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A systematic view on E3 ligase Ring TRIMmers with a focus on cardiac function and disease

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ABSTRACT

Ubiquitination, a post-translational modification via ubiquitin-proteasome-system, is one of the vital cellular processes involved in intracellular signaling, cell death, transcriptional control, etc. Importantly, it prevents the aggregation of non-functional, misfolded or unfolded, potentially toxic proteins to maintain cellular protein homeostasis. Ubiquitination is accomplished by the concerted action of three enzymatic steps involving E1 activating enzymes, E2 conjugating enzymes, and E3 ligases. Tripartite motif-containing (TRIM) proteins are one of the integral members of E3 ubiquitin ligases in metazoans modulating essential cellular pathways. For long, MuRFs (Muscle ring finger proteins) were the most extensively studied TRIMs for their cardiac function. Recent research advances in the field and our analysis presented here, however, demonstrated broader and ever increasing involvement of additional TRIM E3 ligases in the pathophysiology of heart. In this review, we summarize the known cardiac E3 ligases and their targets, and discuss their role and importance in cardiac proteostasis, pathophysiology and potential therapeutic implications with specific focus on TRIM E3 ligases.

The pathophysiology of heart failure is complex and still poorly understood, though it is a leading cause of mortality worldwide [1,2]. The past few decades witnessed exhilarating efforts from researchers across the globe to uncover multiple signaling molecules and pathways that metamorphose gene expression in cardiac hypertrophy and failure, including the prototypical induction of the “embryonic” pro-hypertrophic gene program [3–5]. Only recently, however, protein homeostasis as a key cellular process has caught attention in the context of heart failure and cardiomyopathy. Malfunctioning in protein quality control (PQC) due to extrinsic and/or intrinsic factors such as genetic mutations, ageing, hypertension, biomechanical stress, etc. may result in continued presence and chronic accumulation of misfolded proteins leading to protein aggregation and/or the formation of soluble peptides that are proteotoxic. This in turn precipitates a downward spiral of the cell’s ability to maintain homeostasis and may eventually result in cell death. Such protein misfolding has been reported to culminate in terminal neurodegeneration diseases like Alzheimer’s and Huntington’s [6], type II diabetes, [7], and cancers [8]. In recent times, a growing number of cardiac and skeletal muscle diseases have been reported to feature depositions of misfolded proteins, including cardiac amyloidosis, desmin-related cardiomyopathy (DRM), and dilated cardiomyopathy [9,10]. Therefore, the clearance of misfolded proteins is equally important for cellular homeostasis.

The two most important biological machineries controlling proteostasis, PQC, and degradation are autophagy and the ubiquitin-proteasome system (UPS) (Fig. 1). Autophagy is a lysosome-dependent, tightly regulated catabolic process that degrades unwanted cell organelles and cytoplasmic constituents in lysosomes. Autophagy can be further distinguished as: macroautophagy, microautophagy and chaperone-assisted autophagy (including chaperone-mediated autophagy (CMA) and chaperone-assisted selective autophagy CASA)) [11,12]. Macroautophagy, often deregulated in disease conditions [13], involves the inclusion of cytosolic material, including cell organelles, into double-membraned vesicles termed autophagosomes [14–16]. Autophagosomes then fuse with lysosomes or endosomes where vesicular constituents are degraded. Lysosomes are reformed and the degradation products are then released for intracellular recycling [15]. Macroautophagy is therefore an essential mechanism for cellular adaptation to environmental stress, for example, starvation-induced protein/lipid degradation via autophagy to mobilize diverse nutrient stores for anabolic purposes [17]. Similar to starvation, sustained pressure overload of the heart due to biomechanical stress is also

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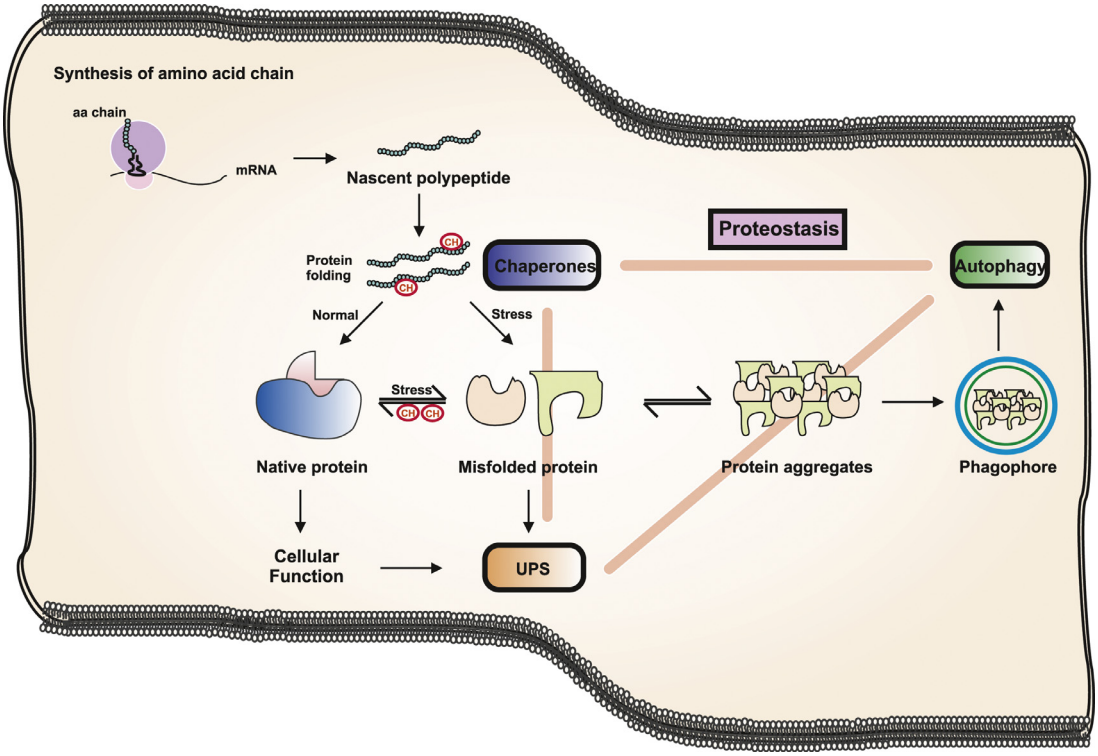


