Minireview

Crosstalk and Interplay between the Ubiquitin-Proteasome System and Autophagy

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Proteolysis in eukaryotic cells is mainly mediated by the ubiquitin (Ub)-proteasome system (UPS) and the autophagy-lysosome system (hereafter autophagy). The UPS is a selective proteolytic system in which substrates are recognized and tagged with ubiquitin for processive degradation by the proteasome. Autophagy is a bulk degradative system that uses lysosomal hydrolases to degrade proteins as well as various other cellular constituents. Since the inception of their discoveries, the UPS and autophagy were thought to be independent of each other in components, action mechanisms, and substrate selectivity. Recent studies suggest that cells operate a single proteolytic network comprising of the UPS and autophagy that share notable similarity in many aspects and functionally cooperate with each other to maintain proteostasis. In this review, we discuss the mechanisms underlying the crosstalk and interplay between the UPS and autophagy, with an emphasis on substrate selectivity and compensatory regulation under cellular stresses.

INTRODUCTION

Central to both the UPS and autophagy is ubiquitination, i.e., the conjugation of the 76-amino acid protein ubiquitin to the lysine (Lys) residues of other proteins (Ciechanover, 2015; Ciechanover and Kwon, 2015; 2017). Ubiquitination can generate degradation signals (degrons) on substrates destined for destruction by the proteasome or lysosome or, alternatively, modulate their non-proteolytic processes (Ohtake and Tsuchiya, 2017). Ubiquitin can be conjugated to a substrate as a monomer at a single (monoubiquitination) or multiple (multi-monoubiquitination) Lys residues. A ubiquitin moiety can be further conjugated by another ubiquitin via any of its seven Lys residues (Lys6, Lys11, Lys27, Lys29, Lys33, Lys48, and Lys63) or, alternatively, the N-terminal methionine (Met1) (Swatek and Komander, 2016). Moreover, a single ubiquitin polymer often contains mixed ubiquitin linkages, in which ubiquitin is conjugated with other ubiquitin through two or more different linkages. Ubiquitin can also be modified at two or more sites, forming a branched conjugate (Yau and Rape, 2016). Additive to the complexity of the ubiquitin code, recent studies show that ubiquitin on substrates can be modified by ubiquitin-like modifiers such as SUMO, NEDD8, and ISG15 (Morris and Garvin, 2017; Seeler and Dejean, 2017) or small molecule chemicals such as phosphate and acetate (Yamano et al., 2016). The ubiquitin linkages and their modifications generate distinct structures and recruit specific downstream effectors, generating a countless variation in information for the substrates (Akutsu et al., 2016).

Ubiquitin chains can serve as the proteasomal degrons which are selectively bound by the ubiquitin-binding domains (UBDs) of adaptors (Grice and Nathan, 2016; Scott et al., 2015). UBDs decode the distinct structures of ubiquitin

chains and transfer the information on the substrates to downstream machinery. Some UBD-containing adaptors link the substrates to the proteasome (e.g., RPN10 and RPN13) or autophagic vacuoles (e.g., p62/SQSTM-1/Sequestosome-1 and neighbor of BRCA1 gene 1 (NBR1)). The recognition of ubiquitin chains by UBD adaptors can induce the removal of damaged or surplus subcellular organelles such as mitochondria or invading pathogens (Deng et al., 2017). Overall, the Lys48 linkage is the most abundant, representing up to half of all linkages, and serves as a strong proteasomal degron. Next to Lys48 linkages in abundance, Lys63 linkages serve as *cis*-mode autophagic degrons for protein substrates and *trans*-mode autophagic degron for their associated non-proteinaceous materials such as damaged mitochondria (Deng et al., 2017). In addition to Lys48 and Lys63 linkages, Lys11 and Lys29 linkages can facilitate proteasomal degradation, whereas K6 linkages have been implicated in autophagic degradation (Dwane et al., 2017). Relatively little is known about the functions of atypical linkages (Dwane et al., 2017).

UBIQUITIN AS A COMMON DEGRON OF THE UPS AND AUTOPHAGY

There has been a general notion that ubiquitination generates the degrons that induce acute degradation by the proteasome. Emerging evidence suggests that ubiquitin chains also play an essential role as general autophagic degrons for proteins as well as their associated subcellular organelles and foreign materials (Ciechanover and Kwon, 2017; Deng et al., 2017). Thus, ubiquitin is a common denominator shared by the UPS and autophagy under the umbrella of a single proteolysis network.

