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Review article

The ubiquitin-proteasome system and autophagy: Coordinated and independent activities

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ABSTRACT

The living cell is an ever changing, responsive, and adaptive environment where proteins play key roles in all processes and functions. While the scientific community focused for a long time on the decoding of the information required for protein synthesis, little attention was paid to the mechanisms by which proteins are removed from the cell. We now realize that the timely and proper activity of proteins is regulated to a large extent by their degradation; that cellular coping with different physiological cues and stress conditions depends on different catabolic pathways; and that many pathological states result from improper protein breakdown.

There are two major protein degradation systems in all eukaryotic cells—the ubiquitin- proteasome and the autophagy-lysosome. The two systems are highly regulated, and—via degradation of a broad array of proteins—are responsible for maintenance of protein homeostasis and adaptation to environmental changes. Each is comprised of numerous components responsible for its coordinated function, and together they encompass a considerable fraction of the entire genome.

In this review, we shall discuss the common and diverse characteristics of the ubiquitin-proteasome system (UPS) and autophagy—their substructure, mechanisms of action, function and concerted regulation under varying pathophysiological conditions.

Contents

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1. Introduction

1.1. The ubiquitin-proteasome and autophagosome–lysosome systems

Although intracellular protein breakdown by lysosomes was described more than half a century ago, our understanding of the underlying molecular and cellular mechanisms, and mostly the regulation of the process, has been advanced significantly much later with the unraveling of the autophagosome-lysosome system. The UPS is recognized as a major highly specific and selective route for cellular protein degradation, whereas autophagy is involved mostly in bulk destruction in response to stress. It is now realized that both systems act simultaneously and in conjunction with one another, and play important roles in the maintenance of the proteome homeostasis and quality.

1.1.1. The ubiquitin-proteasome system

The UPS is a large machinery consisting of numerous components that act in a highly regulated manner, generating a chain of events which results in substrate ubiquitination and their subsequent degradation. Ubiquitination involves three types of enzymes: E1 (the ubiquitin-activating enzyme) encoded by two genes; E2 (a ubiquitin-carrier protein also called ubiquitin-conjugating enzyme) encoded by at least 37 genes; and E3 (a ubiquitin ligase) encoded by ~800 genes. Conjugation of ubiquitin (Ub) begins with an ATP-dependent activation of the C-terminal glycine residue (G76) of the molecule. Ub is then transferred as an activated moiety to an E2. The last step of substrate ubiquitination is carried out by the formation of a complex consisting of Ub-loaded E2 and a specific E3 to which the substrate protein is bound. It is then transferred from the E2 either directly to a lysine residue of the substrate when the E3 is of the RING-finger type, or to an internal cysteine residue in the E3 when the enzyme is of the HECT-domain type. Finally, it is conjugated to the substrate. Additional ubiquitins are then added by the same cascade, creating a Ub chain (Ciechanover, 1994; Finley, 2009). Furthermore, Ub chains can be also elongated by an additional type of ligase—E4, also termed the "Ub-chain elongation factor" (Koegl et al., 1999).

Polyubiquitinated substrates are delivered to the proteasome—the catalytic arm of the UPS. The 26S proteasome is composed of a 20S core particle (CP) that can be capped with one or two 19S regulatory particles (RP). The ubiquitinated substrates are recognized by 19S RP Ub receptors. Subsequent to recognition, the substrate undergoes deubiquitination by deubiquitinating enzymes (DUBs), following by unfolding and translocation to the proteolytic chamber of the 20S CP, the last two processes require metabolic energy (Gallastegui and Groll, 2010; Livneh et al., 2016).

In addition to the 'canonical' proteasomal degradation which depends on Ub and ATP, there are several alternative mechanisms, some of which do not require ubiquitination and/or ATP hydrolysis (see below).

1.1.2. Autophagosome-lysosome system

Autophagy (from Greek- "self-eating") is a process in which cytoplasmic material is degraded by the lysosome. There are three types of autophagy: (1) microautophgy, where the lysosome itself engulfs a small portion of the cytosol; (2) chaperone-mediated autophagy (CMA), in which chaperones target selective substrates to the lysosome; and (3) macroautophagy, usually termed autophagy, in which a phagophore is generated, expands, and forms an autophagosome, which can contain besides cytosol, also subcellular organelles. The autophagosome fuses with the lysosome and pours its contents into it to be degraded (Kroemer et al., 2010). Although macroautophagy was considered for many years as a non-selective process, recent studies reveal that autophagic substrates are also being selectively targeted for degradation, similar to the way substrates are being recognized by the UPS (Onodera and Ohsumi, 2004).

Autophagy consists of three conserved sequential steps: (1) nucleation; (2) elongation and substrate sequestration; and (3) fusion with the lysosome.

More than 35 autophagy related genes (ATGs) have been identified in yeast, many of which are well conserved in mammals. The core of the autophagic machinery is comprised of 18 ATGs (ATG1–10, ATG12–14, ATG16–18, ATG29, and ATG31) that are shared across different types of autophagy and are necessary for the formation of the autophagosome (Suzuki and Ohsumi, 2007).

Upon induction, proteins of the *UNC51-like kinase* (ULK) complex (ULK1 or ULK2 and ATG13, *FAK family kinase-interacting protein of 200 kDa* (FIP200) and ATG101) assemble and initiate phagophore nucleation. Additional nucleation requires the ULK complex to activate a class III PI3K complex (BECLIN1 (or Atg6 in yeast), *vacuolar protein sorting 15* (VPS15), VPS34 and ATG14). This

activation promotes the generation of a specific autophagosome phosphatidylinositol 3-phosphate (Wang and Klionsky, 2003). The origin of the phagophore membrane is still elusive. Historically, it was considered to be a *de novo* synthesis product, but current evidence suggests it originates from pre-existing organelles (such as the endoplasmic reticulum (ER) and Golgi apparatus) (Geng et al., 2010; Yamamoto et al., 1990). Regardless, the autophagosome stems from an expansion of this membranal sheet—the phagophore. As it grows in size, the phagophore curves and is sealed to form the autophagosome (Knævelsrud et al., 2013). As in the case of the phagophore origin, the source of the membrane required for its expansion is still under investigation.

The elongation and expansion step which includes also the recruitment of the substrate receptor LC3, is mediated by two ubiquitin-like conjugation systems. In the first one, the ubiquitin-like protein ATG12 is attached to ATG5 by the E1-like ATG7 and the E2-like ATG10 proteins. Then, ATG16L1 binds ATG5-ATG12 to form the active ligase-like complex (Geng and Klionsky, 2008; Kuma et al., 2002). In the second conjugation process, LC3, which is synthesized as a pro-LC3 form, is cleaved by the cysteine protease ATG4B to expose its C-terminal glycine residue, forming the LC3-I form. LC3-I is then conjugated with a phosphatidylethanolamine (PE) by the combined activity of the E1-like ATG7, E2-like ATG3, and the E3-like ATG16L1-ATG5-ATG12 complex (Hanada et al., 2007; Kabeya et al., 2000; Tanida et al., 2004). LC3-PE (also called LC3-II), incorporates into the expanding autophagosomal membrane, and then binds different adaptor proteins, which facilitate selective sequestration of substrates (e.g. p62/Sequestosome 1 and *neighbor of BRCA1* (NBR1)) (Bjørkøy et al., 2005)

Certain stimuli, such as apoptotic signaling, have been shown to induce 'non-canonical' autophagy in two manners: the first bypasses proteins that are important for initiation (ULK1) and nucleation (BECLIN1) (Cheong et al., 2011). The second bypasses the proteins involved in autophagosome elongation and maturation (ATG7, ATG5 and LC3), and is mediated by fusion events of vesicles positive for the GTPase RAB9, which is known to be involved in vesicular trafficking between the *trans*-Golgi network and late endosomes (Codogno et al., 2011; Moreau et al., 2011; Nair et al., 2011).

