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Review article

The role of ubiquitin ligases in cardiac disease

Monte S. Willis [a,b,*], Ariana Bevilacqua [b], Thomas Pulinilkunnil [c], Petra Kienesberger [c], Manasi Tannu [d], Cam Patterson [e]

[a] McAllister Heart Institute, University of North Carolina, Chapel Hill, NC, USA
[b] Department of Pathology and Laboratory Medicine, University of North Carolina, Chapel Hill, NC, USA
[c] Department of Biochemistry and Molecular Biology, Dalhousie Medicine, Dalhousie, New Brunswick, Canada
[d] College of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
[e] Departments of Cell and Developmental Biology, Medicine (Cardiology), and Pharmacology, University of North Carolina, Chapel Hill, NC, USA

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ABSTRACT

Rigorous surveillance of protein quality control is essential for the maintenance of normal cardiac function, while the dysregulation of protein turnover is present in a diverse array of common cardiac diseases. Central to the protein quality control found in all cells is the ubiquitin proteasome system (UPS). The UPS plays a critical role in protein trafficking, cellular signaling, and most prominently, protein degradation. As ubiquitin ligases (E3s) control the specificity of the UPS, their description in the cardiomyocyte has highlighted how ubiquitin ligases are critical to the turnover and function of the sarcomere complex, responsible for the heart's required continuous contraction. In this review, we provide an overview of the UPS, highlighting a comprehensive overview of the cardiac ubiquitin ligases identified to date. We then focus on recent studies of new cardiac ubiquitin ligases outlining their novel roles in protein turnover, cellular signaling, and the regulation of mitochondrial dynamics and receptor turnover in the pathophysiology of cardiac hypertrophy, cardiac atrophy, myocardial infarction, and heart failure. This article is part of a Special Issue entitled "Cardiac Protein Quality Control".

Contents

Abbreviations: AChRs, acetylcholine receptors; AKAP121, A-kinase anchor protein 121; c-Cbl, Casitas b-lineage lymphoma; Cav3, cavelin 3; CHIP, c-terminus of Hsp70-interacting protein; cIAP, cellular inhibitor of apoptosis; cMyBP-C, cardiac myosin binding protein C; Drp1, dynamin-1-like protein; E1, ubiquitin-activating enzyme; E2, ubiquitin-conjugating enzyme; E3, ubiquitin ligase; Fbxl22, F-box and leucine-rich repeat protein 22; Fis1, fission 1; hERG, human ether-à-go-go-related gene; MAFBx, atrogin-1/muscle atrophy F-box; MDM2, murine double minute 2; Mfn-1 (-2), mitofusin-1 (-2); OMM, outer mitochondrial membrane; MuRF1(2,3), muscle ring finger-1 (-2, -3); Nedd4-2, neural precursor cell expressed developmentally down-regulated protein 4-2; Opa1, optic atrophy 1; Siah1a/2, seven in absentia homolog-1a/2; PINK1, PTEN-induced putative kinase protein 1; UBE3A/E6AP, ubiquitin-protein ligase E3A.

* Corresponding author at: McAllister Heart Institute, University of North Carolina at Chapel Hill, 2340B Medical Biomolecular Research Building, 111 Mason Farm Road, Chapel Hill, NC 27599-7525, USA. Tel.: +1 919 843 1938; fax: +1 919 843 4585.
E-mail address: monte_willis@med.unc.edu (M.S. Willis).

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1. Introduction

Rigorous surveillance of protein quality control is essential for the maintenance of normal cardiac function. Dysregulation of this routine protein turnover has been implicated in common cardiac diseases, including cardiac hypertrophy, cardiac atrophy, ischemic heart disease and heart failure. The ubiquitin proteasome system (UPS) is a fundamental regulator of protein quality control in all cells, including the cardiomyocyte, which participates in protein trafficking, cellular signal transduction, and in prominently, degradation. When components of the UPS function normally, the integrity of proteins that make up the sarcomere, mitochondria and cell membrane is maintained, allowing for normal heart function. Conversely, cardiac dysfunction is prominently associated with alterations in UPS function. As part of the UPS, ubiquitin ligases (E3s) have the key role of directing the addition of ubiquitin to specific target proteins, thereby marking them for degradation, decreasing their activity, and/or changing their physical location within the cell. By maintaining protein quality control and regulating many critical cellular processes, cardiac ubiquitin ligases are critically important to maintaining the heart in health and disease. The role cardiac ubiquitin ligases have in health and disease is rapidly expanding, as new research reveals novel protein targets as well as expanding novel functional roles for each cardiomyocyte-specific ubiquitin ligase. This review provides an overview of the UPS in the heart, focusing on ubiquitin ligase activity in cardiac health and disease.