Ubiquitin-based proteasomal degrons

The primary ubiquitin chain type for proteasomal degradation is the Lys48 linkage. Lys48-linked polymers on substrates are bound by the UBDs of adaptors such as proteasome-associated RPN10 and RPN13 (Collins and Goldberg, 2017). Proteasomal degradation based on Lys48 linkages modulates the half-lives of a large number of short-lived proteins (estimated to exceed 5,000) in various biological processes (Ohtake and Tsuchiya, 2017). Accordingly, a variety of E3 Ub ligases assemble Lys48-linked chains for proteasomal degradation, including UBR box N-recognins (Kwon et al., 1998; Tasaki et al., 2005), gp78 (Liu et al., 2014), E6AP (Kim and Huibregtse, 2009), and SCF (Suber et al., 2017). In addition to Lys48 linkages, recent studies showed that atypical chain types, such as Lys11 and Lys29 linkages, can also act as proteasomal degrons. Lys11 linkages are typically found in a mixed chain with Lys48 and Lys63 and can facilitate proteolysis by the proteasome. The E3 ligases that assemble Lys11 linkages include the anaphase-promoting complex (APC/C) that targets cell cycle regulators (Brown et al., 2016; Lu et al., 2015a) and the HECT-domain protein WWP1 that assembles Lys63, Lys48, and Lys11 linkages (French et al., 2017). Other substrates of Lys11 linkages include misfolded proteins in the endoplasmic reticulum (ER) lumen destined for ERAD (ER-associated degradation) (Locke et al., 2014) and

STING during innate immunity in response to viral infection (Qin et al., 2014). Albeit less frequently, Lys29 linkages are also implicated in proteasomal processing of substrates as exemplified in the yeast ubiquitin fusion degradation (UFD) pathway (Liu et al., 2017). In addition, Lys63-linked chains via the yeast E3 ligase Rsp5 facilitate the proteasome-binding and cleavage of the yeast transcription factors SPT23 (Richly et al., 2005) and Mga2-p120 (Saeki et al., 2009).

Although why Lys48 and Lys11 chains are more frequently used for proteasomal targeting is not yet well understood, it was suggested that any one linkage type may not be sufficient to fully account for proteasomal degradation (Lu et al., 2015b). Contrary to the previously held notion that the most efficient chain type for proteasomal degradation is a tetrameric Lys48 chain, multiple Lys48-linked di-ubiquitin conjugates provide a stronger degron (Lu et al., 2015b). Consistently, there is an observation that multiple chain topologies on several Lys residues are likely required as a result of the physical distance and conformation of the proteasomal ubiquitin receptors and cargo adaptor proteins (Yau and Rape, 2016). Also contrary to traditional views, monoubiquitination is sufficient for proteasomal degradation as well (Braten et al., 2016). Moreover, the majority of ubiquitinated substrates contain more than one site with which bind ubiquitin (Kim et al., 2011), and increasing ubiquitination-permissive lysine residues renders the substrates more prone to proteasomal turnover. For example, the proteasome-associated E3 ligase HUL5 assembles Lys63-linked chains on the substrates marked for degradation (Crosas et al., 2006), highlighting the complexity of ubiquitin chain linkages as proteasomal degrons.

Ubiquitin-based autophagic degrons

In protein quality control, misfolded proteins are recognized by molecular chaperones and ubiquitinated by E3 ligases such as UBR1, UBR2, Parkin, C-terminus of Hsc70-interacting protein (CHIP), San1, E6-AP, and Hul5 (Ciechanover and Kwon, 2017). The ubiquitin chains on substrates are bound by the UBDs of the proteasome-associated adaptors such as RPN10 and RPN13, leading to proteasomal targeting. If ubiquitinated substrates are resistant to proteasome degradation, for example, owing to their aggregation-prone nature, they are directed to macroautophagy or temporarily stored in aggresomes (Ciechanover and Kwon, 2015). In macroautophagy, the cargoes are collected by autophagic adaptors such as p62 or NBR1 (Zaffagnini and Martens, 2016). These adaptors can bind ubiquitin degrons on substrates using their UBDs and LC3 on autophagic vacuoles using their LIR domains (Cha-Molstad et al., 2015). Cargo-loaded p62 molecules undergo self-polymerization and are sequestered in autophagosomes and degraded by lysosomal hydrolases (Stolz et al., 2014). If misfolded protein aggregates cannot be immediately processed by macroautophagy, the cargoes are collected by HDAC6 (histone deacetylase 6) that binds the cargoes' ubiquitin chains using its UBD (Ciechanover and Kwon, 2017). The aggregates stored in the aggresome are eventually degraded in part by lysosomal hydrolases (Hyttinen et al., 2014). In both path-