2. Mechanism of action of the UPS and autophagy

Specific degradation of proteins by both the UPS and the autophagic pathway involve substrate ubiquitination, its targeting to the proteolytic machinery by shuttling proteins, and the recognition of the degradation signal by the catalytic arm of each system.

2.1. Degradation signals

2.1.1. Ubiquitin-dependent degradation in the UPS and autophagy

First discovered as a degradation signal used by the UPS (Hershko and Ciechanover, 1998), Ub was later found to mediate also proteolysis of substrates through endocytosis (Galan and Haguenauer-Tsapis, 1997; Terrell et al., 1998) and autophagy (Kim et al., 2008; Pankiv et al., 2007). Ub can be attached to a substrate either as a single moiety (monoubiquitination), several single moieties on different sites (multiple monoubiquitinations) or as a chain (polyubiquitination). After the first Ub has been conjugated to the substrate, a chain is polymerized by continuous attachment of additional Ub moieties to a lysine (K) residue (K6, K11, K27, K29, K33, K48, or K63 (Ikeda and Dikic, 2008)) or to the N-terminal methionine residue (Kirisako et al., 2006) of the previously attached Ub (Hershko and Ciechanover, 1998). The fate of a ubiquitinated substrate depends on the length of the Ub chain attached, as well as on the K residue through which it is linked (Pickart, 2000).

While it was first suggested that short-lived proteins which are degraded by the proteasome are marked selectively by K48-linked Ub chains (Thrower et al., 2000), it was later shown that all chain types are probably involved in proteasomal degradation (Hofmann and Pickart, 2001; Saeki et al., 2009; Xu et al., 2009).

It is now known that K63 Ub chains serve as a degradation signal also for selective autophagy (Olzmann et al., 2007; Tan et al., 2008; Wooten et al., 2008). Interestingly, deletion of the autophagy genes *ATG5* or *ATG7,* resulted in accumulation of all types of Ub chains (Riley et al., 2010), suggesting the involvement of other chain types in autophagy.

Monoubiquitination was also shown to be sufficient for targeting substrates to both the UPS (Boutet et al., 2007; Braten et al., 2016; Carvallo et al., 2010; Kravtsova-Ivantsiv et al., 2009) and to autophagy (Kim et al., 2008).

Besides common degradation signals, the two machineries also share several substrates and enzymes. The *inhibitor of transcription factor κB*-α (IκBα) was shown to exist in two sub-populations: a short-lived population that is degraded by the 26S proteasome (Alkalay et al., 1995; Mathes et al., 2010), and a long-lived population which is degraded by CMA (Cuervo et al., 1998). The E3 Ub ligase Parkin conjugates K48 polyubiquitin chains to its proteasomal substrates (Chan et al., 2011; Chew et al., 2011), whereas its autophagic substrates are modified with K63 and K27 chains (Geisler et al., 2010; McKeon et al., 2015).

2.1.2. Ubiquitin-independent degradation

The mechanisms that underlie 'non-canonical', Ub-independent proteasomal degradation are still elusive, although several substrates degraded in such manner have been identified. The best studied substrate is *ornithine decarboxylase* (ODC), the degradation of which is regulated by antizyme, a "personal Ub" that binds to ODC in non-covalent manner and targets it to the 26S proteasome. Antizyme itself is regulated by anti-antizyme, and both are targeted for degradation by the proteasome, following ubiquitination (Murakami et al., 1992a,b). Notably, some of the Ub-independent substrates can also be degraded in a 'canonical' Ub-dependent manner (Baugh et al., 2009; Benaroudj et al., 2001; Rao et al., 2012; Takasugi et al., 2016). Several such substrates require the presence of a sequence that mediates their proteasomal targeting ('degron'), such as IκBα (Fortmann et al., 2015), p35 (Takasugi et al., 2016) and Nkx3.1 (Rao et al., 2012). High structural flexibility is also suggested to contribute to Ub-independent degradation of other substrates, including calmodulin, troponin C, and ovalbumin (Benaroudj et al., 2001). Oxidation of proteins was shown to induce the exposure of unstructured regions, allowing their degradation by the 20S CP, the abundance of which is elevated during oxidative stress (Ben-Nissan and Sharon, 2014; Dick et al., 1994; Liu et al., 2003; Wang et al., 2010).

In macroautophagy, several substrates have been shown to be targeted to the autophagosome independently of ubiquitination. One example is the ligand-independent co-activator of the nuclear androgen receptor, NCOA4, which was shown to recruit ferritin into autophagosomes by binding to LC3, and thereby maintain *ferritin* homeostasis (Dowdle et al., 2014; Mancias et al., 2014). Two other examples are NIX and FUNDC1, outer mitochondrial membrane proteins which function as adaptors for binding of damaged mitochondria by LC3 via their *LC3-interacting region* (LIR) (Liu et al., 2012; Novak et al., 2010).

Certain soluble cytoplasmic and nuclear proteins can be recognized by chaperones and degraded via CMA independently of Ub. Their degradation relies on the presence of the pentapeptide motif KFERQ in their amino acid sequence, apparently regardless of its location (Dice, 1992; Massey et al., 2006). Although nearly 30% of all