Fig. 1. Major protein degradation pathways, autophagy and the ubiquitin-proteasome system (UPS), and their interactions are depicted diagrammatically. aa, amino acid; CH, chaperone; mRNA, messenger RNA.

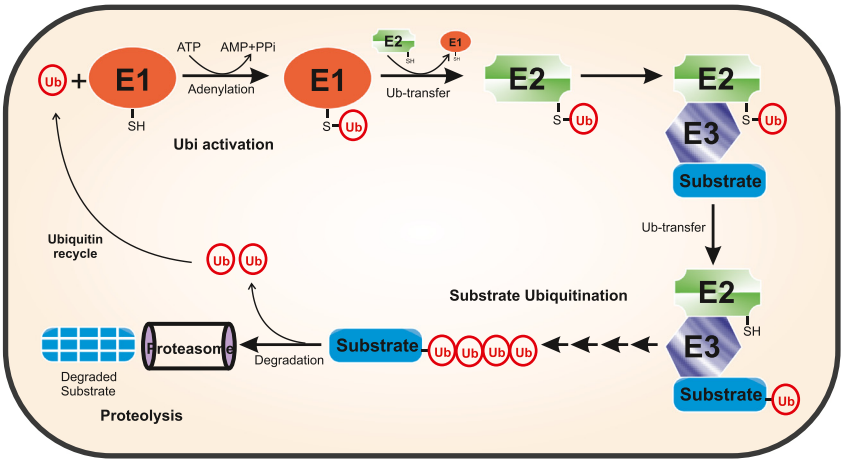


Fig. 2. Ubiquitination process. Ubiquitination is accomplished by the concerted action of three enzymatic steps involving E1 activating enzymes, E2 conjugating enzymes, and E3 ligases.

accompanied by the induction of autophagy [18–20]. Microautophagy on the other hand refers to a direct engulfment of cytoplasmic components by lysosomes [21], while CMA and CASA involve chaperones like heat shock proteins such as BCL2-associated athanogene 3 (BAG3) [11,22].

Ubiquitination, i.e. the covalent attachment of ubiquitin to the target protein, is a primary step in UPS mediated protein degradation. It is accomplished by three enzymatic steps: ubiquitin activation via the enzyme E1, ubiquitin conjugation via E2 conjugating enzyme and ubiquitin ligation by E3 ligase (Fig. 2). These ubiquitin marked, predominantly short-lived and misfolded proteins are subsequently degraded by 26S proteasome in ATP-dependent manner to maintain cell's youthful proteome [23,24].

E3 ligases provide substrate recognition specificity

Ubiquitination diversity and substrate specificity in mammals is achieved by the existence of over six-hundred E3-ubiquitin ligases that catalyze the final step of ubiquitination, compared with only one E1 and very few E2 enzymes known till date [23]. Based on their structural properties, E3 ligases are classified as: RING (really interesting new gene), HECT (homologous to E6AP C-terminus) and RBR (RING-between-RING) ligases [25]. HECT and RBR E3 ligases carry a catalytic cysteine that accepts ubiquitin from E2∼ubiquitin complex to form an E3∼ubiquitin thioester intermediate, which subsequently transfers this ubiquitin to the substrate protein [26]. In contrast, RING E3s, which constitute the most