ways, ubiquitin chains assembled on substrates are the major autophagic degrons. Given that the majority of normally short-lived substrates of the UPS are conjugated with Lys48 linkages, this type of ubiquitin chains should at least partially facilitate their autophagic degradation. Intriguingly, p62, NBR1, and HDAC6 preferentially bind Lys63 chain linkages (Kirkin et al., 2009). This raises a possibility that Lys63 is the primary ubiquitin chain type for autophagic targeting and degradation (Wurzer et al., 2015). Congruent with this emerging notion, various E3 ligases assemble Lys63 linkages on protein substrates in the context of autophagic turnover, such as Parkin (McKeon et al., 2015), TRIM13 (Tomar et al., 2013), and CHIP (Ferreira et al., 2015). These Lys63 chain-linked substrates are often associated with damages or surplus subcellular organelles in the course of autophagic degradation, including mitochondria (mitophagy), ER (ER-phagy), ribosomes (ribophagy), and liposomes (lipophagy) (Deng et al., 2017). Overall, Lys63-linked chains function as general autophagic degrons.

In some cases, other atypical linkages can sufficiently act as autophagic degrons. For example, during antibacterial xe-nophagy, Met1 linear ubiquitin chains coat the surface of pathogenic microbes for ubiquitin-dependent autophagic degradation (van Wijk et al., 2012; Wild et al., 2011). Parkin-assembled Lys6 and Lys11 atypical linkages were observed on ubiquitinated mitochondria upon membrane depolarization (Cunningham et al., 2015). Even Lys48 linkages can partially target α-1-antitrypsin mutant Z (ATZ), a pathologically aggregation-prone protein, for autophagy degradation (Feng et al., 2017). Moreover, in parallel with Lys63, both Lys48 and Lys11 ubiquitin chains accumulate in *Atg5-* and *Atg7*-knockout mice (Riley et al., 2010).

Taken together, cells may employ multiple types of heterotypic chain linkages in both the UPS and autophagy, as opposed to any one homotypic chain type. Moreover, considering the variety of post-translational modifications available to not only substrates and regulatory proteins but also ubiquitin itself, the mere presence or type of ubiquitin chain linkages is unlikely adequate to fully account for thorough understanding proteasomal or autophagic degrons. Further studies are needed to understand how the ubiquitin code is deciphered for autophagic degradation.
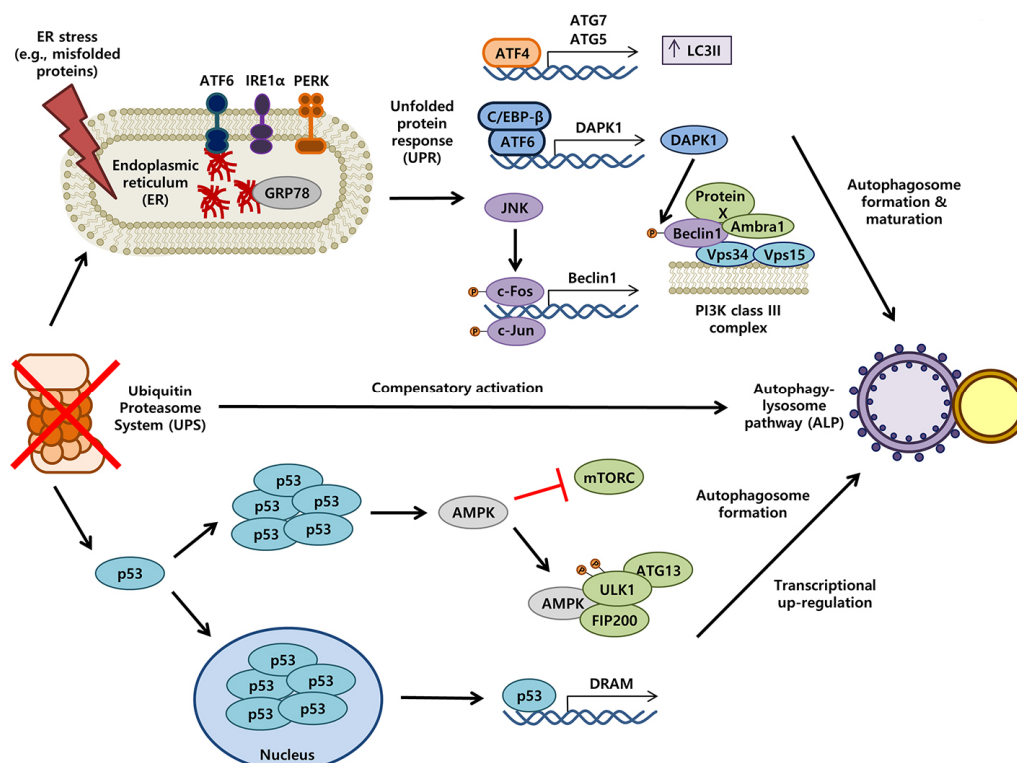

