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Review

Protein quality control (PQC) senses and repairs

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Protein quality control (PQC) senses and repairs misfolded and or unfolded proteins. However, if the repair fails, it degrades the terminally misfolded polypeptides through an intricate collaboration between molecular chaperones and targeted proteolysis. Proteolysis of damaged proteins is performed primarily by the ubiquitin-proteasome system (UPS). Macroautophagy (commonly known as autophagy) may also play a role in PQC-associated proteolysis, especially when UPS function becomes ineffective. The development of a range of heart diseases, including bona fide cardiac proteinopathies and various forms of cardiac dysfunction has been linked to proteasome functional insufficiency (PFI). Proteasome functional insufficiency and activation of autophagy have been observed in the heart of mouse models of cardiac proteinopathy. Recent studies demonstrated that pharmacologically induced proteasome inhibition is sufficient to activate autophagy in cardiomyocytes in both intact animals and cell cultures. This had unveiled a potential cross-talk between the two major degradation pathways in cardiac PQC.

Key words: Proteasome, autophagy, cardiomyocytes.

INTRODUCTION

Protein quality control (PQC) is a basic cellular process that functions to assist protein (re)folding, protect nascent or unfolded polypeptides from aggregating, and selectively degrade terminally misfolded polypeptides (Wang and Robbins, 2006). Like in other cells, PQC plays an indispensable role in maintaining protein homeostasis (also referred to as proteostasis) in cardiomyocytes. PQC senses and repairs misfolded/ unfolded proteins and, if the repair fails, it degrades the terminally misfolded polypeptides through an intricate collaboration between molecular chaperones and targeted proteolysis. Proteolysis of damaged proteins is performed primarily by the ubiquitin proteasome system (UPS) (Wang and Robbins, 2006). But recent studies suggest that macroautophagy (commonly known as autophagy) may also play a role in PQC-associated proteolysis, especially when UPS function becomes inadequate (Su and Wang, 2010). The development of a range of heart diseases, including bona fide cardiac proteinopathies and various forms of cardiac dysfunction has been linked to proteasome functional insufficiency (PFI) (Su and Wang, 2010; Li and Wang, 2011).

Although, proteasome inhibition is clinically employed to treat certain types of cancer, it has shown promising efficacy but severe adversary effects on the heart have also been reported (Li and Wang, 2011). Therefore, it is important to have a better understanding of how cardiomyocytes and the heart respond to proteasome

Inhibition/malfunction.

DEGRADATION PATHWAYS OVERVIEW

The UPS and autophagylysosome pathway are the two major intracellular protein degradation pathways that are responsible for the clearance of proteins and organelles that are no longer needed or unwanted in eukaryotic cells (Klionsky et al., 2011). Based on the degration kinetics, proteins have been divided into two categories namely, "short-lived" and "long-lived" proteins (Fuertes et al., 2003a). The UPS predominantly degrades short-lived normal protein molecules after they have fulfilled their duty in the cell (Hochstrasser, 1995). On the other hand, autophagy is primarily responsible for degrading long-lived proteins (Yoshimori, 2004). Notably, the distinction of substrate preference between the two proteolytic systems is not mutually conclusive, as their roles tend to overlap. For instance, the UPS can participate in the degradation of long-lived proteins while autophagy can also be involved in the degradation of short-lived proteins (Fuertes et al., 2003; Fuertes et al., 2003b).

However, an alternative way of categorising proteolytic mechanisms based on function rather than the degradation kinetics has been proposed. Based on functions, it has been observed that, the UPS degrades two types of proteins: the fully functional proteins which are degraded as a regulatory mechanism, such proteins are involved in regulation of cell division, gene transcription, signal transduction, endocytosis; and abnormal proteins, thereby serving as a critical step for post-translational PQC in the cell (Wang and Robbins, 2006; Gomes et al., 2006). Autophagy also degrades two types of proteins: functional proteins which are degraded in a bulk fashion as a nutrient recycling mechanism during starvation, and perhaps aggregated misfolded proteins or defective organelles. Thus, it appears that these two degradation systems cooperate with each other to degrade the misfolded proteins (Ding and Yin, 2008).