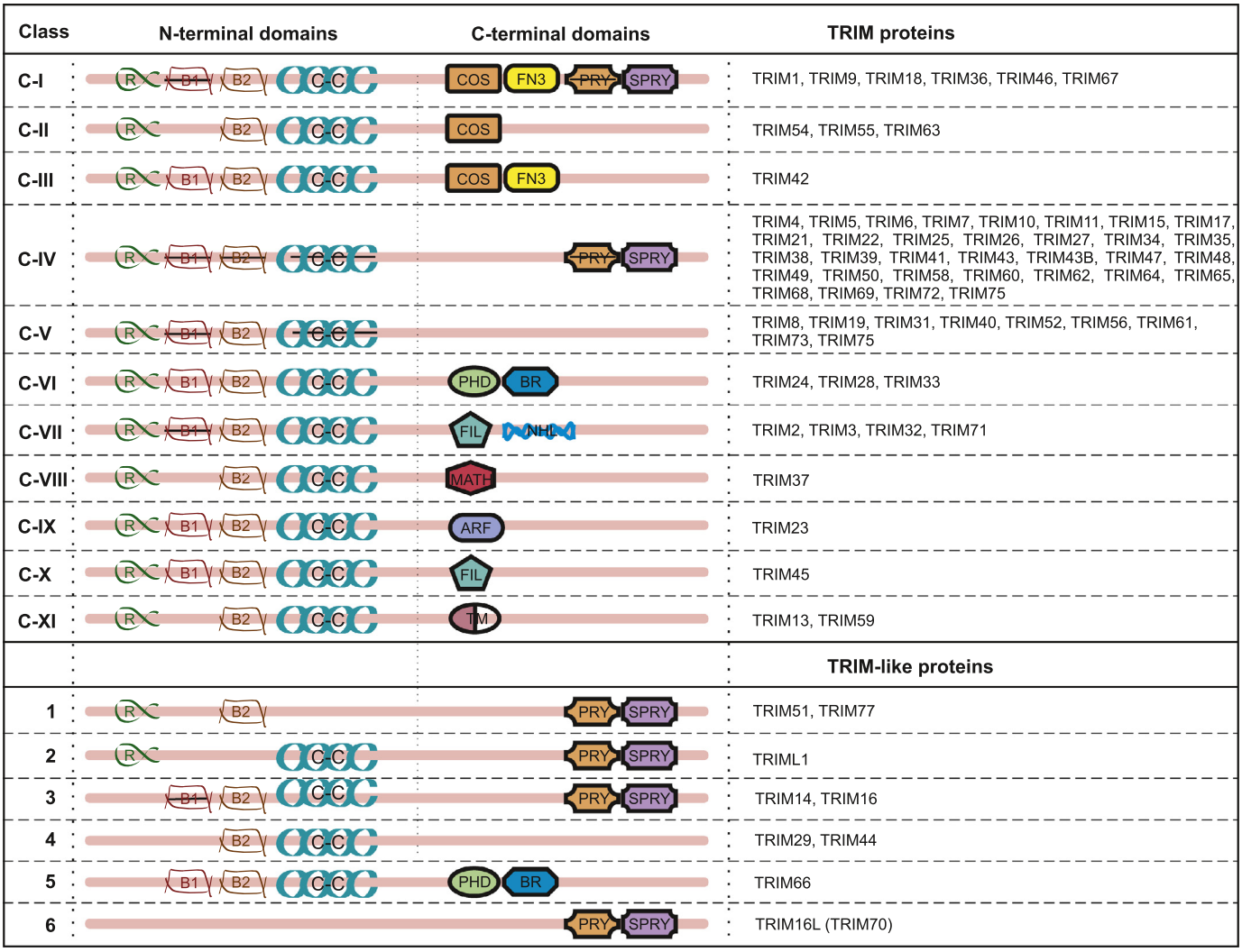


Fig. 3. Classification of TRIM family proteins.

