The International Journal of Biochemistry & Cell Biology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

The International Journal of Biochemistry & Cell Biology

journal homepage: www.elsevier.com/locate/biocel

Review article

Proteostasis and SUMO in the heart

Elisa Da Silva-Ferrada[a,b], Teresa M. Ribeiro-Rodrigues[a,b], Manuel S. Rodríguez[c,d], Henrique Girão[a,b,*]

[a] Institute for Biomedical Imaging and Life Sciences (IBILI) Research Consortium, University of Coimbra, Coimbra, Portugal
[b] Center for Neuroscience and Cell Biology (CNC), Institute for Biomedical Imaging and Life Sciences (IBILI) (CNC.IBILI), University of Coimbra, Coimbra, Portugal
[c] Institut des Technologies Avancées en Sciences du Vivant (ITAV), Université de Toulouse, CNRS, UPS, France
[d] Institut de Pharmacologie et de Biologie Structurale (IPBS), Université de Toulouse, CNRS, UPS, France

ARTICLE INFO

Article history:
Received 15 June 2016
Received in revised form
15 September 2016
Accepted 16 September 2016
Available online xxx

Keywords:
Heart diseases
PTMs
SUMOylation
Proteostasis

ABSTRACT

Heart proteostasis relies on a complex and integrated network of molecular processes surveilling organ performance under physiological and pathological conditions. For this purpose, cardiac cells depend on the correct function of their proteolytic systems, such as the ubiquitin-proteasome system (UPS), autophagy and the calpain system. Recently, the role of protein SUMOylation (an ubiquitin-like modification), has emerged as important modulator of cardiac proteostasis, which will be the focus of this review.

Contents

1. Introduction

Cardiovascular diseases (CVDs) are a large, complex and multifactorial group of heart and blood vessels disorders, representing the first cause of morbidity and mortality worldwide. Thus, it is important to better understand the molecular mechanisms and signalling pathways behind cardiac cells homeostasis and healthy heart function (Mozaffarian et al., 2016). The main function of the heart is to pump blood throughout the organism to meet the energy and metabolic needs of organs and tissues. To accomplish this function, the heart depends on an extremely organized network of interconnected cells that include: cardiomyocytes (the contractile muscle unit of the heart), endothelial and smooth muscle cells (forming blood vessels that ensure blood transport), fibrob-

* Corresponding author.
E-mail address: hmgirao@fmed.uc.pt (H. Girão).