DEGRADATIION PATHWAYS AND CARDIOMYOCITES

Misfolded cytosolic proteins are partitioned into two distinct PQC compartments. Soluble misfolded proteins accumulate in a juxtanuclear compartment preferentially for degradation by the UPS (Kaganovich et al., 2008). In contrast, terminally aggregated proteins are partitioned in a perivascular inclusion and are mainly degraded by Autophagy because they cannot be efficiently degraded by the proteasome (Ding and Yin, 2008; Kaganovich et al., 2008). However, the interplay between the UPS and autophagy in normal and diseased hearts remains poorly understood. In a study using a surrogate substrate reporter system, it revealed PFI in the heart of two bona fide mouse models of cardiac proteinopathy (Liu et al., 2006; Chen et al., 2005). Aberrant protein aggregation was subsequently shown to play a critical role in the proteasome impairment induced by expression of misfolded proteins in cardiomyocytes (Chen et al., 2005; Liu et al., 2006). It was reported that autophagy is adaptively activated in the heart of the well established mouse model of cardiac proteinopathy and this is accompanied by upregulation of p62 (Zheng et al., 2011). The p62 is a substrate of autophagy and its increase is often used as an indicator of decreased autophagic flux. The paradoxical increase of p62 during autophagic activation in cardiac proteinopathy occurs at the transcription level and may in fact mediate the autophagic activation in the cell under a proteotoxic stress (Zheng et al., 2011). Interestingly, a report showed in cultured cardiomyocytes that pharmacological inhibition of the proteasome increased simultaneously autophagosomes and p62 in cultured cardiomyocytes (Tannous et al., 2008). Indeed, it has been shown in non-cardiac cells that p62 is a target gene of the Keap1-Nrf2 regulatory pathway (Jain et al., 2010).

Kelch-like ECH-associated protein 1 (Keap1), a born to bind (BTB) protein, serves as the substrate-specific adaptor in a Cullin3-based ubiquitin ligase for Nrf2. Under unstressed conditions, Keap1 constitutively binds Nrf2 and targets Nrf2 for ubiquitination and proteasome mediated degradation (Kobayashi et al., 2004; Cullinan et al., 2004). Upon oxidative stress, dissociation of Keap1 from Nrf2 stabilizes Nrf2 and allows Nrf2 translocate to the nucleus to activate its target genes (Zhang et al., 2004). More recent studies further demonstrated that p62 can disrupt Keap1-Nrf2 interaction, forming a feed-forward loop (Komatsu et al., 2010). It was found that pharmacologically induced proteasome inhibition (PSMI) increased autophagosomes in mouse hearts and this increase is due to increased autophagic flux in cardiomyocytes (Qingwen et al., 2011).

DISCUSSION

It has been demonstrated that pharmacologically induced PSMI is sufficient to activate autophagy in cardiomyocytes in both intact animals and cell culture (Qingwen et al., 2011). Studies have shown that proteasome inhibitors increase autophagy in cell lines including cortical neurons and HEK293 cells (Qingwen et al., 2011; Iwata et al., 2005). One recent study showed that pharmacologically induced PSMI by 5ƒÝM MG-132 elicited modest increases in LC3-II levels in cultured cardiomyocytes (Qingwen et al., 2011). Some studies extend previous findings in several important ways. First, MG132 and bortezomib, belonging to two mechanistically different groups of proteasome inhibitors, are sufficient to trigger autophagy in cardiomyocytes . Moreover, low doses of proteasome inhibitor were found to be able to activate

autophagy. In a particular study, it was shown that peptidase activity monitors the proteasome inhibition effect (Qingwen et al., 2011). 200 nM of MG132, which inhibits chymotrypsin-like activity to 46%, is able to increase autophagy in cardiomyocytes (Qingwen et al., 2011). In other studies, MG132 at much higher doses was used to activate autophagy (Qingwen et al., 2011; Iwata et al., 2005). Furthermore, MG132 treatment combined with lysosomal inhibition increased accumulation of autophagic vacuoles. PSMI by bortezomib increases autophagosomes in neonatal rat ventricular myocytes (NRVMs). More strikingly, a study reveals that systemic proteasomal inhibition increased autophagosomes in major mouse organs (Qingwen et al., 2011). These experiments demonstrate that pharmacologically induced PSMI is capable of elevating autophagy in cardiomyocytes and intact mice. Therefore, a direct causal link between PFI and autophagy enhancement is suggested (Qingwen et al., 2011).