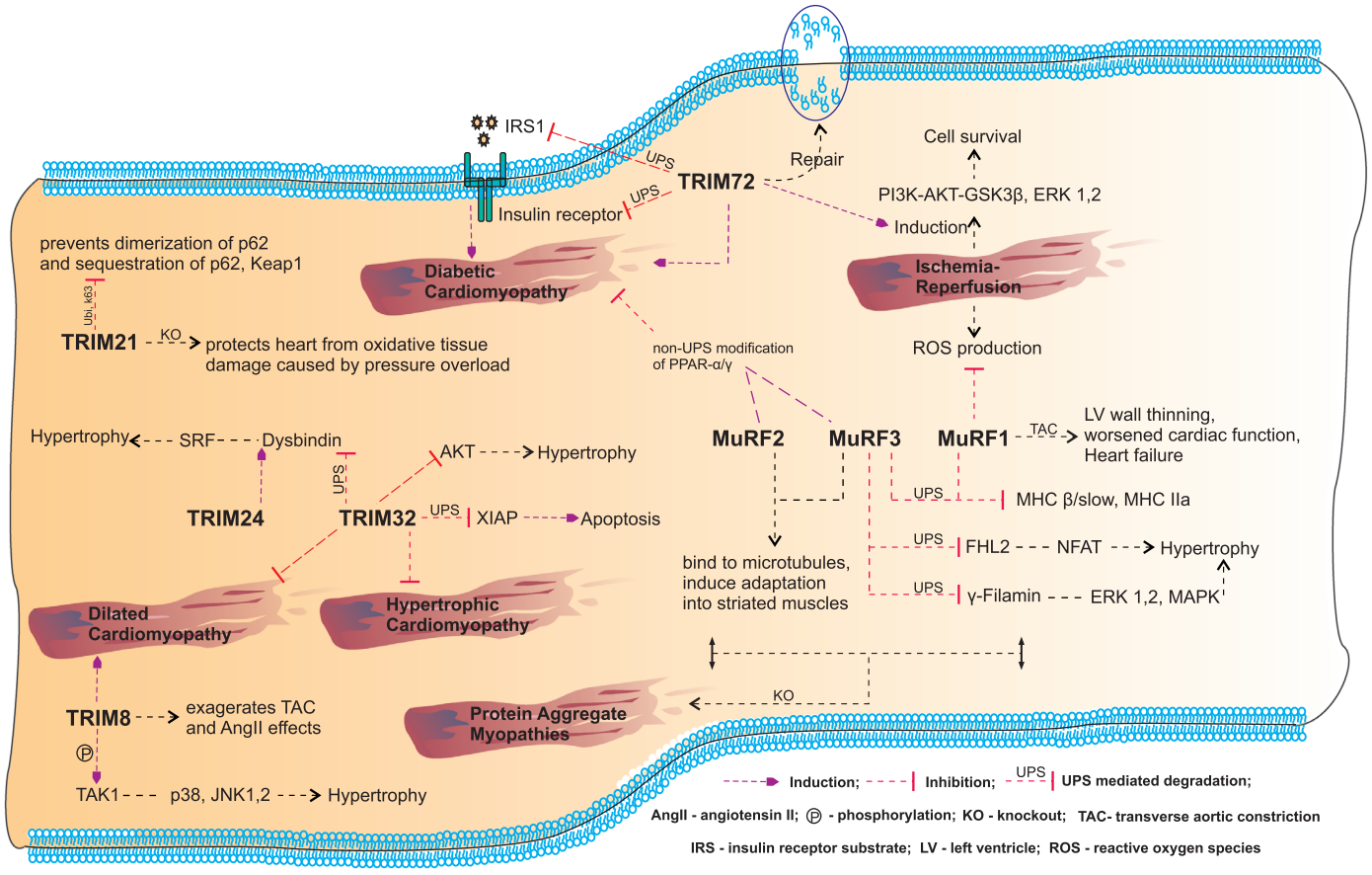
abundant ubiquitin ligases, catalyze the direct transfer of ubiquitin from E2~ubiquitin complex to the substrate [26]. Given the crucial role UPS plays in cardiac homeostasis, it is not surprising that several E3 enzymes have been implicated in various cardiac processes and pathologies like heart development, signaling cascades, ion channel regulation, autophagy regulation, protein degradation, congenital heart diseases and cardiomyopathies [27,28].

Through intensive data mining and literature search in PubMed, we identified in total sixty E3 ligases that have thus far been assigned a cardiac function. The majority of these E3 ligases belong to either single- or multi-subunit RING-type E3 ligases (Supplementary Fig. 1). In Supplementary Table 1, we summarize the details of these sixty E3 ligases including their proposed function, protein targets, affected biomolecules and pathways, and the respective literature. Discussing structural and functional properties of every single cardiac E3 ligase is beyond the scope of a single review. Here, we thus focus and provide comprehensive details only for the proteins belonging to tripartite motif-containing (TRIM) proteins, a subclass of RING ubiquitin ligases (Supplementary Table 1 and Supplementary Fig. 1).

TRIM E3 ubiquitin ligases

The KEGG database shows that TRIMs belong to Ubiquitin ligases (E3), under the Single Ring-Finger type E3 class in *Homo sapiens*. With the concept that similar structures perform similar functions at biochemical level, the width of TRIM family grew significantly, now containing over 65 members [29,30]. The presence of numerous members in higher eukaryotes and species-specific roles of TRIMs suggest that the individual genes have evolved independently and their sequence and functions are highly maintained throughout speciation [31]. TRIMs contain three highly conserved RING finger-B-Box-Coiled-coil domains at amino-terminal of individual members. These three motifs are highly conserved in humans in all individual member proteins, even if one of the domains is absent (Fig. 3). The remaining sequences however have evolved to acquire specific physiological functions through their carboxyl terminal motifs [32]. The RING domain is one of the most prominent domains bestowing E3 ubiquitin ligases their property of covalently tagging specific proteins with ubiquitin from enzyme E2. This domain can recruit one or more ubiquitin moieties, resulting in mono- or poly-ubiquitination effecting different roles [33]. As all TRIM family members contain a RING domain, they are thus potentially involved in ubiquitin conjugation to a specific substrate protein. Generally, TRIMs perform transfer of the ubiquitin by interacting with target proteins through their coiled coil domain [34].

All known vertebrate TRIMs are categorized in 11 distinct subclasses depending on the types of domains present at their carboxyl-terminals (Fig. 3) [29,35]. Beyond conserved N-terminal domains, it is the C-terminal that provides specificity of



AKT - protein kinase B (PKB); **ERK** - extracellular signal-regulated kinase; **FHL2** - four and a half LIM domain; **GSK3β** - glycogen synthase kinase 3 beta; **JNK** - c-Jun N-terminal kinase; **Keap1** - kelch like ECH associated protein 1; **MAPK** - mitogen activated pritein kinase; **MHC** - major histocompatibility complex; **MuRF** - muscle ring finger; **NFAT** - nuclear factor of activated T-cells; **p38** - MAPK 14; **p62** - ubiquitin binding protein 62; **PI3K** - phosphatidylinositol 3-kinase; **PPAR-α/γ** - peroxisome proliferator activated receptor alpha/gamma; **SRF** - serum response factor; **TAK1** - TGF-beta activated kinase 1 (MAP3K7); **TRIM** - tripartite motif containing protein; **XIAP** - X-linked inhibitor of apoptosis.

