3D, thereby limiting cardiomyocyte injury (58). TRIM21 aggravates post-MI cardiac injury by promoting M1 macrophage polarization, whereas TRIM21 deficiency mitigates oxidative stress, prevents atrial inflammation and attenuates post-MI remodeling (59). TRIM44 aggravates post-MI cardiac fibrosis through stabilization of TAK1 (62) and TRIM55 promotes post-MI cardiomyocyte apoptosis through modulation of the Nrf2/HO-1 pathway (60). TRIM28 has been reported to regulate activating transcription factor 5 stability through ubiquitination and SUMOylation, thereby exacerbating MI-induced cardiomyocyte apoptosis (128).

I/R injury. Myocardial I/R injury is a highly complex process characterized by excessive inflammation, dysregulated regulated cell death, mitochondrial dysfunction and loss of sarcolemmal integrity. Increasing evidence indicates that TRIM proteins integrate these stress responses through ubiquitin-dependent signaling (Fig. 4). In parallel, downregulation of TRIM11 alleviates cardiomyocyte apoptosis following I/R through the DUSP1-JNK1/2 pathway (129). Consistently, TRIM11 is reduced in AMI and mitigates ferroptosis by ubiquitinating Dusp6 and suppressing mitochondrial injury (57). More recently, TRIM11 was shown to attenuate cardiac I/R injury by ubiquitinating Nap1L1 and restoring reactive oxygen species (ROS) clearance capacity (130). TRIM16 protects against I/R injury by promoting K48-linked

polyubiquitination and degradation of NLRP3, thereby reducing pyroptosis and inflammation (131). Together, these studies support a central role for TRIM-mediated ubiquitin signaling in restraining multiple forms of regulated cell death under ischemic stress.

By contrast, certain TRIM-related pathways exacerbate I/R injury. The leucine rich repeat containing 8 VRAC subunit A/TRIM21 axis promotes cardiomyocyte apoptosis by blocking FAK/NF-κB signaling, thereby worsening cardiac I/R injury (132). In MI models, TRIM44 aggravates post-MI fibrosis by preventing K48-linked polyubiquitination of TAK1 and activating MAPK signaling (62). Notably, TRIM functions in I/R injury can be highly context dependent. TRIM27 promotes endothelial progenitor cell apoptosis via TBK1 ubiquitination and contributes to ISR after PCI (47), yet has also been reported to protect against cardiac I/R injury by negatively regulating p53 to suppress apoptosis and inflammation (64,133). Recently, Zhu *et al* (134) found that TRIM28 is a protective factor in myocardial I/R-injury. Mechanistically, TRIM28 suppress intracellular iron uptake by promoted K48-linked ubiquitination of IRP2, thereby alleviating cardiomyocyte ferroptosis. This duality highlights the plasticity of TRIM signaling across cell types and disease contexts.

Among TRIM members, TRIM72 (MG53) is the most extensively studied regulator of cardiac I/R injury. MG53 has been implicated as a determinant of ischemic preconditioning (IPC), with IPC-induced cardioprotection partially dependent on H_2O_2-activated protein kinase C-δ signaling that promotes MG53 secretion (135,136). Restoration of MG53 signaling in MG53-deficient mice reconstitutes IPC-mediated protection and markedly reduces myocardial I/R injury. However, because MG53 is reportedly absent or minimally expressed in human cardiac tissue, its translational value as a biomarker or endogenous cardioprotective factor remains debated (137). Mechanistically, MG53 preserves cardiomyocyte homeostasis through multiple pathways. During I/R-induced oxidative stress, MG53 directly binds the mitochondria-specific lipid cardiolipin, maintaining mitochondrial structural integrity and protecting cardiac function (138). In addition, membrane rupture triggers ART1-mediated ADP-ribosylation of MG53 at injury sites, enhancing its interaction with caveolin-3 and promoting rapid repair of damaged sarcolemma (139). MG53 also participates in ischemic postconditioning via activation of reperfusion injury salvage kinase signaling (140). Notably, an E3 ligase-inactive MG53 mutant protects diabetic hearts from acute I/R injury and improves diet-induced cardiac metabolic dysfunction (141), and blockade of $MG53^{S255}$ phosphorylation also protects diabetic hearts from ischemic injury (142).