http://dx.doi.org/10.1016/j.biocel.2016.09.015
1357-2725/

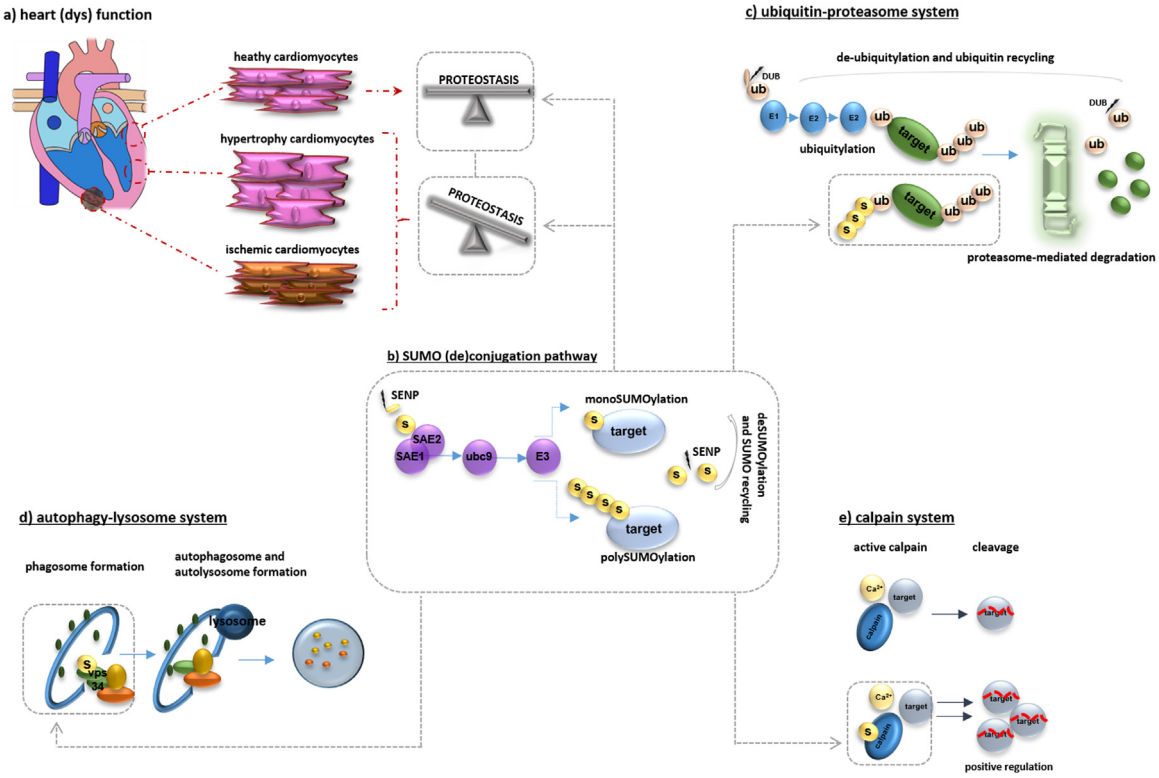

Fig. 1. General schematic illustration of the relation between heart (dys)function, the heart proteolysis mechanisms and SUMOylation. a) illustration of heart (dys) function represented by ischemic or hypertrophy diseases contributing to cardiomyocyte unbalanced proteostasis; b) SUMO (de)conjugation pathway; c) ubiquitin-proteasome system; d) autophagy-lysosome system and e) calpain system. a) the appearance of heart ischemic insults or the development of hypertrophy can result in an unbalanced proteostasis in cardiomyocytes. The association and interplay between the proteolysis systems and other molecular mechanisms as SUMOylation can contribute for an equilibrated proteostasis under physiological and pathological conditions (represented by grey dash square and lines). b) SUMOylation occurs through a cascade of enzymatic reactions initiated by the processing of the pro-protein SUMO by a specific protease (SENP), followed by the activation by the heterodimer E1-activating enzyme (SAE1/SAE2), transferring by the E2 (Ubc9) and ligation by an E3 to target proteins. The covalent attachment of one SUMO molecule is denominated monoSUMOylation and several SUMO molecules polySUMOylation. Additionally, SUMO molecules can be removed by the action of SENPs (deSUMOylation) and be recycled for another cycle of conjugation. c) the pro-form of ubiquitin is processed by a specific protease (DUB), with posterior target conjugation through an enzymatic cascade involving the E1, E2 and E3 enzymes. Ubiquitin chains also can be cleaved by DUBs (de-ubiquitylation) and ubiquitin molecules can be recycled for a new cycle of modification. Cardiac SUMOylated proteins are ubiquitylated to further degradation in the proteasome contributing for proteostasis maintenance (grey dash square and line). d) The autophagy-lysosome system is a multi-step process, involving the phagosome formation, with posterior fusion to the lysosome and final degradation of proteins or organelles. SUMOylation of Vps34 (represented within the grey dashed square and line), promotes phagosome formation, leading to degradation of damaged proteins and organelles, contributing for proteostasis. e) The activation of calpains by Ca^{2+} allows the cleavage of calpain substrates. SUMO modification can potentially positively regulate calpain activity (represented within the grey dashed square and line) contributing for heart proteostasis.

lasts (which produce extracellular matrix and confer support) and immune cells. As in many other organs and tissues, the existence of mechanisms that ensure the quality of cardiac cells proteome is essential for heart function. The maintenance of a healthy proteome, generally called protein homeostasis or proteostasis, relies on an integrated network of mechanisms and signalling pathways, such as protein synthesis, organization and folding (assisted by molecular chaperons); protein trafficking and localization; post translational modifications (PTMs) and protein degradation systems (Martins-Marques et al., 2015). The equilibrium between all of these processes allows the maintenance of a functional group of proteins, selectively eliminating damaged, obsolete and misfolded proteins. Although protein homeostasis is important to the function of any cell type, cells with low mitotic activity such as cardiomyocytes and neurons, are particularly dependent on proteostasis. For this reason, disturbance of proteostasis mechanisms can have severe consequences related to the accumulation of unwanted aggregation prone proteins that lead to cell dysfunction, damage and death, eventually culminating in tissue and organ failure. Unsurprisingly, deregulation of proteostasis in the heart is often associated with cardiac hypertrophy, myocardial ischemic injury, cardiac proteinopathies and heart failure (Sandri and Robbins, 2014) (Fig. 1a). Intracellular protein degradation relies on three major interconnected systems: ubiquitin proteasome system (UPS), autophagy and calpain system. To ensure selective elimination of proteins and organelles these proteolytic systems are highly regulated by many molecular mechanisms, such as PTMs. These modifications can occur on aminoacid side chains or on the termini of proteins, as a result of an enzymatic or chemical reaction, ranging from the addition of large oligosaccharide structures to the formation of protein monomers or polymers. PTMs control numerous processes and signalling cascades involved in cell cycle regulation, DNA repair, protein trafficking/localization and turnover, and protein-protein interactions. The most common PTMs described in the heart include phosphorylation, acetylation, S-nitrosylation, glycosylation and ubiquitylation. Some of these PTMs, such as ubiquitylation, have been demonstrated to be important for protein homeostasis, particularly in the modulation of protein degradation (Porter et al., 2012; Smith and White, 2014). Conjugation of the small ubiquitin-like modifier (SUMO) to proteins (SUMOylation), is emerging as an important player in heart proteostasis. The main purpose of this review is to give an overview of the most recent advances concerning the role played of SUMO in heart pathophysiology.

Please cite this article in press as: Da Silva-Ferrada, E., et al., Proteostasis and SUMO in the heart. Int J Biochem Cell Biol (2016), http://dx.doi.org/10.1016/j.biocel.2016.09.015