Fig. 4. Diagrammatic presentation of involvement of TRIM proteins in cardiac (patho)physiology.

interactions with other proteins. The subclass IV forms almost two third of the TRIM/RBCC family, possessing RFP- like B30.2 (PRY and SPRY) domains at C-terminal. While this ancient family has been reported to greatly diversify in vertebrates, in fish the B30.2 containing subclass appears prominent as well, with other human TRIMs having limited numbers of orthologues [36]. Moreover, Meroni and Diez-Roux (2005) have reported almost 20 members of TRIM family also in invertebrates.

The TRIM E3 ubiquitin ligase family has emerged as a critical component in various cellular processes from cell development to apoptosis. For example, TRIM36 plays central role in arranging somites during *Xenopus* embryogenesis [37]; TRIM59 and TRIM44 promotes proliferation in colorectal cancer and testicular germ tumor, respectively [38,39]; TRIM24, TRIM28 and TRIM33 are well established transcriptional intermediary factors α, β and γ, respectively [40–42]; TRIM13, TRIM21, and Muscle Ring Fingers (MuRFs) are involved in autophagy [43–46]; TRIM5α trimerizes to induce defense against HIV [34], whereas, TRIM21 negatively regulates IFN beta production after pathogen-recognition via degradation of IRF3 [47]. Moreover, many TRIMs have been emerged as markers of carcinogenesis through their interaction with tumor protein p53 like TRIM24, TRIM28, TRIM29, and TRIM32 [48–51]. Interestingly, we found that TRIM is the major 'single ring finger family' that is known to be involved in cardiac pathophysiology including cardiomyocyte differentiation, signaling, apoptosis, cardiac hypertrophy/atrophy/ischemia, and dilated cardiomyopathy (Supplementary Table 1 and Supplementary Fig. 1).

Muscle Ring Fingers (MuRFs) comprising TRIM63 (MuRF1), TRIM55 (MuRF2) and TRIM54 (MuRF3) are the most studied TRIMs in the heart. However, with increasing knowledge of E3 ligases and recent advancements in the field, many other TRIMs such as TRIM8, TRIM21, TRIM24, TRIM32, TRIM45, TRIM69 and TRIM72 were found to play essential roles in cardiac function and disease pathways as discussed below and diagrammatically represented in Fig. 4.

MuRFs

MuRF1, MuRF2, and MuRF3 have critical roles in skeletal and cardiac muscle. MuRF2 is found to be expressed at early onset of mouse cardiac differentiation, specifically at embryonic day 8.5 and thus is a sensitive marker for differentiating myocardium. In contrast, MuRF1 displays a strong upregulation postnatally, whereas, MuRF3 is expressed significantly only after birth [52]. They characteristically lack B-box 1 and only have a COS domain at their carboxyl terminus. Nevertheless, MuRF1, 2, and 3 carries highly conserved RING domain at N-terminus and can form heterodimers by shared coiled-coil domains [53]. Heterodimerization of MuRFs is possibly responsible for their multiple cellular localization and has been proposed to link titin filament and microtubule-dependent signal transduction pathways in striated muscles [53]. Genetic mouse models of loss- or gain-of-function of MuRFs have provided deep insights into their cardiac roles. Cardiac-specific overexpression of MuRF1 led to thinning of left ventricular walls,

worsened cardiac function, and heart failure upon TAC [54]. MuRF1 has also been reported to regulate cardiac reactive oxygen species (ROS) production in mitochondria, revealing an additional cardioprotective role in ischemia reperfusion injury [55]. Furthermore, MuRF1 inhibits cardiac fatty acid oxidation by specifically inhibiting its nuclear localization, suggesting a possible role in cardiac metabolism and pathophysiology [56].

MuRF1 and MuRF2, two closely related family members, redundantly share functional similarities and can heterodimerize [57]. Their functional similarity extends to a degree that presence of either MuRF1 or MuRF2 is sufficient for normal cardiac function and regulation of developmental physiological hypertrophy by modulating the expression and localization of E2F transcription factors [57]. Simultaneous absence of both proteins however results in spontaneous development of skeletal and cardiac hypertrophy [54]. MuRF2 labeled microtubules study in cardiac sarcomeres have demonstrated its vital contribution as a transient adaptor between microtubules, titin and nascent myosin filaments, thereby playing a significant role in signaling from sarcomere to nucleus [58]. Also, rare variants of both MuRF1 & MuRF2 were found to be associated with human hypertrophic cardiomyopathy [59].