Fig. 1. The crosstalk from the UPS to autophagy. The inhibition of the UPS results in the compensatory activation of autophagy. Proteasomal inhibition in the ER impairs ERAD and causes ER stress and the UPR. PERK and IRE1α subsequently activate downstream pathways toward autophagy. The PERK- eIF2α circuit accelerates the synthesis of the transcription factors ATF4 and CHOP, leading to the expression of ATG genes. Activated IRE1 recruits TRAF2, leading to the phosphorylation of JNK and the expression of autophagic core genes. In parallel, ATF6 is cleaved in the Golgi and translocates to the nucleus, where it induces the expression of DAPK1 and its phosphorylation of beclin-1 for autophagosome biogenesis. In addition, accumulated p53 upon proteasomal inhibition translocates to the nucleus and acts as a transcription factor for autophagy housekeeping genes such as DRAM. Alternatively, increased p53 levels may activate AMPK-dependent autophagy by inhibiting the mTOR pathway.
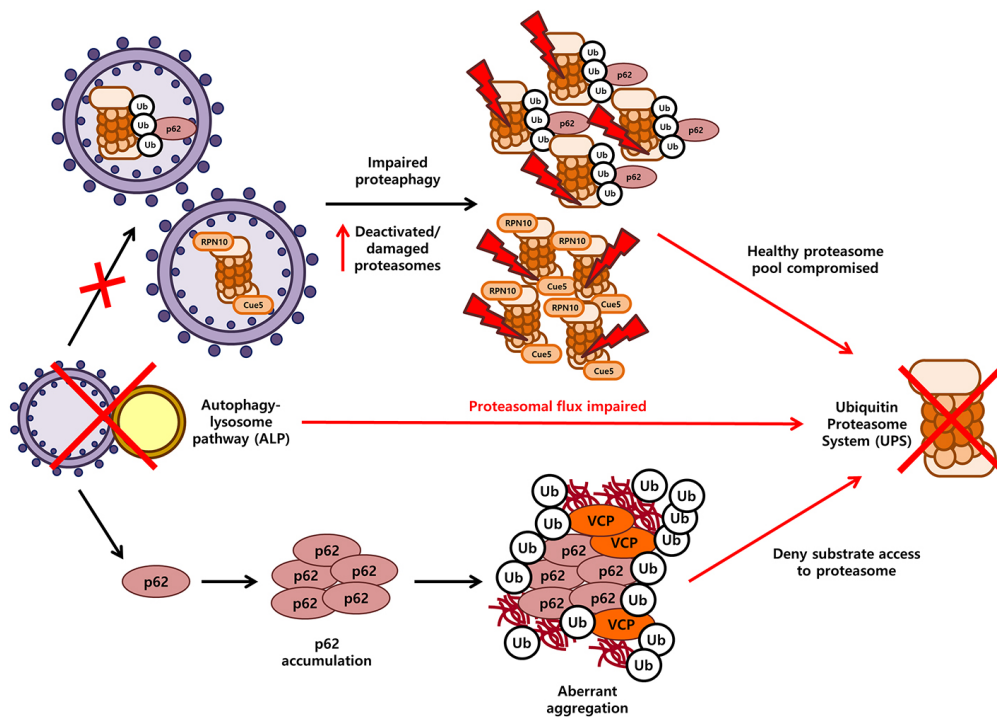
Fig. 2. The crosstalk from autophagy to the UPS. Autophagic inhibition can impair proteasomal flux, leading to the accumulation of ubiquitinated substrates and their aggregates. In this model, autophagic inhibition causes the accumulation of misfolded proteins and aggregates associated with p62 aggregates, which, in turn, sequester ubiquitinated substrates from the UPS machinery and the regulators of the UPS, such as p97/VCP. In addition, autophagy inhibition can impair the autophagic degradation of the proteasome, leading to the accumulation of aging or damaged proteasomes at the expense of healthy and normal proteasomes.