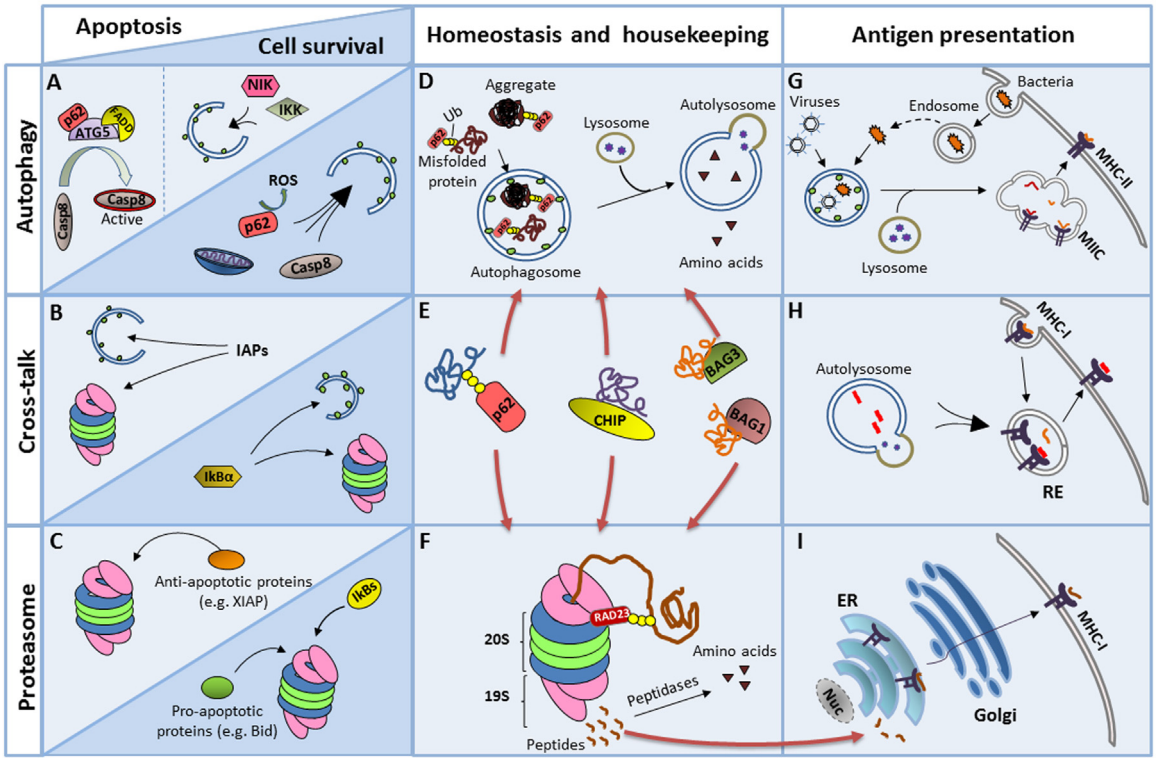

Fig. 1. Coordinated activities of the UPS and autophagy in several cellular functions.
Cell survival is determined, in part, by the two proteolytic systems (A–C). The autophagic components ATG5 and p62, in cooperation with FADD, can mediate the activation of caspase-8, thereby inducing apoptosis. The autophagic degradation of IKK and NIK may also promote apoptosis (A, upper panel). In contrast, the autophagic degradation of p62 (an inducer of ROS production) and caspase-8, as well as the clearance of defective mitochondria, are supporting cell survival (A, lower panel). Both autophagy and the UPS may stimulate apoptosis via the elimination of IAPs (B, upper panel), while maintaining cell viability through the degradation of IκBα (B, lower panel). The degradation of several anti-apoptotic proteins (e.g. XIAP, cIAP1 and BCL-2) by the UPS induces apoptosis (C, upper panel), while the removal of pro-apoptotic proteins (e.g. Bid, Bax, p53, p27, and p21) and different IκBs inhibits cell death (C, lower panel).
Both catabolic systems are responsible for maintaining cellular homeostasis via breaking down proteins to amino acids, as well as via clearing misfolded proteins (D–F). Aggregates and misfolded proteins are selectively targeted to the autophagosome in a Ub-dependent manner (D). Delivering substrates either to autophagy or the proteasome may also involve shuttling proteins (e.g. p62) and co-chaperones (e.g. CHIP, BAG3 and BAG1) (E). The proteasome constitutively degrades proteins into short peptides, a small fraction of them serve for antigen presentation. Most of them are further degraded to amino acids by carboxy- and aminopeptidases. These combined activities replenish the amino acid pool (F).
Antigens presented by MHC molecules on the cell surface are derived from the proteolytic activities of the UPS and autophagy (G–I). Viruses and endocytosed bacteria are degraded by autophagy into peptides that are delivered into *MHC class II-containing compartments* (MIICs) for their subsequent presentation by MHC class II molecules (G). The autolysosome can fuse with *recycling endosomes* (RE) containing MHC class I molecules, leading to antigen cross-presentation (i.e. presentation of autophagy-derived peptides by MHC class I molecules) (H). Peptides derived from proteasomal degradation are loaded onto MHC class I molecules in the ER, and are delivered to the cell surface through the Golgi apparatus (I).

cytoplasmic proteins possess one or more KFERQ homologues, only proteins that contain an exposed KFERQ peptide are recognized as substrates by the HSC70/HSP40/HSP90/HIP/HOP complex. This complex, together with several co-chaperones, initiates the unfolding of substrates in an ATP-dependent manner, and directs them to the lysosomal surface, where they interact with the lysosomal receptor LAMP2-A.

2.2. Shuttling of substrates to the proteolytic machineries

Ubiquitinated substrates are recognized by shuttling proteins of both the UPS and the autophagy systems, with each relying on its own set of adaptors. However, cross-talk between the two systems is evident as some shuttling proteins can target substrates to both. Moreover, mediators belonging to one proteolytic machinery are degraded by the other, exerting mutual regulation between the two (Fig. 1).

2.2.1. Shuttling to the proteasome

The UPS relies on a group of Ub-associated (UBA)-Ub-like (UBL) shuttling proteins, including the yeast *radiation sensitivity abnormal 23* (Rad23), *dual-specificity protein kinase 2* (Dsk2), and *DNA damage-inducible 1* (Ddi1), and their human orthologues. They bind to the ubiquitinated substrate with their C-terminal UBA domain and to Rpn1 (Elsasser et al., 2002), Rpn10 (Hiyama et al., 1999; Walters et al., 2002) and Rpn13 (Husnjak et al., 2008) 19S RP subunits with their N-terminal UBL domain. These UBA-UBL proteins were shown to preferentially bind K48-linked polyubiquitin chains (Lowe et al., 2006; Nathan et al., 2013; Rao and Sastry, 2002), in agreement with their role in proteasomal degradation.

Ubiquilins, the human orthologues of yeast Dsk2, were also found to be involved in the delivery of the autophagosome to the lysosome (N'Diaye et al., 2009). Ubiquilin-1 itself is a substrate for degradation by CMA and macroautophagy (Rothenberg et al., 2010).

In addition to these UBA-UBL shuttling proteins, other proteins have been shown to mediate association of ubiquitinated substrates with the proteasome. Among them is p97/VCP/Cdc48, which is a conserved hexameric ATPase involved in numerous cellular pathways (Meyer et al., 2012). p97 was also shown to mediate autophagic degradation, as mutations in the protein inhibit autophagosome maturation and result in accumulation of p62 and lipidated-LC3 (Ju and Weihl, 2010; Tresse et al., 2010).

Table 1
Mediators of Substrate Shuttling to the UPS/Autophagosome.

Mediator	Degradation pathway(s)	Ub-binding domain	Ub-chain type	Proteasome/ Autophagosome-binding domain	Reference
Ub-dependent					
Rad23	UPS	Two UBA domains	K48 K63	UBL	Raasi et al., 2005; Rao and Sastry, 2002
Dsk2/ Ubiquilin	UPS Autophagy	UBA	K48 K63	UBL UBA	Funakoshi et al., 2002; Rothenberg et al., 2010
Ddi1	UPS	UBA	K48	UBL	Kaplun et al., 2005
p97	UPS Ribophagy (ribosome engulfment) Mitophagy Aggrephagy	N-domain	K48 K11	D1 and D2 N/A	Dargemont and Ossareh-Nazari, 2012; Hao et al., 2015
p62	UPS Mitophagy Aggrephagy Xenophagy Zymophagy (zymogen engulfment) Virophagy	UBA	K63 K48 K27	PB1 LIR	Bjørkøy et al., 2005; Geisler et al., 2010; Grasso et al., 2011; Kim et al., 2008; Zheng et al., 2009
NBR1	Aggrephagy Pexophagy (peroxisome engulfment)	UBA	K63 K48	Two LIR motifs	Deosaran et al., 2013; Kirkin et al., 2009a
NDP52	Mitophagy Xenophagy	Ub-binding zinc finger (UBZ)	K48 K63 Linear (M1)	CLIR	Lazarou et al., 2015; Thurston et al., 2009; von Muhlinen et al., 2012; Xie et al., 2015
Optineurin	Mitophagy Xenophagy	Ub-binding in ABIN and NEMO domain (UBAN)	K63 Linear (M1)	LIR	Wild et al., 2011; Wong and Holzbaur, 2014
Tollip	Aggrephagy	CUE	K63 K48	AIM1, AIM2	Lu et al., 2014
Tax1bp	Mitophagy Xenophagy	Two Ub-binding zinc fingers (UBZ)	K63	LIR	Lazarou et al., 2015; Tumbarello et al., 2015
HDAC6*	Aggrephagy Mitophagy	Znf-UBP	K63	–	Lee et al., 2010a,b
ALFY*	Aggrephagy	–		WD-40	Filimonenko et al., 2010
Rpn10	Proteaphagy	UIM1		UIM2	Marshall et al., 2015
Ub-independent					
NIX	Mitophagy	–	–	LIR	Novak et al., 2010
FUNDC1	Mitophagy	–	–	LIR	Liu et al., 2012
SMURF1	Mitophagy Virophagy	–	–	C2 (either direct or indirect)	Orvedahl et al., 2011
Tecpr1	Mitophagy Aggrephagy Xenophagy	–	–	AIR	Chen et al., 2012; Ogawa and Sasakawa, 2011; Ogawa et al., 2011
TRIM5α	Virophagy	–	–	Two LIR motifs	Mandell et al., 2014
NCOA4	Ferritinophagy (ferritin engulfment)	–	–	N/A	Mancias et al., 2015
Cbl	Signalophagy (Src engulfment)	–	–	LIR	Khaminets et al., 2016; Sandilands et al., 2012
NDP52	Xenophagy	–	–	LIR	Thurston et al., 2012
p62	Virophagy	–	–	LIR	Orvedahl et al., 2010
Optineurin	Aggrephagy	–	–	LIR	Korac et al., 2013

Asterisk (*) denotes mediators that facilitate indirect association between Ub and the autophagosome (bind directly to either Ub or the autophagosome, but not simultaneously).
N/A—not available. Denotes mediators for which a direct binding has not been shown.