Collectively, TRIM proteins regulate inflammation, regulated cell death, mitochondrial homeostasis and membrane repair in cardiac I/R injury. Their functional diversity and context dependence suggest that selective targeting of specific TRIM-centered signaling axes-rather than global inhibition-may represent a more promising therapeutic strategy for limiting myocardial I/R injury and improving clinical outcomes.

Diabetic cardiomyopathy (DCM). Mounting evidence positions TRIM family proteins as integrators linking systemic metabolic dysregulation in diabetes to myocardial structural and functional remodeling in DCM. MG53 has emerged as a central node that connects insulin sensitivity, metabolic homeostasis and cardiac stress responses. Genetic and biochemical studies indicate that MG53 controls systemic insulin signaling and glucose metabolism, implicating it as a key determinant of insulin resistance and metabolic imbalance in diabetes (143,144). In diabetic hearts, MG53 upregulation drives pathological remodeling by transcriptionally activating peroxisome proliferator-activated receptor-α, promoting lipid metabolic reprogramming and DCM development (145). Importantly, MG53 function in DCM appears highly context dependent. Whereas sustained MG53 activation exacerbates metabolic injury, a dominant-negative MG53 mutant confers cardioprotection by attenuating acute I/R injury and improving diet-induced cardiac metabolic dysfunction in diabetic models (141). These observations underscore the duality of MG53 signaling and highlight the importance of temporal and mechanistic specificity in TRIM-targeted interventions.

Additional TRIM-centered pathways regulate stress-induced senescence programs in diabetic hearts. In murine DCM, TRIM24 promotes proteasomal degradation of p53, whereas the (pro)renin receptor stabilizes p53 by inhibiting TRIM24 ubiquitination, thereby activating the p53-p21 axis, driving cardiomyocyte senescence, fibrosis and progressive dysfunction (146). This axis establishes TRIM24 as a key regulator of stress-induced senescence in the diabetic myocardium. Hydrogen sulfide exerts cardioprotection by inducing persulfidation of MuRF1/TRIM63 at Cys44, preventing diabetes-associated structural injury (147). H_2S-dependent MuRF1 persulfidation also modulates SERCA2a ubiquitination and improves myocardial contractility in db/db mice (147). Rnd3 has been reported to alleviate diabetic cardiac microvascular injury by promoting Trim40-mediated ubiquitination of ROCK1 (95). Overall, these findings position TRIM proteins as integrative regulators of metabolic stress, proteostasis and cellular aging in DCM. Their context-dependent actions, ranging from maladaptive metabolic remodeling to stress protection, highlight both the therapeutic potential and the complexity of TRIM-centered ubiquitin pathways in diabetic heart disease.

Myocarditis and atrial fibrillation (AF). TRIM proteins are deeply involved in innate antiviral immunity relevant to viral myocarditis. TRIM41 is required for effective antiviral responses by mediating polyubiquitination of BCL10 and recruiting NF-κB essential modulator to activate downstream inflammatory and antiviral signaling (13). Conversely, TRIM28-mediated SUMOylation of viral nucleocapsid proteins can enhance SARS-CoV-2 virulence, suggesting that TRIM28 may promote pathogenicity in specific viral contexts (33). HDAC6 negatively regulates cytosolic DNA sensor cyclic GMP-AMP synthase and its downstream stimulator of interferon genes (cGAS-STING)-mediated type I interferon signaling by deacetylating TRIM56, thereby limiting excessive antiviral immune activation (39). In a viral myocarditis model, TRIM21 interacts with mitochondrial antiviral signaling protein to enhance IRF3-dependent type I interferon production, thereby restricting coxsackievirus B3 (CVB3) replication and alleviating associated cardiac and pancreatic injury (148). Notably, a recent study reported by Song *et al* (149) found

that TRIM21 promotes K27-linked ubiquitination of TRAF3 followed by lysosomal degradation in fibroblast, amplifying IL-17A signaling and driving autoimmune myocarditis. MG53 protects mice from CVB3-induced acute viral myocarditis by suppressing NLRP3 inflammasome-mediated pyroptosis via NF-κB signaling (150). In addition, TRIM29 deficiency has been reported to attenuate myocarditis severity in male mice by weakening protein kinase RNA-like endoplasmic reticulum kinase (PERK) driven ER stress responses, revealing sex-dependent pathological relevance of a TRIM-ER stress axis in myocarditis (151). Recent work further suggests that aberrant reactivation of endogenous retroviruses can induce myocarditis and promote HF, expanding the potential scope of TRIM-innate immunity-virus axes in cardiac disease (152). As well as infection-related disease, TRIM proteins also modulate cardiac electrophysiology and structural remodeling. MG53 has been implicated in TGF-β1-induced atrial fibrosis and susceptibility to AF (67). Mechanistically, MG53 forms a complex with caveolin-1 to regulate TGF-β1 signaling activation status, thereby promoting AF-associated atrial fibrotic remodeling (153).