CROSSTALK AND INTERPLAY BETWEEN THE UPS AND AUTOPHAGY

In part due to their differences in nature, mode of action and core machinery, the UPS and autophagy have been viewed as two separate networks with little room for crosstalk or interplay. Recent studies show that cells operate a delicate network of molecular mechanisms that modulate the functional crosstalk and interplay between the two systems under fluctuating environments (Figs. 1 and 2).

Crosstalk from the UPS to autophagy

A number of isolated studies reported phenomena that autophagy is activated if ubiquitinated proteins are not properly processed by the proteasome. For example, proteasome inhibitors, including the anti-cancer drug bortezomib, were found to induce compensatory autophagy (Bao et al., 2017; Cha-Molstad et al., 2015) (Fig. 1). Autophagic induction by the mTOR (mechanistic target of rapamycin) inhibitor rapamycin was also shown to relieve the proteolytic load and cellular proteotoxicity from proteasomal inhibition (Harada et al., 2008; Pan et al., 2008). Impaired proteasomal function and consequent neurodegeneration in a *Drosophila* model could be rescued by activating HDAC6-dependent aggresome pathway (Pandey et al., 2007). Several mechanisms have been proposed to explain this compensatory activation. Known players or pathways that link the UPS to

autophagy include the N-terminal arginylation of the N-end rule pathway (Cha-Molstad et al., 2015) (Fig. 3), the unfolded protein response (UPR) (Hetz et al., 2015), and p53 (White, 2016)