2.2.2. Shuttling to the autophagosome

Selective autophagy shuttling proteins, such as p62 and NBR1, mediate degradation as they bind ubiquitinated substrates via their Ub-binding domains (UBDs) and dock to the autophagosomes via interaction of their LIR motif with LC3 and GABARAP (Kirkin et al., 2009b; Lamark et al., 2009; Pankiv et al., 2007). Both p62 and NBR1 are substrates for selective autophagy (Pankiv et al., 2007; Svenning et al., 2011), and are degraded along with their substrates. In addition to its role in autophagy, p62 also shuttles ubiquitinated substrates to the proteasome (e.g. tau (Babu et al., 2005)), though its preference to bind K63-based chains rather than K48 ones may imply that it primarily functions as a shuttling protein in autophagy. p62 binds to the Rpn10 and Rpt1 subunits of the proteasome via its N-terminal PB1 domain (Seibenhener et al., 2004). Interestingly, p62 was shown to be degraded by the proteasome following its ubiquitination on K13 by Parkin (Song et al., 2016).

In addition to p62 and NBR1, other adaptors can also recognize ubiquitinated substrates and target them to the autophagosome, as in the case of NDP52, optineurin, and Tax1BP1, which are involved in both mitophagy and xenophagy (Geisler et al., 2010; Lazarou et al., 2015; Thurston et al., 2009; Tumbarello et al., 2015; Wild et al., 2011; Wong and Holzbaur, 2014; Zheng et al., 2009). As mentioned earlier, substrates are also targeted to the autophagosome in a Ub-independent manner. For example, p62, NDP52 and optineurin have also been found to facilitate Ub-independent degradation in virophagy (Orvedahl et al., 2010), aggrephagy (Korac et al., 2013), and xenophagy (Thurston et al., 2012).

Table 1 summarizes various mediators of substrate shuttling to both the UPS and the autophagic system.

2.3. Substrate recognition by the proteolytic machineries

2.3.1. Proteasome receptors

Four intrinsic subunits of the proteasome function as receptors for ubiquitinated substrates: Rpn13 (Husnjak et al., 2008), Rpn1 (Shi et al., 2016), Rpn15 (Paraskevopoulos et al., 2014) and Rpn10 (Fu et al., 1998).

Rpn13 binds Ub and the UBL domain of shuttling proteins via its N-terminal *pleckstrin-like receptor for ubiquitin* (Pru) domain (Husnjak et al., 2008). Rpn1 can also bind ubiquitinated substrates both directly (preferentially those that are conjugated by K48 and K6 Ub-chains), or via shuttling proteins through its T1 site (Shi et al., 2016). Rpn15 is an intrinsically disordered protein of the 19S RP that binds Ub via its two unstructured *Ub-binding sites* (UBS). These sites also mediate Rpn15 integration into the 26S proteasome, as mutation inserted to both sites prevent its incorporation. Rpn15 binds both K48- and K63-linked polyubiquitin chains (Paraskevopoulos et al., 2014).

Rpn10 is an exceptional Ub receptor, as it functions both as part of the 26S proteasome complex and as a free entity, as shown in *A. thaliana* (van Nocker et al., 1996a), *S. cerevisiae* (van Nocker et al., 1996b), and *D. melanogaster* (Haracska and Udvardy, 1997). Rpn10 binds Ub via its *Ub-interacting motif* (UIM) (Fu et al., 1998; Haracska and Udvardy, 1997; Young et al., 1998) and can either bind K48- or K63-linked polyubiquitin chains with preference to long chains (Wang et al., 2005).

2.3.2. Autophagosome receptors

Several Ub-like proteins associate with the autophagosome membrane and act as receptors for autophagic shuttling proteins transporting substrates to the autophagosome. In mammals, these proteins constitute a group of 7 homologues divided into three sub-families: LC3 (LC3A, LC3B, LC3B2, Lc3C), GABARAP (GABARAP, GABARAPL1), and GATE-16 (Slobodkin and Elazar, 2013).

In CMA, LAMP-2A is a lysosomal receptor that interacts with incoming substrates via its C-terminus (Cuervo and Dice, 1996). This interaction initiates the formation of a channel, which is assembled by LAMP-2A, and through which the unfolded substrate traverses the lysosomal membrane (Bandyopadhyay et al., 2010). Internalization of the substrate is mediated by intra-lysosomal HSC70, whereas cytosolic HSC70 is suggested to facilitate unfolding of substrates prior to their translocation and disassembly of the LAMP-2A channel following substrate translocation (Agarraberes and Dice, 2001; Bandyopadhyay et al., 2008).

3. Functions of proteasome and autophagy

It has been suggested that the UPS and autophagy function in parallel during cell's life. However, growing evidence has indicated the existence of multiple points of communication between the two systems at different layers of regulation. In addition to their system-specific functions, both of them are also involved in the regulation of similar cellular processes, such as cell stress response, protein quality control (PQC), apoptosis and antigen presentation.

3.1. Regulation of cellular homeostasis by the UPS and autophagy

The UPS and autophagy are the two main systems involved in the regulation of protein homeostasis and housekeeping functions. They are involved in maintaining the correct levels of functional proteins, their distribution, and the elimination of damaged/misfolded proteins. Aberrations in protein homeostasis underlie the pathogenesis of many diseases that affect numerous patients, including malignancies, inflammatory and neurodegenerative disorders. The proteolytic activities of the UPS and autophagy are tightly controlled and coordinated through cell's life, and their relative contribution in proteolysis varies between different cell types and tissues. Under normal growth conditions, proteasomal degradation contributes the majority of the proteolytic activity, apart from non- or slowly proliferating cells (e.g. neuronal and muscle cells), in which the autophagosomal proteolysis accounts for approximately half of the activity (Fuertes et al., 2003a; Hara et al., 2006; Liang et al., 2010; Zhao et al., 2007).

Cellular proteins are generally classified into "short-lived" (rapidly degraded proteins) and "long-lived" (slowly degraded proteins) (Bradley et al., 1975; Dice et al., 1973; Fuertes et al., 2003b; Mortimore and Pösö, 1987). The UPS "commonly" mediates the degradation of "short-lived" proteins, many of them are regulatory, and are degraded as a controlling mechanism of vital cellular processes, such as cell proliferation (e.g. cyclins and Cdk inhibitors), signal transduction (e.g. β-catenin), gene transcription (e.g. Myc), quality control checkpoint (e.g. p53), and others (Hershko and Ciechanover, 1998; Naujokat and Hoffmann, 2002).

By contrast, "long-lived" proteins are preferentially degraded by autophagy, and under basal metabolic conditions mostly via microautophagy (Mortimore et al., 1988). However, this distinction has become relative, as different studies indicate that "long-lived" proteins can also be substrates of the proteasome (Lee and Goldberg, 1996), and "short-lived" proteins can also be degraded—to a small extent—by autophagy (Fuertes et al., 2003a, 2003b).

A more recent classification divides proteolytic substrates into functional (Type-I), soluble misfolded (Type-II), and structural (Type-III) proteins. The first two are "short-lived", degraded mostly by the proteasome. However, certain proteins of Type-II can also be degraded by autophagy, especially when they become insoluble (oligomerized and aggregated). When the capacity of the proteasome is exceeded, all Type-II proteins are redirected for autophagosomal degradation. The third type are "long-lived" proteins degraded mostly by autophagy. These proteins can also be degraded in a non-specific manner, as a result of nutrient deficiency in an attempt to re-supplement the cell with the missing nutrients (Ding and Yin, 2008; Kabuta et al., 2006; Shin et al., 2005).

