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Review article

Proteasomal and lysosomal protein degradation and heart disease

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ABSTRACT

In the cell, the proteasome and lysosomes represent the most important proteolytic machineries, responsible for the protein degradation in the ubiquitin–proteasome system (UPS) and autophagy, respectively. Both the UPS and autophagy are essential to protein quality and quantity control. Alterations in cardiac proteasomal and lysosomal degradation are remarkably associated with most heart disease in humans and are implicated in the pathogenesis of congestive heart failure. Studies carried out in animal models and in cell culture have begun to establish both sufficiency and, in some cases, the necessity of proteasomal functional insufficiency or lysosomal insufficiency as a major pathogenic factor in the heart. This review article highlights some recent advances in the research into proteasome and lysosome protein degradation in relation to cardiac pathology and examines the emerging evidence for enhancing degradative capacities of the proteasome and/or lysosome as a new therapeutic strategy for heart disease. This article is part of a Special Issue entitled Cardiac Protein Quality Control.

Contents

1. Introduction

Defining how the protein complement of the heart is regulated remains fundamental to our ability to productively identify the processes and proteins that underlie normal and abnormal cardiac function. As heart disease remains the most common cause of death and significant disability worldwide, it is imperative that we understand the mechanistic bases that are responsible for controlling the normal and abnormal protein complements of the different cell types that make up the heart [1]. Protein homeostasis (also known as proteostasis) is the sum total of protein synthesis (translation), post-translational processing and transport, folding, assembly and disassembly into macromolecular complexes, stability and clearance [2]. Protein degradation by either proteasomes or lysosomes plays indispensable roles in protein quantity and quality control in the cell; therefore, proteasomal and lysosomal

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function is essential to proteostasis (Fig. 1) [3]. Generally, the proteasome can degrade individual cellular proteins in a highly targeted fashion via the ubiquitin–proteasome system (UPS) while lysosomes degrade cytoplasmic components, including some individual proteins, protein aggregates, and defective or surplus organelles, through autophagy.

Both the UPS and autophagy have increasingly attracted attention from cardiovascular researchers in the past decade. Many aspects of these degradative and quality control pathways are covered elsewhere in this Special Issue. Exciting progress in elucidating the pathophysiological significance of protein degradation and protein quality control in heart disease has occurred in the past several years; this review will serve to highlight recent advances in proteasomal and lysosomal protein degradation with respect to cardiac pathogenesis, with the primary focus on proteasomes.

2. The proteasome

The UPS is responsible for the degradation of most cellular proteins, native or misfolded. As illustrated by Fig. 2, UPS-mediated proteolysis is highly regulated and is capable of target degradation of individual protein molecules in an ATP-dependent manner. The targeting property is conferred by the ubiquitination step, which covalently attaches one ubiquitin (Ub) or a chain of Ub proteins to the side chain of a lysine residue of the target protein molecule. Ubiquitination is catalyzed sequentially by the Ub activating enzyme (E1), Ub conjugating enzymes (E2), and Ub ligases (E3). The E3 is substrate-specific and therefore its function determines the specificity of UPS-mediated protein degradation. Ubiquitination is countered by deubiquitination, which is catalyzed by deubiquitinases (DUBs). Poly-ubiquitinated proteins can be recognized and delivered by Ub receptors to the 26S proteasome where the substrate is de-ubiquitinated, unfolded, and degraded [4].