MuRF1 and MuRF3 in cooperation with the E2 ubiquitin-conjugating enzymes UbcH5a, -b, and -c were found to mediate degradation of myosin heavy chain β/slow (MHC β/slow) and MHC IIa via UPS, both, in vitro and in vivo [60]. Mice lacking both MuRF1 and MuRF3 developed skeletal muscle myopathy and hypertrophic cardiomyopathy with sub-sarcolemmal MHC accumulation, myofibril fragmentation and diminished muscle performance, leading to myosin storage myopathy [60]. These findings identify MuRF1 and MuRF3 as key E3 ubiquitin ligases for UPS-dependent turnover of sarcomeric proteins and reveal a potential molecular basis for myosin storage myopathies.

MuRF2 and MuRF3 are also known to have considerable functional overlap in binding to microtubules and in sarcomere formation in the process of adaptation of striated muscle cells [61]. Double knockout of MuRF1 and 3 in mice resulted in protein aggregate-associated myopathy in striated muscles [61]. Moreover, hearts from this mouse line displayed reduced systolic and diastolic function, increased expression of the MHC-β/slow, and calcium handling defects in the sarcomere. Interestingly, MuRF2 and MuRF3 reportedly protect heart against diabetic cardiomyopathy via non-proteasomal modification of peroxisome proliferator activating receptors (PPAR)-α/γ transcription factors, suggesting a pivotal role in metabolic pathways as well [62,63].

MuRF3 interacts with four-and-a-half LIM domain (FHL2) and γ-filamin leading to their degradation via UPS [64]. Conversely, abnormal aggregation of these proteins was observed in mice lacking MuRF3. Moreover, MuRF3-/- mice were found more prone to cardiac rupture after acute myocardial infarction (AMI) [64]. Recently, a clinical study aimed to find cardiac specific circulating E3 ubiquitin ligases that may aid in early prognosis of AMI identified increased blood plasma levels of MuRF1, MuRF3, and three other non-TRIM E3 ligases (Rnf207, Fbxo32 and Kbtbd10) in rats and AMI patients [65]. Interestingly, an unbiased metabolomics analysis revealed overlapping substrate specificities for all three MuRFs, where authors detected similarly altered metabolome for MuRF1-/-, MuRF2-/- and MuRF3-/- mouse hearts [66]. These findings suggest that via regulating metabolic pathways in the intact heart, MuRFs have pronounced protective effects on cardiac metabolism during disease states.

TRIM8 (RNF27)

TRIM8, also known as Ring finger 27, characteristically contains both B-boxes while lacks any C-terminal domain (Fig. 3). Recently, Chen et al., (2017) have found upregulation of TRIM8 in human dilated cardiomyopathy patients and hypertrophied mice [67]. TRIM8-deficient mice ameliorated pressure-overload effects after TAC preventing heart failure. On the other hand, its cardiac specific overexpression exaggerated pressure overload hypertrophy after TAC leading to heart failure. Similarly, angiotensin-II mediated pro-hypertrophic effects were also exacerbated in vitro by TRIM8 overexpression. Mechanistically, pro-hypertrophic effects of TRIM8 were found to be mediated via poly-ubiquitination of TAK1 which further activates p38 and JNK1/2 hypertrophic signaling cascades. Prior to its cardiac role, TRIM8 has been intensively characterized in cancer associated studies [68,69].

TRIM21

Along with conserved RBCC frame at N-terminal, TRIM21 (Ro52) possesses PRY/SPRY domains at C-terminal (Fig. 3), which are necessary for its cytoplasmic localization and interaction with IRF3 [47]. It is a principle target for chronic autoimmune disorders like Sjögren's syndrome and systemic lupus erythematosus [70]. Recently, it has also been implicated in cardiac redox homeostasis by non-proteasomal ubiquitination, thus abrogating oligomerization of p62 [71]. TRIM21-deficient mice are protected from oxidative damage caused by pressure overload heart injury due to pronounced accumulation of p62, increased antioxidant response, and reduced ROS release.

TRIM24 (TIF1A, RNF82)

TRIM24 contains a RING-both B-boxes-coiled coil conserved structure at the N-terminus with bromo and PHD domains prior to C-terminal end (Fig. 3). This transcriptional intermediary factor is well studied in the context of transcriptional activation of nuclear receptor via activation function 2 (AF2), owing to its nuclear presence and thus capability to indulge with histones. We recently discovered that TRIM24 is consistently upregulated in the hearts of human patients suffering from hypertrophic and dilated cardiomyopathies [51]. We additionally identified TRIM24 as a bona fide cardiac binding partner of a pro-hypertrophic protein Dysbindin [51,72]. Functionally, we found that binding of Dysbindin to TRIM24 protects it from proteasomal degradation due to TRIM32. This in turn adds to the Dysbindin-mediated activation of RhoA-SRF signaling and cardiomyocyte hypertrophy [51].

TRIM32

TRIM32 harbors RING-B-box-coiled coil tripartite motif at its N-terminus whit six C-terminal NHL repeats (Fig. 3). Its genetic mutations have been linked with muscular dystrophies like Limb girdle muscular dystrophy, Bardet-Biedl syndrome, sarcotubular myopathy, and dystrophic myopathy [73]. TRIM32 has recently been shown to play a protective role in aortic banding mediated pathological hypertrophy by blocking AKT-mediated signaling to prevent heart failure [74]. Using a gain of function approach Chen et al. demonstrated attenuation of excessive hypertrophy and altered cellular architecture of heart in mice overexpressing TRIM32, prompting them to suggest it as a novel therapeutic target in cardiac hypertrophy and heart failure.