It has been an outstanding question how cells sense and react to accumulating autophagic cargoes by activating autophagy in a timely manner. A recent study (Cha-Molstad et al., 2015) showed that one key mechanism underlying the UPS-to-autophagy crosstalk is the N-end rule pathway, a proteolytic system in which single N-terminal amino acids of proteins act as a class of degrons, called N-degrons (Bachmair et al., 1986; Sriram et al., 2011; Tasaki et al., 2012). Known N-degrons include positively charged (Arg, Lys, and His) and bulky hydrophobic (Phe, Trp, Tyr, le, and Ile) residues exposed on the N-termini (Tasaki et al., 2005). Amongst these, the N-terminal Arg can be generated through post-translational incorporation of the amino acid L-Arg to N-terminal Asp or Glu (Kwon et al., 1999; 2002). In the classical N-end rule pathway, the N-terminal Arg of arginylated substrates is recognized by recognition components, called N-recognins, such as the UBR box family (UBR1, UBR2, UBR4 and UBR5), leading to substrate ubiquitination and proteasomal degradation (Tasaki et al., 2013). Recent studies showed that the N-end rule pathway mediates autophagic proteolysis and modulates the activity of the autophagic adaptor p62 as well as autophagosome biogenesis (Cha-Molstad et al., 2016). In this crosstalk, the accumulation
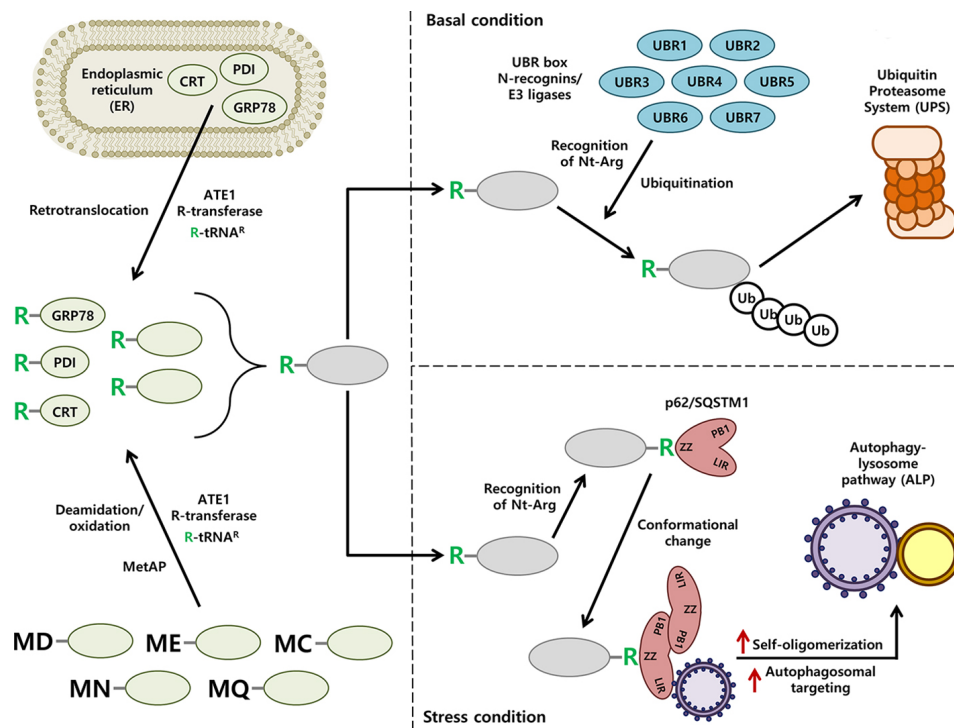
Fig. 3. Modulation of macroautophagy by the N-terminal arginylation. The accumulation of misfolded proteins and their aggregates stimulates the cytosolic relocalization and N-terminal arginylation of ER-residing chaperones such as BiP, calreticulin, and protein disulfide isomerase. Cytosolic R-BiP is associated with cargoes and bind the ZZ domain of p62, facilitating p62 self-polymerization and interaction with LC3. In addition, the ligand-bound p62 induces autophagosome biogenesis. Through this dual regulation, cells can efficiently remove misfolded proteins in a real time basis.

of autophagic cargoes such as ubiquitinated proteins and aggregates induces the N-terminal arginylation of ER-resident chaperones such as BiP/GRP78, calreticulin, and protein disulfide isomerase, resulting in the cytosolic accumulation of their arginylated species. Amongst these, arginylated BiP, R-BiP, is associated with misfolded proteins, and its N-terminal Arg binds the ZZ domain of p62. This N-end rule interaction induces a conformational change of p62, exposing its PB1 and LC3-interacting domains, which accelerates its self-oligomerization and targeting to autophagosomes (Cha-Molstad et al., 2015). In addition, p62, whose ZZ domain is occupied with N-terminal Arg, acts as an autophagic inducer that facilitates autophagosome biogenesis (Cha-Molstad et al., in press). Thus, the autophagic p62 is an N-recognin of the N-end rule pathway that modulates macroautophagy in response to proteotoxicity.

In the UPS-ER-autophagy circuit, proteasome inhibition causes the excessive accumulation of misfolded proteins in the ER lumen, which in turn leads to the dissociation of the molecular chaperone BiP from the ER membrane receptors PERK, IRE1α and ATF6α (Hetz et al., 2015; Park et al., 2011). The activated receptors initiate the UPR to temporarily halt global translation and facilitate the synthesis of ER-residing molecular chaperones. These recruited chaperones assist the folding of incoming ER clients and the degradation of terminally misfolded clients through ERAD. In parallel, each of