The proteasome may be considered as a specialized organelle for targeted degradation of most cellular proteins [5,6]. These large multisubunit proteolytic machines are found in the cytosol, both free and attached to the endoplasmic reticulum (ER), and in the nucleus of eukaryotic cells [7]. It is generally believed that a functional proteasome in the cell is composed of two parts: a 20S proteasome and the regulatory particle (RP) that binds at one or both ends of the 20S (Fig. 2). The 20S proteasome is an axial stack of four rings: two inner antiparallel β rings flanked by two outer α rings. Each β ring harbors 3 protease subunits: β1, β2, and β5, with the proteolytic activities restricted to the inner chamber formed by the two β rings. The α rings function to gate the entry of the substrates into the proteolytic chamber. Some reports show that the 20S can selectively degrade damaged/oxidized proteins [8], but this remains controversial. It is generally accepted that RP is required for proteasomal protein degradation. The RP can be the 19S proteasome, the 11S proteasome, or both [9]. The 19S associated 20S proteasome (i.e., the 26S) is the most studied and is believed to mediate housekeeping protein degradation. The degradation of a polyubiquitinated protein requires the 19S, which recognizes and binds the polyubiquitinated substrates directly or via extra-proteasomal Ub receptors, deubiquitinates the substrate for Ub recycling, and unfolds the substrate and channels the unfolded polypeptide into the 20S proteasome where peptide cleavage takes place. Some polyubiquitinated proteins are recognized and bound to the intra-proteasomal Ub receptors, including Rpn10/S5a and Rpn13/ARM1. Rpn10 and Rpn13 harbor UIM (Ub interacting motif) domains and a Pru (pleckstrin-like receptor for Ub) domain, respectively; hence, they can recruit nearby polyubiquitinated proteins to the proteasome [10]. However, the recruitment of remote

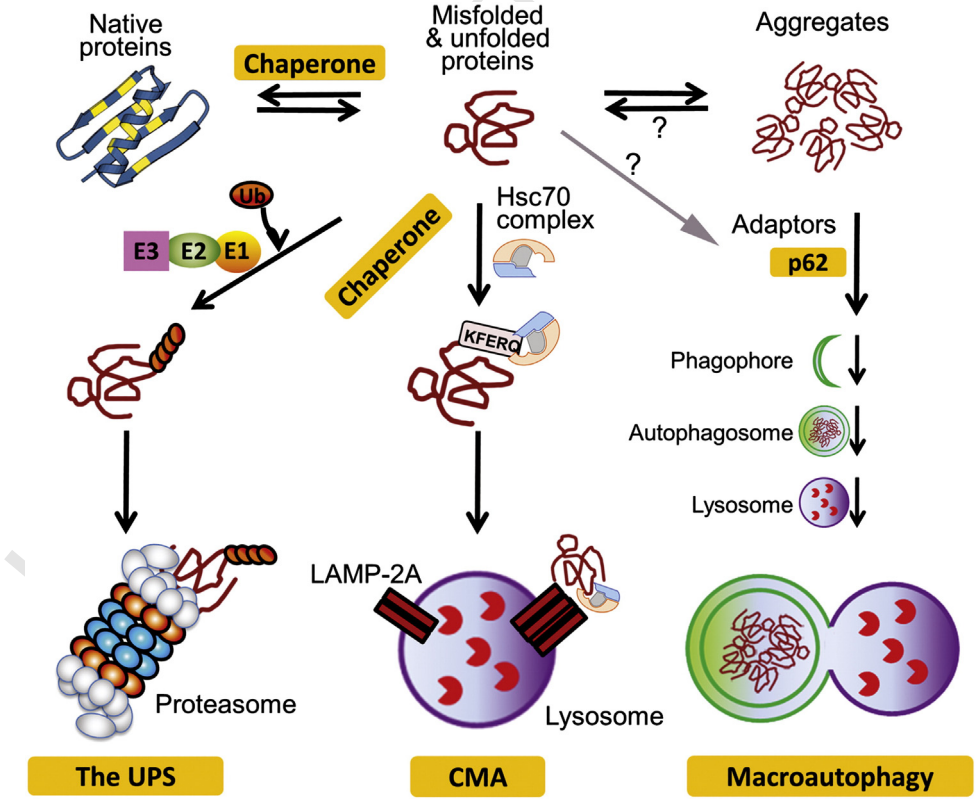

Fig. 1. A schematic illustration of cellular mechanisms protecting against proteotoxicity. Chaperones help fold nascent polypeptides, unfold misfolded proteins and refold them, and escort terminally misfolded proteins for degradation by the ubiquitin–proteasome system (UPS) or chaperone-mediated autophagy (CMA). When escaped from targeted degradation, misfolded proteins form aggregates via hydrophobic interactions. The higher order of aggregation is likely promoted by ubiquitin binding proteins and trafficking via microtubules. Aggregated proteins can be selectively targeted by macroautophagy to, and degraded by, the lysosome.
Modified from Wang et al. [29].

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