We also found downregulation of TRIM32 in the hearts of dilated and hypertrophic cardiomyopathy patients in addition to TAC and phenylephrine treated mice [51]. TRIM32 and Dysbindin are known to interact in skeletal muscle, and we could confirm this interaction in cardiomyocytes as well. In cardiomyocytes, we found that by means of degradation, TRIM32 diminished the pro-hypertrophic effects of Dysbindin. Furthermore, we also found that TRIM32 protect apoptotic inducer p53 and degrades apoptotic inhibitor XIAP through upregulation of Caspase3 and

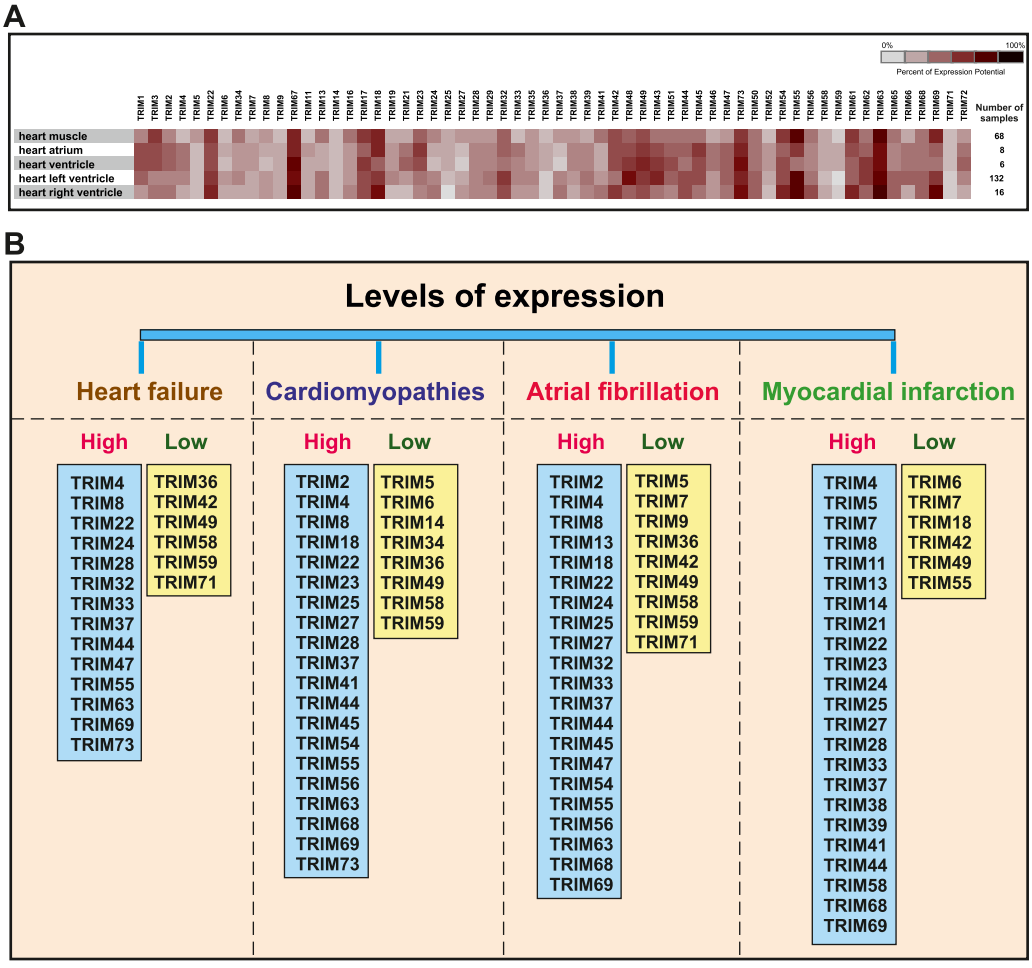


Fig. 5. Affymetrix data analysis indicates (A) significant expression of various TRIMs in the heart and its sub-compartments, and (B) several of these TRIMs are found to be differentially expressed in the heart under disease conditions like atrial fibrillation, cardiomyopathies, heart failure, and myocardial infarction.

Caspase7, thereby critically affecting cellular viability. Thus, we caution against putting TRIM32 forward as a therapeutic agent for cardiac hypertrophy, as this approach may have unwanted side effects due to increased apoptosis and reduced cell viability.