3.2. Cellular housekeeping—degradation of misfolded proteins

The appearance of misfolded or damaged proteins is due to various causes, such as ER-stress, improper folding and mutations, or due to unfolding induced by oxidation, heat, exposure to heavy metals and UV irradiation. Accumulation of abnormal proteins causes cell toxicity and cell death, which can be prevented by the counter activity of PQC pathways that monitor proteins' quality both during and after their synthesis. PQC pathways correct folding mistakes using chaperones (e.g. Hsp70 and TRiC), or target proteins that cannot be re-folded for degradation by one of the two catabolic pathways (Gamerdinger et al., 2009; Marques et al., 2006; McClellan et al., 2005) (Fig. 1).

The UPS acts constitutively as the first line of defense in the elimination of misfolded proteins, so that the cell must recruit compensatory mechanisms in case of a compromised proteasomal degradation. For example, following proteasome inhibition, the E3 ligase TRIM50 was shown to co-localize with p62 at aggresomes and to recruit and ubiquitinate its component proteins. This leads to recognition of the aggresome by the autophagic machinery and its subsequent removal (Fusco et al., 2012).

3.2.1. Co-chaperones define the degradation pathway of misfolded proteins

The selection of the degradation pathway (proteasomal or autophagic) for abnormal proteins may be accomplished by individual co-chaperones such as *C-terminus of Hsc70-interacting protein* (CHIP) and the *Bcl-2- associated athanogene* (BAG) family proteins, which act as molecular switches between the two systems. It has been shown that CHIP mediates proteasomal degradation of α-synuclein by its *tetratricopeptide repeat* (TPR) domain, whereas its U-box domain directs α-synuclein towards the macroautophagosomal degradation pathway (Shin et al., 2005; Webb et al., 2003). Additionally, the co-chaperone BAG1 promotes the proteasomal degradation of unfolded proteins by linking between the Hsc70/Hsp70 chaperone complex, which binds to the substrate, and the proteasome (through BAG1 UBL domain). By contrast, BAG3, another member of the BAG co-chaperones family, targets misfolded proteins to macroautophagy. BAG3 associates with the multi-chaperone complex consisting of HSPB8 and HSP70, and mediates the recruitment of p62, as well as the transfer of HSP70-bound substrates to LC3 (Gamerdinger et al., 2011). Furthermore, BAG3 can mediate the interaction of the HSC70/HSPB8 complex with CHIP, which in turn recruits p62 that transfers the substrate (e.g. SOD1) to autophagy (Arndt et al., 2010). In aged cells/tissues and also under different stresses (e.g. proteasome inhibition or oxidative stress), the expression of BAG1 shifts towards BAG3, resulting in predominance of autophagy as an alternative pathway for PQC (relative to the proteasome). These findings indicate the strong dependence of aged/stressed cells on autophagy in abnormal protein degradation (Gamerdinger et al., 2011).

3.3. Aggresome clearance

Aggresomes are a form of multiple proteins clustered together in insoluble inclusion bodies. Dispersed aggregates are being trafficked to the microtubule organizing center (MTOC),where they are clamped together and form a large structure—the aggresome (Johnston et al., 1998). These aggresomes can be either harmful for cells as is the case in many neurodegenerative diseases (Ross and Poirier, 2004) or by contrast, serve as a protective mechanism, sequestering otherwise hazardous proteins (Arrasate et al., 2004).

3.3.1. The role of the UPS and autophagy in aggresome clearance

Protein misfolding is one of the leading causes of aggresome formation. The folding process is an event in which the molecule is folded in several competing folding tracks, finally locked in the lowest free energy form—the native protein conformation (Schröder and Kaufman, 2005).

Although protein synthesis is a tightly regulated process, misfolded proteins comprise about 20% of the newly synthesized proteins (Wickner, 1999). The generation of misfolded proteins is the result of diverse events (e.g. mutations, RNA modifications, uneven translation of individual subunits in a multisubunit protein, as well as environmental conditions such as pH, redox state etc. (Bonifacino et al., 1989; Hurle et al., 1994; Wetzel, 1994)) that cause intra and intermolecular interactions otherwise not present in the native protein, facilitating the generation of a locked misfolded protein. Chaperones, such as HSP70, are able to correct the folding of some polypeptides. If not successful, the irreversibly locked misfolded protein can form aggregates, some of which are permeable to cellular membranes (Aguzzi and O'Connor, 2010; Kinnunen et al., 2012).

The ER lumen retains most of the soluble misfolded proteins prior to their retro-translocation across the ER membrane where they are marked by Ub for proteasomal degradation (*ER-associated degradation*—ERAD). Insoluble aggregates which do not "fit" the proteasomal catalytic center are eliminated by the autophagic machinery (García-Mata et al., 1999; Lee et al., 2002). As mentioned above, dispersed aggregates will make their way to the MTOC in a dynein-dependent manner to specialized sites to form large aggresomes. The trafficking of aggregated substrates to aggresomes is probably a selective process, as substrates are conjugated with K63-based Ub chains by distinct E3 ligases and associate with *histone deacetylase 6* (HDAC6) which require both its catalytic activity as well as its ability to bind Ub chains (Olzmann et al., 2007). HDAC6 serves as a link between ubiquitinated substrates and the dynein motor. The importance of ubiquitination in aggresome formation is further demonstrated in the case of Ataxin3. This protein is a DUB which affects both the formation of aggresomes by generating unanchored free K63 chains, as well as by processing and shortening the K63 chains of misfolded substrates to the optimal length recognized by HDAC6, thus promoting their trafficking to aggresomes (Burnett and Pittman, 2005; Ouyang et al., 2012; Wang et al., 2012). However, a recent study suggested that ubiquitination is neither necessary nor sufficient for protein aggregation, and that the folding state of a protein is the crucial element promoting its targeting to inclusion bodies (Bersuker et al., 2016).

Aggresomes are not a stagnant junkyard. Chaperones and proteasomes associate with aggresomes on a "per-need-base" attempting to clear it. If they fail, the cell recruits a different disposal machinery, autophagy (Hartl, 1996). Since the aggresome is a loose structure of several aggregates (García-Mata et al., 1999), chaperones and proteasomes are probably involved in maintenance of quality control of its surface proteins, but as the process continues, the autophagic machinery directs the entire structure to lysosomal degradation.

The removal of aggresomes by autophagy was demonstrated in several models. In astrocytes, proteasomal inhibition elevated the number of aggresomes, ubiquitinated proteins in the insoluble fraction, and autophagosomes. Inhibition of autophagy resulted in a decline in viability of the astrocytes (Jänen et al., 2010). Similarly, in rat cardiac myocytes, glucose deprivation resulted in oxidized stress-related aggresome formation and activation of autophagy (Marambio et al., 2010).

Naturally, autophagy will be more dominant in the elimination of misfolded proteins when the amount of their level is high or the cell is under stress and other quality control machineries (i.e. chaperone-mediated refolding and UPS-mediated degradation) are exhausted (Hyttinen et al., 2014).

The homeostatic levels of p62 and its ability to oligomerize with substrates were linked to the formation of cytoplasmic inclusion bodies (Komatsu et al., 2007; Watanabe and Tanaka, 2011). In addition, it is plausible to assume that it serves as a key protein in the elimination of aggresomes via autophagy as it was shown to: (1) bind to HDAC6 and modulate its deacetylase activity; (2) serve as an adaptor-shuttle protein; (3) affect the fusion of autophagosome and lysosome; and (4) co-localize to aggresomes and affect their formation (Komatsu et al., 2007; Pankiv et al., 2007; Watanabe and Tanaka, 2011; Yan et al., 2013)

Autophagy-linked FYVE protein (ALFY), a phosphatidylinositol 3-phosphate binding protein acts as a bridge between the sequestering mechanism and the autophagosome. Upon aggresome formation, ALFY exits the nucleus and binds to p62 which is localized to aggresomes. It then binds to the forming autophagosome and the ATG12-ATG5-ATG16L complex, thus stabilizing the LC3-PE form. Therefore, mechanistically ALFY forms a bridge between all the selective components responsible for aggrephagy (Filimonenko et al., 2010).