PERK, IRE1α and ATF6α on the ER cytosolic surface activates its own downstream pathways toward autophagy. Amongst these, the PERK-eIF2α sub-pathway facilitates the synthesis of the transcription factors ATF4 and CHOP, upregulating the expression of more than a dozen ATG genes (B'Chir et al., 2013; Wang et al., 2014) as well as LC3 lipidation and autophagosome biogenesis (Bao et al., 2017). Meanwhile, activated IRE1 recruits TRAF2 to induce the phosphorylation of JNK. Phospho-JNK activates the expression of autophagic core genes via the XBP1s transcription factor and phosphorylates Bcl-2, leading to the dissociation of phospho-Bcl-2 from the PI3K class II complex and, thus, autophagosome biogenesis (Deegan et al., 2013). Finally, ATF6 migrates to and cleaved in the Golgi body and translocates to the nucleus, where it forms a heterodimeric transcription factor with C/EBP-β to induce the expression of DAPK1 and its phosphorylation of beclin-1 for autophagosome formation (Gade et al., 2012; Zalckvar et al., 2009)

Proteasome inhibition can induce autophagy via the metabolic stabilization of the transcriptional factor p53 (Gu et al., 2014; Lagunas-Martinez et al., 2017). Upon accumulation, the nuclear subpopulation of p53 acts as a transcription factor for autophagy housekeeping genes such as damage-regulated autophagy modifier (DRAM) (Mrschtik et al., 2015; Zhang et al., 2013). In contrast, the cytosolic population of p53 counteracts autophagic induction because it

inhibits the nuclear translocation of the transcription factor TFEB and, thus, the expression of autophagic genes (Zhang et al., 2017). Thus, nuclear and cytosolic p53 species may play opposite roles in autophagy regulation under proteasomal inhibition. This p53-autophagy circuit is also activated to induce autophagy under starvation, in which the phosphorylation of AMPK results in the accumulation of p53, leading to the inhibition of the mTOR pathway and autophagic activation (Jing et al., 2011).

Crosstalk from autophagy to the UPS

Autophagic inhibition can impair proteasomal flux and result in the accumulation of ubiquitinated substrates and their aggregates (Matsumoto et al., 2011; Munch et al., 2014) (Fig. 2). Although this accumulation may be only logical given that ubiquitination is important for selective autophagy, long-term inhibition of autophagy can interfere with proteasomal flux in a manner depending on p62 (Korolchuk et al., 2009). Autophagic inhibition causes the accumulation of protein aggregates in complex with p62, which, in turn, sequester ubiquitinated substrates from proteasomal degradation. In addition to sequestering proteasomal substrates, aberrant p62-containing aggregates may also recruit and, thus, functionally inactivate the regulators of the UPS such as p97/VCP (Bayraktar et al., 2016). This recruitment may be facilitated by specific interactions with the PB1 or UBA domain of p62, potentiating the widespread disruption of proteasomal flux. Thus, while p62 mediates the aggregation-dependent removal of cytotoxic materials in normal conditions, its ability to co-aggregate with autophagic cargoes may be a double-edge blade that aggravates proteolytic flux if autophagy fails. The exact conditions and mechanisms for such a pathological aggregation of p62 are yet unclear. Since proteotoxicity from misfolded/unfolded protein aggregation is naturally quite distinct from starvation-induced stress, this dichotomy in regulation of proteasomal flux upon autophagy inhibition most likely depends on the cellular stress context.

Another possible mechanism by which autophagy inhibition impairs proteasomal flux is proteaphagy, i.e., selective autophagic degradation of the proteasome and its subunits. Proteaphagy constitutively removes aged or inactivated proteasomes for maintenance of the total proteasome pool, which is activated by stresses such as starvation (Marshall et al., 2016). The disruption of proteaphagy may lead to the accumulation of aging or damaged proteasomes, which may compete against healthy proteasomes and, thus, decrease overall proteasomal flux. Recent studies showed that the proteasome is ubiquitinated under cellular stresses, such as starvation and proteasomal inactivation, and delivered to autophagy for lysosomal degradation (Cohen-Kaplan et al., 2017). In plants, the autophagic targeting of proteasomes is facilitated when the proteasome subunit RPN10 interacts with LC3 on autophagic membranes (Marshall et al., 2015). A similar mechanism was observed with another proteasome subunit Cue5 in yeast (Marshall et al., 2016). In addition the ubiquitin chains on proteasomes may be recognized by p62 for autophagic targeting (Cohen-Kaplan et al., 2017).