Other cardiac disorders. Across diverse cardiac disease states, TRIM proteins function as integrative regulators coordinating stress sensing, ubiquitin signaling, cell fate decisions and intercellular communication. Rather than exerting uniform actions, TRIM proteins operate in a highly context-dependent manner shaped by disease stage, cell type and metabolic environment. This functional plasticity helps reconcile apparently paradoxical observations in which the same TRIM protein is cardioprotective in one setting yet pathogenic in another. Accordingly, systematic dissection of TRIM-centered signaling networks with single-cell resolution and temporal granularity will be essential for translating mechanistic insights into effective therapies. Compared with global inhibition of TRIM proteins, selective and finely tuned modulation of TRIM activity may offer a more viable route to precision intervention, preserving adaptive stress responses while preventing decompensated remodeling. In addition, MG53 has been reported to preserve membrane integrity in aortic valve interstitial cells, thereby limiting membrane injury and fibro-calcific remodeling (154). MG53 also protects against septic cardiac dysfunction by ubiquitinating ATF2 to suppress TLR4 transcriptional activity, reducing TLR4 expression (155). Mechanistic study further suggests that TRIM10 contributes to the initiation and progression of septic cardiomyopathy (156).

Cardiac regeneration is an important but comparatively underexplored dimension of cardiovascular TRIM biology. Transcriptomic/proteomic profiling of regenerating neonatal mouse hearts has identified Trim72 among candidate regeneration-associated genes, but such association does not establish a causal regenerative mechanism (157). Bian *et al* (158) demonstrated that MG53 enhanced wound healing and skeletal-muscle injury repair/regeneration without detectable impairment of glucose handling or skeletal-muscle insulin signaling. The study further showed that circulating MG53 can accumulate at sites of tissue injury and noted that intravenous recombinant human MG53 had previously protected multiple organs, including the heart, from acute injury.

6. TRIM proteins as biomarkers and therapeutic targets

TRIM proteins are increasingly recognized as central regulators of cardiovascular stress responses, fueling interest in their translational potential. As well as mechanistic insight, TRIM proteins offer distinct opportunities and challenges as diagnostic biomarkers and therapeutic targets. Their enzymatic activity, context-dependent signaling and dynamic regulation place them at the intersection of disease detection and intervention, but also necessitate precision strategies tailored to disease stage and cell type.

TRIM proteins as biomarkers for CVDs. As precision medicine advances in cardiovascular care, there is an urgent need for molecular biomarkers that reflect underlying mechanisms, disease stage and treatment response. As TRIM proteins often occupy upstream regulatory positions across cardiovascular pathobiology and exhibit marked context dependence, they have emerged as promising candidate biomarkers. Multiple studies report differential expression of specific TRIM family members in cardiac tissue, vascular tissue or peripheral blood from patients with CVDs (159-161). These expression changes are frequently associated with disease severity, inflammatory status, metabolic derangement or the extent of tissue remodeling.

Clinical evidence linking TRIM proteins levels to CVDs. Emerging clinical evidence suggests that TRIM proteins may have potential value as biomarkers across distinct CVD settings (Table II). In a prospective case-control study involving 137 patients with atherosclerosis and 137 healthy controls, Jiang *et al* (159) found markedly higher serum TRIM24 concentrations in patients with atherosclerosis, with further increases observed in patients with more severe disease. Serum TRIM24 showed good discriminatory performance for atherosclerosis [area under the curve (AUC)=0.928; sensitivity 90.51%; specificity 87.59%] and was also associated with severe atherosclerosis (AUC=0.826) and severe coronary stenosis defined by a Gensini score ≥55 (AUC=0.928) (162). These associations remained significant after adjustment for selected clinical and inflammatory variables, supporting the potential of circulating TRIM24 to reflect both the presence and severity of atherosclerotic disease.