Proteasomes are associated with aggresomes in a dynamic manner. Since aggresomes are too large to be digested by the proteasome, one of the roles the proteasome might play is to enhance the conditions that trigger autophagy. Indeed, it was shown that the 26S proteasome dissociates to its sub-complexes—the 19S RP and

20S CP, allowing the Rpn11 subunit to deubiquitinate K63 Ub chains of surface substrates. Free K63 chains upregulate the autophagic machinery, recruiting it to the aggresome for further engulfment (Nanduri et al., 2015).

The activity of the proteasome serves as a molecular sensor for the clearance of aggresomes via autophagy. Inhibition of the proteasome was shown to modulate cytoskeletal dynamics, and results in retaining large number of lysosomes at centrosomes. Thus, under aggregates forming conditions, the cell recruits (and retains) the "garbage workers" to the vicinity of the aggresomes (Zaarur et al., 2014).

3.4. Development and differentiation

Development and cellular differentiation are tightly regulated processes, the progression of which is controlled by gene expression as well as by protein degradation, which is accomplished by both the UPS and autophagy.

3.4.1. Role of the UPS in development and differentiation

The proteasome has been implicated in the regulation of development and appears to play a role in: (1) termination of meiosis via changes in proteasome assembly and activity (Sawada et al., 1999; Tokumoto et al., 1999); (2) oocyte maturation, which is dependent on the proteolytic activity of the 26S proteasome (Josefsberg, 2000; Reverte et al., 2001); (3) initiation of embryonal mitosis and development mediated by degradation of cell cycle regulatory molecules (e.g. Cyclin B1) (Josefsberg et al., 2001; Kawahara et al., 2000); (iv) metamorphosis in an insect model, as evident by proteasome upregulation and the degradation of proteins involved in this process (Arnold, 1995; Löw et al., 1997).

The proteasome is also involved in terminal differentiation of eukaryotic cells, regulating the cell cycle by degrading its activators or inhibitors. Negative regulation of differentiation is mediated by proteasomal degradation of most *cyclin-dependent kinase inhibitors* (CKIs), such as $p27^{Kip1}$, $p57^{Kip2}$ and $p19^{Ink4d}$, which control the activities of *cyclin-dependent kinases* (CDKs) (Sherr and Roberts, 1999). In fact, it has been shown that neuronal differentiation and growth arrest of embryonal carcinoma cells depend on decreased proteasomal degradation of $p27^{Kip1}$, induced by retinoic acid (Baldassarre et al., 2000). Additionally, TGFβ1-induced proteasomal degradation of $p57^{Kip2}$ inhibits differentiation of osteoblastic cells (Urano et al., 1999). By contrast, induction of differentiation can be also accomplished by proteasomal degradation of certain cell cycle regulators, such as $p21^{WAF1/Cip1}$, cyclin D1, and CDC25A phosphatase (Bernardi et al., 2000; Negishi et al., 2001; Spinella et al., 1999).

3.4.2. Role of autophagy in development and differentiation

Autophagy also plays an important role in development and cell differentiation. Autophagic activity has been detected in the initial stages of mammalian development, appearing already in fertilized oocytes during the early phase of pre-implantation. In the two-cell stage, elimination of maternal RNAs and proteins by autophagy is required for the induction of zygotic transcription and translation, which results in an alteration of the protein profile at the four-to-eight cell stage. Accordingly, oocyte-specific knockout of *ATG5* in mice results in embryonic lethality at the four-to-eight cell stage. The involvement of autophagy in early neonatal period is probably required for maintaining appropriate amino acid levels, and high autophagic activity is detected in all tissues except for the brain (Mizushima and Levine, 2010).

Autophagy has also been implicated in differentiation and in remodeling of many cells and tissues. It has been shown that B- and T-lymphocyte-specific deletion of *ATG* genes impairs lymphocyte differentiation and reduces the number of circulating mature B and T cells. It has been suggested that autophagic clearance of mitochondria is accounted, at least in part, for T-lymphocyte maturation (Pua et al., 2009; Stephenson et al., 2009). Additionally, autophagy is involved in adipocyte differentiation, as deletion of *ATG7* or *ATG5* results in decreased mass of white adipose tissue, a smaller number of multi-locular lipid droplets, and increased number of mitochondria (Baerga et al., 2009; Nedjic et al., 2008; Singh et al., 2009; Zhang et al., 2009).

3.5. Antigen presentation

Proteasome/immuno-proteasome and autophagy participate in the regulation of cell-mediated immune response via generation of antigenic and self-peptides which are presented on the *major histocompatibility complex* (MHC) class I and class II molecules, respectively (Fig. 1).

3.5.1. Role of the proteasome in antigen presentation

The products of proteasomal degradation, which are generated in the cytosol and nucleus from endogenous, as well as pathogenic proteins (e.g. *Epstein Barr Nuclear Antigen* 1 (EBNA1)), are subsequently transported to the ER lumen by *transporters associated with antigen processing* (TAPs) and loaded on MHC class I molecules, which are then delivered to the cell surface through the Golgi apparatus and are recognized by $CD8^+$ T cells (Joffre et al., 2012; Neefjes et al., 2011; Rock et al., 2014). In case the peptide presented on the cell surface is derived from a foreign protein (e.g. viral), the $CD8^+$ T cell kills the presenting cell.

3.5.2. Role of autophagy in antigen presentation

Autophagic degradation is involved mostly in generation of peptides presented on MHC Class II molecules. Such antigenic fragments are derived either from (1) endocytosed material via endosome-autophagosome fusion, yielding amphisomes; or (2) via direct uptake of cytosolic pathogens (e.g. Herpes virus) by autophagosomes. At times, small fraction of antigenic proteins is also taken up by autophagosomes (e.g. EBNA1). Subsequently, antigen-containing amphisomes/autophagosomes fuse with *MHC class II-containing compartments* (MIICs), in which their content is broken down by lysosomal hydrolases to form peptides which are then loaded onto MHC class II molecules, with the assistance of the HLA-DM chaperone. MHC class II presented antigens are recognized on the cell surface by helper $CD4^+$ T cells (adaptive immunity) (Münz, 2012, 2010; Paludan et al., 2005).

3.5.2.1. Cross-presentation. Recent studies have indicated the existence of cross-presentation, in which extracellular material can also be presented on MHC class I molecules. However, the exact molecular and cellular mechanisms of this process are still obscure (Apcher et al., 2016). One suggested mechanism includes the engulfment of endosome-released cytosolic pathogens (or their *de novo* synthetized proteins) by autophagosomes. Fusion of these autophagosomes with lysosomes and recycling endosomes (containing MHC class I molecules) leads to antigen degradation and loading onto MHC class I molecules (Desai et al., 2015). Autophagy was also shown to support exosome formation and exocytosis of pathogenic proteins from a donor cell and their endocytosis by a neighboring cell, where antigen processing and loading onto MHC class I molecules occur (e.g. in Influenza A viral infection)(Joffre et al., 2012; Münz, 2016; Shibutani et al., 2015).

3.6. Apoptosis and cell survival regulation

Apoptosis is highly conserved from lower eukaryotes to mammals. The process is involved in morphogenesis and tissue remodeling during embryonic development, in the regulation of

cell number and organ size, and in the elimination of abnormal and potentially dangerous cells. It is tightly regulated by different pathways, including the UPS and autophagy (Fuchs and Steller, 2011) (Fig. 1).

3.6.1. The UPS in apoptosis and cell survival regulation

The importance of proteasomal activity in the apoptotic process has been demonstrated in numerous developmental models. In *Manduca sexta,* the conversion of the back muscles in the caterpillar to the wing muscles in the adult butterfly requires initial proteasomal activity (Arnold, 1995). In mammalian cells, proteasomal degradation is essential for the programmed cell death of neurons during nervous system development, as well as for apoptosis of thymocytes following different stimuli, implicating a role for the proteasome in thymocyte negative selection (Grimm et al., 1996; Sadoul et al., 1996).