Mammalian cells are endowed with the ability to defend against the potentially toxic effects of misfolded proteins. The UPS and autophagy are important players for maintaining protein homeostasis in cells. Together with another recent report (Zheng et al., 2011), it has been established that autophagy is upregulated in bona fide mouse models of cardiac proteinopathy as well as in response to pharmacologically induced PSMI. Given that UPS proteolytic function is inadequate in the cardiac proteinopathy mice (Liu et al., 2006; Chen et al., 2005), this leads to the proposition that autophagy is activated to compensate for the impaired or insufficient UPS function in order to protect cells from misfolded protein stresses. Autophagy has been generally characterized as a non-selective degradation pathway. Recently, there is a growing body of evidence suggesting that autophagy also selectively degrades various cellular structures, including protein aggregates, damaged mitochondria and invading microbes (Xie and Klionsky, 2007; Kirkin et al., 2009). It has been found that the removal of aggregate-prone proteins related to neurodegenerative diseases is largely dependent on autophagy (Yamada et al., 2002; Rubinsztein et al., 2005). Moreover, protein aggregates are accumulated in autophagy deficient mice (Komatsu et al., 2006; Hara et al., 2006; Nakai et al., 2007). When cells are subjected to misfolded protein stress, the accumulation of unfolded/misfolded proteins induces endoplasmic reticulum (ER) stress. The unfolded protein response (UPR) triggered by ER stress is an integral part of intracellular PQC (Schroder and Kaufman, 2005).

Terminally misfolded ER proteins are retrogradely transported out of the ER and immediately subjected to ubiquitination and proteasomal degradation via ER-associated protein degradation (ERAD) in the cytosol (Hebert and Molinari, 2007). However, sustained ER stress causes accumulation of UPS reporter substrates, which indicates that sustained ER stress has an inhibitory effect on the UPS (Menendez-Benito et al., 2005). When ERAD is overloaded by ER inhibitors or blocked by proteasome inhibitors, autophagy is mobilized to degrade terminally misfolded ER proteins via the ER-activated autophagy (ERAA) pathway (Fujita et al., 2007; Kouroku et al., 2007; Ding et al., 2007; Ogata et al., 2006).

In autophagy-defective tumor cells, although no accumulation of polyubiquitinated proteins occurs, the accumulation of ER chaperones and the oxidative protein folding machinery in autophagy-deficient cells and tumors indicates a defect in the management of protein turnover (Mathew et al., 2009). Several reports have suggested that autophagy is activated by misfolded protein stress via upregulated ER signaling. In a recent study, Hill's group reported that accumulation and aggregation of ubiquitinated proteins upregulated the UPR regulator Bip and triggered activation of autophagy in a mouse model of load induced heart failure (Tannous et al., 2008). Additionally, accumulation of misfolded proteins, such as polyQ72 aggregates, in the ER stimulated LC3 conversion from LC3-I to LC3-II through phosphorylation of PERK (RNA-dependent protein kinase-like ER kinase) and eukaryotic initiation factor 2á (eIF2á) (Kouroku et al., 2007). A related study with human tumor cells revealed that UPR protects against hypoxic tumor cells by inducing LC3 and Atg5 gene expression via the PERK/eIF2ƒÑ signalling branch (Rouschop et al., 2011).