2. The components of the UPS and how they interact

The process of protein quality control involves the turnover of cellular proteins as they become damaged over time. This process occurs in multiple steps, whereby damaged proteins (e.g. recognized as chronically misfolded proteins) are recognized and degraded so that newly synthesized proteins can replace them. This process preserves critical cellular functions throughout the cell. The rate of protein turnover varies widely between cellular components, reflecting their function in the cell. For example, proteins in the nucleus and cytosol may be degraded within minutes; muscle actin and myosin turnover occurs in days to weeks [1]. There are two proteolytic systems responsible for protein degradation, the UPS and autophagy-driven lysosomal degradation, and both of these systems are tightly controlled by complex regulatory mechanisms to ensure that protein degradation occurs selectively and in a timely manner [2–4]. The UPS is a tightly regulated signaling cascade generally involving three classes of enzymes: E1 (ubiquitin-activating enzyme), E2 (ubiquitin-conjugating enzyme), and E3 (ubiquitin ligase). As the names of these enzymes imply, the activated ubiquitin created by E1 is handed off to the E2 to prepare the ubiquitin for conjugation, which then interacts with the E3 (Fig. 1). In addition to disposing of proteins as part of the cellular protein quality control process, the UPS is also involved in the regulation of transcription factors, functioning of the immune system, the regulation of lysosomal-mediated protein degradation (autophagy), and as a source of amino acids [5,6].

3. The role of ubiquitin ligases in cardiac disease

Ubiquitin ligases enact the final step in the ubiquitination cascade and give specificity to the UPS by interacting with specific substrates and tagging them with ubiquitin. Of the hundreds of purported ubiquitin ligases identified in the genome, at least nine have been found in cardiac myocytes and are critical to the pathophysiology of common cardiac disease (summarized in Table 1). These include the muscle ring finger family (MuRF1, 2 and 3), atrogin-1/muscle atrophy F-box (MAFBx), c-terminus of heat shock protein 70-interacting protein (CHIP), and the murine double minute 2 (MDM2). Casitas b-lineage lymphoma (c-Cb1), ubiquitin-protein ligase E3A (UBE3A/E6AP), and cellular inhibitor of apoptosis (cIAP) have also been described in the heart and most recently, F-box and leucine-rich repeat protein 22 (Fbxl22) has been reported [7]. The number of ubiquitin ligases found in the heart, and the fact that each ubiquitin ligase can target multiple proteins, illustrate the high level of influence the UPS has on cardiac function.

Whereas the UPS plays a critical role in maintaining cellular homeostasis under physiologic conditions, the regulation of protein degradation also occurs during the process of cardiac hypertrophy and cardiac atrophy. In cardiac atrophy, increases in protein degradation occur concomitantly with parallel decrease in protein synthesis [8]. Conversely, protein synthesis increases to a greater degree than protein degradation during cardiac hypertrophy [9,10]. Specific ubiquitin ligases have been implicated in the processes of cardiac hypertrophy and atrophy. In mice lacking MuRF1 and atrogin-1, an exaggerated cardiac hypertrophy occurs in response to pressure overload-induced; similarly, MuRF1 −/− mice are resistant to dexamethasone-induced cardiac atrophy [11–14]. These studies have been interpreted to illustrated how MuRF1 and Atrogin-1 inhibit pathologic cardiac hypertrophy [11,12] and how MuRF1 inhibits cardiac atrophy [13,14], whereas other ubiquitin ligases, such as MDM2 and CHIP, have demonstrated a protective role against cardiomyocyte apoptosis in ischemia/reperfusion injury by targeting p53 for proteasomal degradation [15–18]. Although our understanding of ubiquitin ligases in cardiac disease is growing (Table 1), many more are yet to be found and our understanding of their mechanisms continues to grow.

4. Ubiquitin ligases in protein turnover

Though the sarcomere is often envisioned as a static structure, the proteins that make up this contractile unit undergo constant turnover to maintain homeostatic conditions and adapt to physiologic changes. Initial studies of the protein turnover in the heart showed alterations to both protein synthesis and degradation rates after starvation in rats and rabbits [8–10,19,20]. Prior to 2001, the proteasome itself had been implicated in sarcomeric protein turnover [21], but the discovery of the involvement of muscle-specific ubiquitin ligases Atrogin-1 and MuRF1 [22] opened the door for a greater understanding of this highly regulated pathway (Table 1). Subsequent studies illustrated how these and other ubiquitin ligases facilitate the degradation of older, damaged and misfolded sarcomeric proteins so they can be replaced. While these studies illustrate a limited number of substrates for each E3, there is considerably more complexity to E3s in cardiac disease than is suggested by our current knowledge. However, many of the important details that make cardiac E3s disease/stressor dependent is unclear — one possible reason is that the specific substrate may not exist until the heart is stressed as is likely the case of MuRF1's recognition of phospho-c-Jun in ischemia–reperfusion injury (Table 1). Additionally, the types of ubiquitination chains added to substrates depends on the specific E2(s) that various E3s partner with. Recent studies have illustrated that MuRF1 and CHIP, for example, form different types of ubiquitin chains depending on the E2 they are partnered with [23]. It is not clear how these studies are relevant in different cell types or

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