The proteasome can act as a pro-apoptotic or anti-apoptotic agent. The mechanism by which the proteasome accomplishes its pro-apoptotic functions is carried out by degradation of *inhibitors of apoptotic proteins* (IAPs), such as XIAP and c-IAP1 (Yang and Li, 2000), as well as by degradation of BCL-2, a protein that blocks apoptosis (Breitschopf et al., 2000; Dimmeler et al., 1999). On the other hand, it has been shown that induction of apoptosis (e.g. by depriving neurons from nerve growth factor) can be prevented by proteasome inhibitors (Canu et al., 2000; Sadoul et al., 1996).

The anti-apoptotic activity of the proteasome has been well established in the survival and proliferation of rapidly growing and neoplastic cells. The plentiful of proteins which are involved in the regulation of the balance between survival and apoptotic signals, are controlled, at least in part, by proteasomal degradation. For example, the degradation of pro-apoptotic proteins such as Bax and Bid (Li and Dou, 2000), as well as the degradation of cell cycle regulating proteins such as $p27^{Kip1}$, $p21^{WAF1/Cip1}$, and p53—the accumulation of which induces apoptosis—decreases the rate of ACD (Catzavelos et al., 1997; Chiarle et al., 2000; Lopes et al., 1997; Maki et al., 1996; Naujokat et al., 2000; Rieber and Strasberg Rieber, 2000). An additional anti-apoptotic protein is NF-κB which is activated by the proteasome in multiple steps, including the degradation of its inhibitory IκB proteins, which results in translocation of the transcription factor to the nucleus where it induces numerous downstream genes (Fribley and Wang, 2006; Karin and Ben-Neriah, 2000; Karin, 1999; Ni et al., 2001).

3.6.2. Autophagy in apoptosis and cell survival regulation

Autophagy is also involved in the regulation of apoptosis either by its stimulation or suppression. The facilitation of apoptotic events by autophagy has been demonstrated via genetic and chemical inhibition of the pathway in different organisms. It has been shown that autophagic proteins can have additional roles besides their 'canonical' function. For instance, ATG5, in complex with the death receptor adaptor protein *FAS-associated death domain* (FADD) and p62 (following treatment with SKI-I kinase and proteasome inhibitors), was shown to promote activation of caspase-8, an effector of caspase-3. Also, it has been shown that ATG12 can activate caspases through the mitochondrial pathway, in particular by its interaction with BCL-2 and MCL1. ATG7 has been also implicated in apoptosis induction following lysosomal membrane photodamage (Mariño et al., 2014). Another mechanism by which autophagy can promote apoptosis is via degradation of IAPs (similar to the proteasome), which are Ub ligases that target caspases for degradation. Genetic inhibition of autophagy in *D. melanogaster* by mutating *ATG1*, *ATG13* or *VPS34*, abolishes the degradation of the IAP *BIR-containing ubiquitin-conjugating enzyme* (Bruce), resulting in inhibition of the developmental apoptosis of nurse cells in late oogenesis (Nezis et al., 2010).

Autophagy can be also involved in inhibition of cell death. One of the mechanisms by which autophagy decreases apoptosis is via elimination of damaged mitochondria (mitophagy), which induces the apoptotic program by the release of catabolic hydrolases and caspase activators (e.g. cytochrome C). In addition, autophagy has been suggested to alleviate pancreatitis by the exclusion of granules containing abnormally activated trypsin (in acinar cells) which would have otherwise leaked into the cytosol and cause cell death. Moreover, autophagy can prevent cell death by selective reduction of the amount of pro-apoptotic proteins in the cytosol, such as caspase-8 and p62, the last one induces apoptosis via *reactive oxygen species* (ROS) production (Mariño et al., 2014; Mathew et al., 2009).

Autophagy regulates the activation of both 'canonical' and 'non-canonical' NF-κB signaling pathways by selective degradation of IκBα, *IκB kinases* (IKKs), and *NF-κB inducing kinase* (NIK). Degradation of IκBα by autophagy results in the activation of the 'canonical' NF-κB pathway which supports survival, whereas the degradation of IKKs and NIK attenuates the activation of the 'canonical' and 'non-canonical' NF-κB pathways, respectively (Djavaheri-Mergny and Codogno, 2007; Jia et al., 2012; Niida et al., 2010; Qing et al., 2007).

Autophagy also promotes cell survival by increasing the level of free amino acids via the stimulation of protein degradation. These amino acids are subsequently reused for the synthesis of new proteins, as well as for gluconeogenesis (via the Cahill cycle) and ATP production (through the TCA cycle) (Periyasamy-Thandavan et al., 2009).

3.7. Pathogen elimination (Xenophagy)

There is no evidence for UPS-mediated clearance of entire pathogens. On the other hand, immune-related induction of autophagy has been described (Rikihisa, 1984). Autophagy was shown to target a range of pathogens, including group A streptococci, *S. flexneri, T. gondii,* and *S. enterica.* Identification and targeting of pathogens to autophagy was termed xenophagy (from Greek: eat foreign matter).

The mechanism by which cells target pathogens to autophagy is analogous to other types of selective autophagy, namely tagging the cargo with modifiers such as Ub (but not exclusively), followed by their recognition by autophagic receptors. Both K63- and K48-Ub chains were shown to mediate the recognition of different pathogens (Collins et al., 2009). Several autophagic Ub receptors were implicated in xenophagy, such as p62, optineurin and NDP52 (Thurston et al., 2009; Wild et al., 2011; Zheng et al., 2009).

S. enterica resides in intracellular vacuoles. Damage to these vacuoles results in entrance of the bacteria to the cytoplasm accompanied by rapid ubiquitination and recognition by p62, optineurin and NDP52 in a non-redundant manner (Wild et al., 2011; Zheng et al., 2009). It is speculated that the steady state level of autophagy is sufficient for xenophagy of all the invading bacteria, and that the pathogens have to interfere with autophagy in order to survive. For example, infection by Listeria, Salmonella and Shigella were all shown to inhibit signaling pathways underlying autophagic activity (Tattoli et al., 2012a,b; Tattoli et al., 2013).

After infecting cells, *M. tuberculosis* (Mtb) can stay dormant in the host for decades and survive inside macrophages due to its ability to escape autophagic degradation. Following activation by IFN-γ, macrophages can bypass autophagic inhibition by Mtb, leading to the clearance of the pathogen. This process is mediated, at least in part, via the interaction of the shuttling protein ubiquilin-1 with Mtb proteins, and the subsequent recruitment of the autophagic machinery (Sakowski et al., 2015).

3.8. Amino acid recycling

Besides supply of amino acids by the breakdown of dietary proteins, the degradation of cellular proteins by both the UPS and autophagy is also essential for the maintenance of amino acid pool. Essential amino acids are required for the synthesis of acute phase proteins, as well as for energy generation under pathophysiological conditions such as starvation, cancer-induced cachexia, renal insufficiency and sepsis. At the organism level, the supply of essential amino acids under shortage is largely relying on protein breakdown in skeletal muscles – the largest amino acids reservoir in the body (Essén et al., 1992; Evans, 2010; Felig, 1975; Lecker et al., 2004, 2006; Piccirillo and Goldberg, 2012; Reeds et al., 1994; Siegel et al., 1979).

3.8.1. The role of the UPS in amino acid recycling

Under basal metabolic conditions, homeostasis of intracellular amino acid pool is primarily maintained by proteasomal protein breakdown (Rock et al., 1994; Zhao et al., 2015, 2007). It has been suggested that the UPS also takes part in enhanced proteolysis under different stress conditions (Zhao et al., 2015). Additionally, prolonged proteasome inhibition is lethal partially due to a shortage of amino acids, and supplementation of cells with specific amino acids during such inhibition rescues the starving cells (Suraweera et al., 2012).