Han *et al* (160) evaluated circulating ring finger protein 207 (RNF207) in 65 patients with AMI, 31 patients with coronary heart disease without AMI, and 28 healthy controls after initial identification of RNF207 as a cardiac-enriched E3 ubiquitin ligase in experimental models. Plasma RNF207 increased within 1 h after AMI and peaked at ~3 h, suggesting a rapid release profile following myocardial injury. Receiver operating characteristic analysis yielded an AUC of 0.968 for RNF207 compared with 0.983 for cardiac troponin I, with RNF207 achieving 90.5% sensitivity at 100% specificity (160). These observations raise the possibility that RNF207 could complement established markers for early myocardial injury. Nevertheless, the diagnostic analysis was performed in a relatively small population and primarily discriminated AMI patients from healthy controls rather than from a broad spectrum of patients presenting with acute chest pain. Moreover, cardiac enrichment of RNF207 was

Table II. Clinical evidence supporting TRIM-related biomarkers in cardiovascular diseases

Authors, year	Design and sample size	Patient characteristics	TRIM findings	Clinical outcomes	(Refs.)
Jiang *et al*, 2025	Prospective case-control study; AS (n=137) Age- and sex-matched healthy controls (n=137)	AS diagnosed by vascular ultrasound or coronary CTA; 68.61% had severe AS requiring intervention; 79.56% had severe coronary stenosis (Gensini score ≥55)	TRIM24: Increased in AS and with disease severity. AUC=0.928 for AS; 0.826 for severe AS; 0.928 for severe coronary stenosis	Circulating TRIM24 was associated with AS presence and severity, supporting its potential for disease detection and severity assessment	(159)
Han *et al*, 2015	Clinical study with experimental validation; AMI (n=65) CHD without AMI (n=31) healthy controls (n=28)	AMI and non-AMI CHD populations; RNF207 initially identified as relatively cardiac-enriched experimentally	RNF207: Increased within 1 h after AMI and peaked at ~3 h. AUC=0.968 vs. 0.983 for cTnI; sensitivity 90.5% at 100% specificity	Rapid release kinetics and high discriminatory performance suggest potential value for early detection of myocardial injury	(160)
Xie *et al*, 2020	Cross-sectional study; n=639: no coronary stenosis (n=205), stable CAD (n=222), AMI (n=212)	Consecutive patients undergoing coronary angiography; disease severity assessed using SYNTAX and GRACE scores	MG53: Increased in stable CAD and further elevated in AMI; associated with SYNTAX score and GRACE risk categories	Circulating MG53 was associated with CAD/AMI presence and severity, suggesting potential diagnostic and risk-stratification value	(161)
Salazar-Mendiguchía *et al*, 2020	Genetic screening/family study; HCM (n=4,867) Other cardiomyopathies (n=3,628) familial cardiovascular disease controls (n=3,136)	Large cardiomyopathy referral population with family segregation analyses	TRIM63: Rare biallelic variants identified in a small subset; segregation supported autosomal-recessive inheritance	TRIM63 represents an uncommon genetic cause of HCM and may contribute to molecular diagnosis in selected patients	(165)

TRIM, tripartite motif-containing protein; AUC, area under the receiver operating characteristic curve; CTA, computed tomography angiography; AS, atherosclerosis; AMI, acute myocardial infarction; CHD, coronary heart disease; CAD, coronary artery disease; cTnI, cardiac troponin I; GRACE, Global Registry of Acute Coronary Events; HCM, hypertrophic cardiomyopathy; MG53, mitsugumin 53; SYNTAX, Synergy Between PCI With Taxus and Cardiac Surgery.

established predominantly from animal tissue-expression studies, whereas its tissue origin and specificity in humans remain insufficiently characterized. Thus, whether RNF207 provides clinically meaningful information as well as contemporary high-sensitivity troponin-based diagnostic algorithms remains unknown.

Similarly, in a cross-sectional study involving 639 patients, Xie *et al* (161) reported that serum MG53 levels were associated with the presence and severity of coronary artery disease (CAD) and AMI, suggesting MG53 as a novel circulating biomarker candidate. Furthermore, higher MG53 levels were associated with greater CAD severity assessed by the Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) score and higher Global Registry of Acute Coronary Events (GRACE) risk categories in patients with AMI (163,164). Importantly, these associations persisted after adjustment for multiple cardiovascular risk factors and clinical variables, including diabetes, hypertension, dyslipidemia, hs-CRP, NT-proBNP, LVEF, LDL cholesterol and renal function (161). These findings suggest that circulating MG53 may provide information related to both the presence and severity of coronary disease.