Previously, ubiquitination was generally considered as a signal for a protein to be degraded by the proteasome. Misfolded proteins, which are often ubiquitinated, were thought to be mainly degraded by UPS. Recent findings suggest that ubiquitinated proteins are also a major class of substrate for selective autophagy. This is suggested by the elevated ubiquitinated protein levels in tissue-specific knockout of Atg7 or Atg5 in mouse brains, livers and hearts (Pankiv et al., 2007). Therefore, attachment of ubiquitin to various cellular cargos constitutes a universal degradation signal recognized by both UPS and the autophagy-lysosome pathways. The question arises as to what determines if a ubiquitinlabeled protein substrate will enter one or the other pathway. Recent studies suggest that K48-linked polyubiquitination is associated with the UPS, whereas K63-linked polyubiquitination chains provide a signal for selective autophagic degradation (Kirkin et al., 2009; Tan et al., 2008). A potential working model is that under the circumstance of PFI or PSMI, polyubiquitinated proteins accumulate. This accumulation of polyubiquitinated proteins may provide a signal that leads to activation of selective autophagy. Under this condition, autophagy functions as a compensatory mechanism to eliminate proteins that have escaped the surveillance of the UPS. The p62 and other ubiquitin binding protein may mediate this cross-talk between the UPS and autophagy. To date, for at least cardiomyocytes, this remains an attractive hypothesis to be formerly tested. The p62 is a multi-functional adaptor protein that has been implicated in homeostatic cell function. As an adaptor molecule, p62 links ubiquitinated

proteins to the autophagic machinery (Bjorkoy et al., 2005). The C-terminal portion of p62 binds poly-ubiquitinated substrates through itsubiquitin-associated (UBA) domain and directly binds to LC3 via the LC3 interacting region (LIR) motif (Pankiv et al., 2007). p62 can also polymerize via its Nterminal Phox/Bem1p (PB1) domain and interact with the proteasome via an N-terminal ubiquitin-like (UBL) domain. Interaction of the UBL domain with proteasomes may be involved in shuttling substrates for proteasomal degradation (Seibenhener et al., 2004).

In cultured neuronal cells, the increase in both transcript and protein levels of p62 in response to PSMI has been reported and p62 was purported to sense proteolytic stress with PSMI and be involved in mediating the alternative degradation pathway to alleviate proteolytic stress (Kuusisto et al., 2001). PFI, upregulation of both the transcript and protein levels of p62, and increased autophagic flux have been found to coexist in mouse hearts overexpressing human disease-linked misfolded proteins.

It will be very important to sort out the inter-relationship among these derangements. The findings of the present study favor the model that PFI accumulates Nrf2; increased Nrf2 in turn increases the transcription of p62; and p62 further activates Nrf2 through a positive feedback on one hand and activates autophagy on the other hand. Increased autophagy will attempt to compensate for PFI by selectively removing misfolded proteins in the cell, thereby helping the cell to survive. In support of the above model, reduction of p62 protein levels or interference with p62 function significantly increases cell death induced by the expression of mutant huntingtin proteins (Bjorkoy et al., 2005). However, one study using mice with genetic inactivation of p62 and Atg7 showed that loss of p62 markedly attenuated liver injury caused by autophagy deficiency; whereas p62 deficiency had little effect on neuronal degeneration (Komatsu et al., 2007). The reason for this apparent discrepancy is not yet clear. With the loss of Atg7 in the liver, accumulated p62 might be above the level of optimum cell survival and the detrimental function of p62 might be activated (Moscat and Diaz-Mec, 2009). Furthermore, when autophagy is inhibited, the accumulation of p62 was shown to account for the impaired degradation of UPS substrates (Korolchuk et al., 2009). Moreover, p62 overexpression at levels similar to those in autophagy-deficient cells increases polyQ aggregation and toxicity. This effect is proteasome dependent and autophagy independent (Korolchuk et al., 2009).

CONCLUSION

Therefore, it appears that p62 is a double-edge sword and the consequence of its upregulation in the cell depends heavily on the functional status of the autophagic-lysosomal pathway and may also be cell-type specific. Further investigation of the cross-talk between the UPS and autophagy in the heart is clearly warranted.

Conflict of interest

The authors have not declared any conflict of interest.

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