3.8.2. The role of autophagy in amino acid recycling

Nutrient depletion is a known inducer of autophagy (Mizushima and Klionsky, 2007), that serves the cell to adapt to starvation. It has been suggested that as starvation is prolonged, amino acid pool maintenance becomes more dependent on autophagy (Vabulas and Hartl, 2005). Cells that lack ATG7 cannot maintain physiological amino acid levels, which fall below the critical concentration, affecting *de novo* protein synthesis (Onodera and Ohsumi, 2005). The re-generated amino acids are used mostly for the synthesis of specific proteins such as heat shock proteins that take part in the cellular response to nitrogen depletion (Onodera and Ohsumi, 2005). In yeast, it was shown that the amino acids originated from starvation-induced non-selective autophagy, are in part responsible for the maintenance of the respiratory function and the elimination of ROS (Suzuki et al., 2011).

Following birth, neonates are subjected to starvation until nutrients are supplied by milk feeding. Therefore, autophagy is induced immediately following birth in order to produce essential amino acids. In mice, it was shown that autophagy deficient neonates develop significantly lower levels of amino acids (by 30–40% compared to the WT mice), resulting in their death (Kuma et al., 2004).

Amino acid pool serves as a link in the cross-talk between the UPS and autophagy, as compromised proteasome function which impairs amino acid homeostasis, results in activation of autophagy. Thus, concerted degradation of proteins by both systems is required in order to maintain an adequate amino acid pool (Suraweera et al., 2012).

4. Regulation of the UPS and autophagy function

Degradation of each protein is regulated by its recognition, modification, and targeting by the different catalytic machineries. Along with such regulation at the individual level, the activity of both UPS and autophagy is regulated at the system level, both under basal conditions and in response to environmental challenges.

The UPS is a constitutively active proteolytic pathway, having the proteasome—its proteolytic arm—highly abundant and active throughout the life of the cell. Proteasomal function is directly regulated at different layers, including gene expression, assembly, structural changes, *post translational modifications* (PTMs), and co-factors affecting its activity (Finley et al., 2016).

It has been shown that following proteasome inhibition, the transcription factor Nrf1 stimulates the biosynthesis of proteasomal subunits in mammals, probably as a compensation mechanism for the loss of proteasome activity (Radhakrishnan et al., 2010; Steffen et al., 2010). Under oxidative stress, it is the Nrf2 homologue which is responsible for upregulation in the expression of proteasomal genes (Kwak et al., 2003).

SKN-1 is an orthologue of both Nrf1 and Nrf2 in *C. elegans*, which mediates proteasomal upregulation in response to proteasome inhibition as well as to oxidative stress (Li et al., 2011; Pickering et al., 2013). In *S. cerevisiae*, Rpn4 is a transcription factor which is imported to the nucleus upon impaired proteasome activity, thereby inducing proteasomal gene expression (Xie and Varshavsky, 2001). Interestingly, all four transcription factors are substrates of the proteasome, forming a feedback loop between its activity level and the extent of its gene transcription (Choe et al., 2009; Kwak et al., 2003; Sha and Goldberg, 2014; Wang et al., 2004).

Some proteasomal subunits have been suggested to play a particular role in the regulation of proteasome assembly and activity, either with (Chondrogianni et al., 2005) or without (Vilchez et al., 2012a,b) upregulation of proteasome biogenesis. Direct monitoring of proteasome function is also achieved through external regulators, such as Ecm29. This proteasome adaptor plays a role in proteasome assembly (Lehmann et al., 2010), but may also promote its disassembly in response to oxidative stress, thereby enhancing the abundance of the free 20S CP. The 20S CP is suggested to degrade oxidized proteins more efficiently than the 26S proteasome (Davies, 2001; Wang et al., 2010).

Numerous PTMs of the proteasome are currently known. Though many of them are of an uncertain role, in several cases the effect of a given modification on proteasome assembly, activity and/or localization, has been elucidated (Hirano et al., 2015). Interesting such instances include phosphorylation of the Rpn6 subunit which enhances proteasome activity (Lokireddy et al., 2015), and the ubiquitination of the proteasome (at an unknown site), which was shown to target it for proteaphagy, i.e. degradation by the autophagy-lysosome system (Marshall et al., 2015).

Autophagic protein degradation occurs also under basal cellular conditions, though its rate is considerably lower than that observed following its induction by different stimuli (Mizushima et al., 2010). The best characterized stimulation of autophagy is the deprivation of nutrients (Abada and Elazar, 2014), and though autophagy is now known also as a selective catabolic machinery, its remarkable upregulation under starvation, together with its ability to degrade bulks of cellular material, makes autophagy an important mechanism in the cell's ability to replenish its supply of amino acids under shortage. Although autophagy may serve as a self-salvage mechanism, it can also, when excessive, lead to cell death (Maiuri et al., 2007).

Among the stimuli that upregulate the autophagic pathway are amino acids or glucose starvation, limited hormones or growth factors supply, low energetic state, oxidative stress, hypoxia, ER stress, heat, and different pharmacological agents affecting either the activity of cyclic-AMP or the concentration of calcium ions within the cell (Abada and Elazar, 2014; Mizushima et al., 2010; Sarkar, 2013).

The main signaling hub known to integrate the various pathways regulating autophagy is the *mammalian target of rapamycin complex 1* (mTORC1). Besides its role as a main nutrient sensor (Bar-Peled and Sabatini, 2014), mTORC1 is also a target for many signaling pathways in the cell, coordinating the cellular response to many external and internal cues, and regulating a diverse array of downstream processes, including protein and lipid synthesis, energy metabolism, and autophagy (Laplante and Sabatini, 2013).

In well-fed cells, active mTORC1 interacts with the ULK1-ATG13-FIP200 complex and phosphorylates ULK1 and ATG13, thereby inhibiting them. Following starvation or mTORC1 inhibition, it no longer phosphorylates ULK1 and ATG13, leading to ULK1 activation, which in turn phosphorylates itself as well as the two other complex members. This chain of events leads to the initiation of autophagosome formation (Ganley et al., 2009; Hosokawa et al., 2009; Jung et al., 2009).

It has been recently established that proteasome function is also subjected to regulation by mTORC1. It is yet to be determined whether it stimulates or represses proteasome activity, and whether such an effect is mediated by *de novo* synthesis of proteasomal subunits, or by tuning the activity of pre-existing proteasomes (Zhang et al., 2014; Zhao et al., 2015).

Signaling pathways other than mTORC1 have also been shown to regulate autophagy. The transcription factor FoxO3 upregulates genes that facilitate protein degradation both by the UPS and autophagy, and is inhibited by the protein kinase Akt in non-stressed cells (Mammucari et al., 2007; Zhao et al., 2008, 2007). The kinase GCN2 is another sensor for amino acid shortage, primarily through its binding of uncharged tRNAs, which upon starvation upregulates stress-related genes via ATF4, among them are autophagy-related genes (Neufeld, 2012). AMPK is a kinase which is sensitive to cellular energy and glucose level. AMPK can promote autophagy by phosphorylating ULK1 on serine residues different than mTORC1, thereby activating ULK1 (Kim et al., 2011). Notably, although Akt, GCN2 and AMPK can each regulate autophagy directly, all three can do so indirectly as well, primarily via mTORC1 (Sarkar, 2013; Ye et al., 2015). Other stimuli and signals, such as calcium channel blockers, lithium, and the inositol signaling pathway have also been shown to regulate autophagy in an mTOR-independent manner (Sarkar, 2013).

5. Conclusion

The UPS and the autophagy-lysosome machinery are sharing several common characteristics, as well as joint accessory proteins and even substrates. Though they have much in common, and their regulating factors are somewhat interrelated, each of them also possesses unique features and roles. While the importance of each pathway for proper cellular function has been extensively studied in relation to many processes, how they interact (and perhaps complement one another) in maintaining homeostasis is still largely unknown. The two systems also constrain one another, as there are components of each which are known to be degraded by the other. Better understanding of each system, and moreover—the relationship between the two, will hopefully give rise to new and improved pharmacological solutions in the battle against cancer, neurodegeneration and other diseases.

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