In a murine I/R injury model, Lemckert *et al* (137) found that MG53 strongly correlated with myocardial injury (r=0.79-0.85; P<0.05), supporting its potential as a biomarker of cardiomyocyte damage. Although MG53 is abundant in skeletal muscle, its expression in human myocardium remains controversial. Lemckert *et al* (137) reported minimal-to-undetectable MG53 protein in human myocardial specimens using multiple validated antibodies, whereas subsequent proteomic

analyses detected MG53 in human left ventricular tissue, albeit at substantially lower abundance than in skeletal muscle. This discrepancy may reflect differences in detection methods, tissue characteristics or biological sources of circulating MG53 and therefore warrants particular caution when interpreting serum MG53 as a cardiac-derived biomarker. Furthermore, circulating MG53 is influenced by conditions such as diabetes and chronic kidney disease, suggesting that metabolic, renal, skeletal-muscle or inflammatory factors may contribute to its circulating concentrations. Accordingly, the available evidence supports MG53 as a promising marker associated with CAD and AMI severity but does not yet establish its cardiac specificity or incremental value As well as troponins, natriuretic peptides, imaging and established clinical risk scores.

In addition to circulating measures, genetic evidence also supports TRIM proteins as clinically informative biomarkers. In a multicenter clinical study including 16 cases of hypertrophic cardiomyopathy (HCM), TRIM63 mutations were shown to cause an autosomal recessive form of HCM (165). Familial segregation analyses further supported an autosomal-recessive inheritance pattern, indicating that biallelic TRIM63 variants represent an uncommon genetic cause of HCM. Rather than functioning as a conventional circulating biomarker, TRIM63 may therefore have value in the molecular diagnosis and genetic stratification of selected patients with inherited cardiomyopathy. Its low prevalence and the predominantly European ancestry of the study population, however, limit its broader diagnostic applicability and highlight the need for validation in more diverse populations.

Despite these associations, cardiovascular biomarkers of TRIM proteins remain largely at the preclinical stage and further studies are needed to clarify disease specificity, assay reproducibility, safety and translational feasibility. Furthermore, it also introduces challenges: TRIM expression and function are highly dependent on cell type, disease stage and microenvironmental context, requiring careful interpretation within a defined clinical and biological framework.

Therapeutic strategies targeting TRIM proteins. Therapeutically targeting TRIM proteins is conceptually appealing yet practically challenging. As E3 ubiquitin ligases, TRIM proteins occupy upstream nodal positions with the capacity to reshape broader signaling networks. This centrality, however, also raises concerns regarding off-target effects and disruption of physiological stress-adaptive responses.

Small-molecule modulators. As E3 ubiquitin ligases often lack classic catalytic pockets, direct pharmacological modulation has historically been difficult. Recent strategies, including allosteric modulators, inhibitors of substrate-ligase interactions and molecular glues, have created new opportunities to target TRIM proteins. Several preclinical studies targeting MuRF1/TRIM63 have shown meaningful functional benefit, including improvement of myocardial and skeletal muscle performance in models of HFpEF, providing proof-of-concept that selective modulation of TRIM activity can be feasible and therapeutically advantageous. Compound ID#704946 has been reported to protect cardiac function by targeting MuRF1/MuRF2, thereby attenuating chronic HF-associated diaphragm fiber atrophy, contractile dysfunction and reductions in mitochondrial enzyme activity (166). In HFpEF animal models, small-molecule targeting of MuRF1 (MyoMed-205) improved diastolic function and prevented skeletal muscle atrophy and functional decline (106). In a rat model of unilateral diaphragm denervation-induced diaphragmatic dysfunction, MyoMed-205 enhanced sarcomeric integrity, Ca^{2+} handling, antioxidant defenses, activation of chaperone-mediated unfolded protein responses and pro-growth programs, while also reducing intramuscular fat deposition and denervation-induced profibrotic remodeling (167). These findings provide pharmacological proof, but they do not establish clinical efficacy or long-term safety. Indeed, complete genetic inactivation of MuRF proteins can itself produce adverse cardiac phenotypes, emphasizing that partial pharmacological modulation cannot be assumed to reproduce the consequences of gene deletion. Prior to clinical translation, MuRF-directed compounds require rigorous assessment of binding selectivity and direct target engagement, dose-response relationships, chronic toxicology, effects on skeletal vs. cardiac muscle and conservation of relevant ligase-substrate interactions in humans.