Cooperation of the UPS and autophagy

The complementary natures of the UPS and autophagy have been well-documented in a myriad of pathways and substrates, some of which are the hallmark substrates of proteinopathies. To name but a few, Huntington's disease (Bates et al., 2015), Parkinson's disease (Poewe et al., 2017), amyotrophic lateral sclerosis (Taylor et al., 2016) and α1-antitrypsin deficiency (Greene et al., 2016) are all characterized by pathological aggregation of their hallmark substrates such as Htt, α-synuclein, TDP-43, and ATZ. Prolonged aggregation leads to progressive cell death and local tissue damage, leading to cell death. In all these and for many other proteinopathies, both the proteasome and lysosome are required for degradation of aggregation-prone substrates (Cha-Molstad et al., 2015; Ciechanover and Kwon, 2015). In principle, monomeric and soluble substrates are degraded by the UPS, whereas their aggregates and insoluble complexes are removed by autophagy. As a telling example, ATZ is degraded by the proteasome via ERAD in a monomeric form and by autophagy if it turns to a pathologically aggregated form (Hidvegi et al., 2010). Such division of labor can be explained by the narrow entry point from the 19S gate to the 20S proteolytic core (Budenholzer et al., 2017). That the cell employs both the UPS and autophagy hand-in-hand to degrade a common substrate is also supported by the numerous observations that disease-associated hallmark mutated proteins often inhibit either or both systems directly or indirectly (Ciechanover and Kwon, 2017; Hipp et al., 2012).

Several molecular chaperones such as the cochaperones CHIP and BAG play a role in the decision-making process and mechanisms of this inter-proteolytic cooperation. CHIP normally acts as a cochaperone for Hsp70 and Hsp90 for selective ubiquitination and proteasomal degradation of denatured/misfolded proteins via Lys48 ubiquitin linkages (Blessing et al., 2014; Zhang et al., 2016). However, CHIP can also mediate autophagic degradation of misfolded proteins and their aggregates with Lys63 specificity (Ferreira et al., 2015). Thus, CHIP plays an important role in decision making when targeting substrates for proteasomal or autophagic degradation, depending on its chaperone and/or E2 partners. Another decision maker is the BAG family. While BAG1 mediates proteasomal degradation, BAG3 associates with Hsp70, CHIP and p62 for autophagic degradation of substrates (Cristofani et al., 2017). It has been suggested that the ratio between BAG1 and BAG3 modulates autophagic activity during cell aging and stress (Minoia et al., 2014).

CONCLUSIONS

The UPS and autophagy were initially thought to be two mutually independent degradative systems. Recent studies now suggest that a single proteolytic network comprising the UPS and autophagy that share similarity in substrate recognition and action mode. One common denominator of the two degradative systems is ubiquitination that assembles ubiquitin-based degrons on substrates. Overall, Lys48 linkages act as proteasomal degrons, and Lys63 linkages serve as a lysosomal degron for protein cargoes such as misfolded

proteins and their aggregates. Lys63 linkages also spatio-temporally mark the autophagic degradation of damaged or surplus materials, such as mitochondria and ER, ribosomes (ribophagy) and liposomes (lipophagy) as well as invading pathogens such as viruses or bacteria. Recent advance in mass spectrometric techniques revealed that atypical linkages such as Lys6, Lys11, Lys29, and Met1 also participate in proteasomal or lysosomal degradation of proteins and non-proteinaceous cellular constituents. In addition, recent studies show that proteostasis requires the crosstalk and interplay between the UPS and autophagy. One emerging UPS-to-autophagy circuit involves the N-terminal arginylation of the N-end rule pathway, in which the N-terminal Arg of arginylated proteins modulate macroautophagy in response to accumulating ubiquitin conjugates. The UPR and p53 pathways are also important in the crosstalk from the UPS to autophagy. Despite the advances in understanding the functional relationship between the UPS and autophagy, several key questions remain to be answered. How are the diverse surface structures of ubiquitin linkages precisely decoded by UBD-containing adaptors for proteasomal and lysosomal degradation? What is the molecular decision-making process when the same protein substrates are delivered to the UPS or autophagy? How do cells modulate the activities of the UPS and autophagy in response to various stresses? As proteolysis plays a central role in various biological processes underlying human diseases, our understanding on the functional relationship between the UPS and autophagy will contribute to the development of therapeutic means to modulate proteostasis and the timely removal of pathogenic protein species.

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