TRIM72 (MG53)

TRIM72, also known as Mitsugumin53 (MG53), possesses the most common structure of TRIM family members, with RING-Bbox1-Coiled coil-PRY/SPRY domains conservatively aligned from N-terminus to C-terminus. Mammalian Gene Collection (MGC) indicates two possible mammalian isoforms of TRIM72, one of which has been stated canonical and studied intensively in the context of preserving muscle integrity by sarcomere repair in skeletal and cardiac muscles [75]. MG53 is noted to play a central role in insulin resistance and thus metabolic disorders such as obesity and diabetes, with possible involvement in cardiovascular diseases like diabetic cardiomyopathy. MG53 has been reported to mediate degradation of both insulin receptor and insulin receptor substrate 1 (IRS1), causing dyslipidemia and hypertension besides metabolic disorders. In contrast, its ablation has been credited with preserving insulin receptor and IRS1. Thus, the mechanistic role of MG53 has been defined by investigating it as therapeutic agent for metabolic disorders and their cardiovascular complications [76]. In the heart, MG53 has been reported to be a vital player in both preconditioning and post-conditioning by activating PI3K-Akt-GSK3β and ERK1/2 cell survival signaling pathways in ischemia-reperfusion [77,78]. For example, myocardial injury resulting from ischemia/reperfusion in the dysferlin murine KO model is strongly correlated with myocardial muscle impairment, resulting in a clinical trial in pediatric patients undergoing corrective heart surgery. Notably, human myocardium does not express MG53; suggesting rhMG53 might be an effective tool for muscular injuries in both skeletal and cardiac muscle repair [79]. Furthermore, MG53 (TRIM72) has been reported with dual roles, beneficial in phosphatidylserine-dependent prevention of skeletal muscle damage, protection of heart against ischemia-reperfusion injury, protection of other vital organs by membrane repair; while being maladaptive in the development of skeletal muscle insulin resistance, in the regulation of myogenesis [80]. This 'Janus-faced' nature of TRIM72 makes it a double-edged-sword for human diseases, taking in question its usage as a therapeutic agent.

Expression data suggest involvement of additional TRIMs in heart function

Given the complexity of the cardiac function, involved molecular pathways and processes, and the fact that only a few of the TRIMs have thus far been shown to have a cardiac role, we hypothesized that there would be more TRIMs mediating important functions in the heart. Along these lines, we checked the expression of all known human TRIMs in various heart regions using human affymetrix data publicly available with Genevestigator (https://genevestigator.com/gv/). Several of the yet

uncharacterized TRIMs were found to be significantly expressed in the heart, such as TRIM18, TRIM22, TRIM42, TRIM49, TRIM67, TRIM69, and TRIM73 (Fig. 5A). We additionally determined the expression of all TRIMs present in myocardium under cardiac disease settings like heart failure, cardiomyopathies, myocardial infarction, and atrial fibrillation. Interestingly, in addition to known cardiac TRIMs, several other TRIMs were found to be differentially regulated in these disease conditions (Fig. 5B). Moreover, majority of the TRIMs which were found significantly expressed in the heart e.g. TRIM17, TRIM18, TRIM22, TRIM42, TRIM48, TRIM49, TRIM67, TRIM69, and TRIM73, were also part of the dysregulated TRIMs in cardiac disease conditions. Although these bioinformatics findings need experimental validations, overall, these data suggests the potential of more cardiac specific research for TRIMs in disease context (Fig. 5B).

Concluding remarks and prospective

Cardiac proteinopathy, a more common disease condition and more frequent cause of cardiomyocyte decay than previously thought, is largely neglected and no effective therapy exists yet. Protein quality control and protein degradation via autophagy or the ubiquitination proteasome system are essential mechanisms in the maintenance of cellular homeostasis. Perturbations of these tightly regulated pathways are involved in several diseases, such as, Parkinson's and Alzheimer's disease, cancer, Crohnś disease, skeletal myopathies, and heart diseases including cardiac hypertrophy and failure. Moreover, several inherited cardiomyopathies are associated with disruption of autophagy and/or pathological protein aggregation, such as mutations in the sarcomeric z-disc proteins BAG3 or desmin and its chaperone α-B-crystallin, leading to proteotoxicity and dilated cardiomyopathy in affected patients. Interestingly, several anti-cancer drugs such as tyrosine kinase inhibitors (e.g. imatinib), anthracyclines (e.g. doxorubicin) or proteasome inhibitors (e.g. bortezomib) impair the UPS or autophagy, thereby secondarily causing cardiomyopathy as a side effect. Thus, there is an urgent need to further investigate and develop innovative therapeutic approaches of cardiomyopathy and heart failure in the context of proteinopathies. Modulation of E3 ligases in the heart poses great potential as an alternative and specific therapeutic strategy. For example, an unbiased high-throughput screen by Robbins lab has recently identified several potential candidates including E3 ligases that accelerate or attenuate formation of cardiomyocyte protein aggregates [81]. Similarly, downregulation of TRIM8 or TRIM21 is proven to be beneficial and suggested as potential therapeutic approaches for pathological hypertrophy and heart failure. Moreover, it is also important to understand that E3-ligases selectively ubiquitinates distinct target proteins because of the presence of distinct target binding domains. This very fact can be therapeutically exploited, (i) to activate or supplement an E3-ligase that can selectively degrade a misfolded or unfolded protein of interest to reduce or dissolve protein aggregates formed, and (ii) to activate or inhibit downstream signaling pathways or cellular processes, in order to improve cardiac function in heart disease conditions.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tcm.2018.05.007.

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