Natural compounds and traditional formulations. Natural products and traditional formulations have also been reported to influence TRIM expression or activity, but these observations warrant particularly cautious interpretation because most such agents are pleiotropic and direct engagement of a TRIM protein is rarely demonstrated. For example, Zenglv Fumai Granule has been reported to protect AC16 cardiomyocytes from hypoxia/reoxygenation-induced apoptosis by suppressing TRIM28 expression (168). However, the study was predominantly cell based, the formulation contains multiple bioactive components and suppression of TRIM28 expression does not establish direct molecular binding or pharmacological specificity. Salvianolic acid B has been reported to inhibit I/R-induced ROS production and apoptosis by modulating the TRIM8/GPX1 signaling axis (169). In addition, nutrient-sensing pathways such as FoxO1/3 and mTOR may act under coordinated regulation of a central leptin-PPARβ/δ axis and have been implicated in cardiac remodeling (170). Sevoflurane has been reported to alleviate myocardial I/R injury by modulating TRIM65-mediated ubiquitination of arachidonate 5-lipoxygenase (171), but this mechanistic association likewise requires independent confirmation of direct target engagement and pathway selectivity. While these observations suggest potential therapeutic value, specificity, reproducibility and mechanism-of-action require validation through more rigorous genetic and biochemical approaches.

Recombinant protein-based approaches. Among TRIM family members, TRIM72 (MG53) represents the most extensively explored candidate in translational research. Recombinant MG53 has demonstrated robust cardioprotective effects in multiple preclinical models, through mechanisms that include enhanced membrane repair, preservation of mitochondrial integrity and attenuation of oxidative stress (172). These findings support a strategy in which a TRIM protein is deployed as a biologic therapeutic agent rather than targeted solely as an intracellular enzymatic node. Nevertheless, the clinical promise of MG53 remains debated, particularly due

to species-specific expression patterns and potential metabolic effects. Careful patient stratification and deeper mechanistic clarification will be essential before broader clinical translation.

Gene silencing and genetic interventions. Gene-silencing technologies hold substantial promise for cardiovascular therapeutics by enabling targeted regulation of disease-driving genes and signaling pathways. For example, Liu *et al* (53) reported that TRIM28 knockdown markedly suppresses PDGF-BB-induced VSMC proliferation and migration, thereby attenuating atherogenesis. In cardiac fibrosis models, TRIM35 overexpression has been closely linked to fibrotic progression, whereas TRIM35 deletion markedly alleviated fibrosis and hypertrophy (61). In a murine MI model, TRIM44 deletion similarly improved post-MI cardiac fibrosis (62). Together, these studies suggest that gene-silencing approaches can not only selectively suppress TRIM expression but also can be combined with targeting of downstream effectors to slow disease progression, offering a mechanistically grounded avenue for therapeutic development in CVD.

Therapeutically, targeting TRIM protein represents a promising strategy in CVDs. However, most cardiovascular evidence for TRIM-directed intervention remains preclinical, and manipulating a TRIM protein may alter multiple substrates and ubiquitin-chain-dependent processes As well as the intended disease pathway. Translation will therefore require demonstration of target engagement in the relevant cardiovascular cell type, rather than systemic modulation alone, together with careful definition of therapeutic window, disease stage, dose and timing. Particular concerns include efficient delivery to cardiomyocytes or vascular cells, off-target disruption of ubiquitin networks, immune consequences, interspecies differences in TRIM expression and substrate usage, and the possibility that sustained inhibition of a stress-responsive TRIM may abolish adaptive responses that are beneficial during acute injury.

7. Conclusions and future perspectives

A substantial body of evidence now positions the TRIM protein family as a central regulatory axis in cardiovascular biology. As well as their classical designation as E3 ubiquitin ligases, TRIM proteins function as integrative signaling nodes that coordinate proteostasis, inflammatory responses, metabolic adaptation and cell fate determination. Through this strategic regulatory positioning, TRIM proteins translate diverse exogenous and endogenous cues, including mechanical stress, metabolic imbalance and inflammatory stimulation, into coordinated cellular programs that ultimately shape structural and functional remodeling of the heart and vasculature.

Across a wide spectrum of CVDs, including atherosclerosis, vascular calcification, PAH, MI, HF, cardiomyopathy and cardiac fibrosis, TRIM proteins consistently emerge at critical transition points between adaptive compensation and maladaptive remodeling. Importantly, this recurring involvement does not represent a disease-specific coincidence but rather reflects a shared regulatory logic underlying cardiovascular pathophysiology. By encoding context-dependent ubiquitin signals and engaging in extensive crosstalk with other PTMs, TRIM proteins fine-tune the magnitude, duration and cell specificity of stress responses. In doing so, they influence disease trajectory not as simple binary on/off switches, but as dynamic modulators of signaling amplitude and network integration.

A defining feature of TRIM biology is its pronounced context dependence. A single TRIM family member may confer protection during acute injury or early adaptive stress responses yet promote pathological remodeling under chronic stress or altered metabolic conditions. These seemingly paradoxical observations should not be interpreted as experimental inconsistencies, but rather as inherent properties of adaptive regulatory networks operating within complex multicellular systems. Recognizing this principle is essential for integrating findings across experimental models and clinical contexts, and for avoiding overly reductionist interpretations of TRIM function.

From a translational perspective, TRIM proteins represent both opportunity and challenge. Their upstream regulatory position makes them attractive candidates for biomarker development and therapeutic targeting; however, their pleiotropic and dynamically regulated nature cautions against indiscriminate inhibition. Emerging precision strategies, including selective modulation of ligase-substrate interactions, targeting of specific ubiquitin chain topologies and cell type or stage-restricted intervention offer more rational approaches that may preserve physiological stress adaptation while limiting pathological signal amplification. Proof-of-concept studies, particularly those centered on TRIM72, demonstrate the feasibility of targeting TRIM pathways, yet rigorous evaluation in clinically relevant models remains necessary before widespread translation.

How TRIM proteins achieve substrate specificity in cardiovascular cells remains an important mechanistic question. Structural studies indicate that substrate recognition is primarily encoded by variable C-terminal interaction modules, particularly PRY/SPRY domains, whose structurally diverse surface loops recognize specific linear motifs or conformational epitopes; this intrinsic recognition is further constrained by TRIM oligomerization and subcellular localization, whereas E2-E3 pairing contributes to the topology and biochemical consequence of the resulting ubiquitin signal (25). In the cardiovascular system, the present review proposed that this structural specificity is further filtered by cell-specific substrate availability and stress-dependent changes in protein abundance, localization and post-translational state, providing a plausible explanation for why the same TRIM can engage distinct signaling programs in cardiomyocytes, ECs, VSMCs, fibroblasts and immune cells. However, direct evidence defining cardiovascular cell-specific TRIM-substrate recognition remains limited and future studies integrating structural analysis with site-specific ubiquitinomics, RING-deficient mutants and substrate lysine-site rescue will be required to distinguish intrinsic substrate recognition from context-dependent substrate availability and to establish how TRIM specificity is dynamically rewired during CVD progression (173).

Looking forward, several key scientific questions must be addressed to fully harness the potential of TRIM biology in cardiovascular medicine. First, elucidating how TRIM-mediated ubiquitin signals encode context-specific functions will require integration of

quantitative ubiquitinomics with structural biology and biochemical analysis, enabling causal linkage between ubiquitin chain topology and functional output. Second, defining the temporal dynamics of TRIM activity during the transition from acute injury to chronic remodeling will depend on inducible, cell type-specific genetic models coupled with longitudinal multi-omics approaches. At the same time, emerging single-cell and spatial omics technologies provide unprecedented resolution for dissecting how TRIM proteins coordinate intercellular communication among cardiomyocytes, fibroblasts, ECs and immune cells within the cardiovascular microenvironment. Large-scale clinical cohort studies will be required to systematically evaluate the sensitivity, specificity and prognostic value of TRIM proteins as diagnostic and stratification biomarkers, as well as to determine their complementarity with conventional clinical and imaging parameters. Integration of single-cell and spatial transcriptomics may further refine TRIM-based precision biomarker strategies by defining cell type-specific expression patterns in human disease.

In summary, TRIM proteins define a previously underappreciated ubiquitin-centered regulatory layer with profound influence on the initiation and progression of CVD. Viewing TRIM proteins as context-dependent regulators of stress adaptation provides a unifying conceptual framework for understanding cardiovascular heterogeneity and lays the foundation for temporally and spatially precise modulation of ubiquitin signaling in future therapeutic strategies.

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FW and ZX collected materials and wrote the original draft. YuG prepared all figures and revised the manuscript. YaG conceived the study and reviewed the paper. All authors read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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