Deep Insight Section

Mechanisms and regulation of autophagy in mammalian cells

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Introduction

Cell homeostasis depends on the balance between the production and destruction of macromolecules and organelles. There are two major systems in eukaryotic cells that degrade cellular components: the ubiquitin proteasome system (UPS) and the lysosome. The UPS only degrades proteins, mainly short-lived proteins that have to be tagged by ubiquitin to be recognized by the proteasome (Ciechanover et al., 2000). The lysosomal system is responsible for degrading macromolecules, including proteins, and for the turnover of organelles by autophagy (Mizushima et al., 2008). Recent evidence demonstrates that cross-talk and cooperation exist between the UPS and autophagy (Korolchuk et al., 2009; Lamark and Johansen, 2009; Nedelsky et al., 2008). The term "autophagy" was coined by Christian de Duve soon after his discovery of lysosomes (see reference Klionsky, 2007 for an historical view of autophagy). The seminal discovery of *ATG* (*AuTophaGy*) genes, originally in yeast and subsequently in multicellular organisms, has provided an important breakthrough in the understanding of macroautophagy and of its functions in physiology and diseases (Klionsky et al., 2003; Nakatogawa et al., 2009). However the term "autophagy" also embraces microautophagy and chaperone-mediated autophagy (Klionsky, 2007) that we will briefly describe here. In contrast to macroautophagy, which starts with the formation of a vacuole, known as the autophagosome, that sequesters cytoplasmic components, microautophagy consists of the direct uptake of fractions of the cytoplasm by the lysosomal membrane. Macro- and microautophagy are conserved from yeast to humans. These processes were originally described as bulk degradation mechanisms. However, selective forms of macroautophagy and microautophagy target organelles (mitophagy, pexophagy, ribophagy, ERphagy, piecemeal microautophagy of the nucleus), protein aggregates (aggrephagy), lipid droplets (lipophagy), glycogen and microorganisms that invade the intracellular milieu (xenophagy) (Beau et al., 2008; Kraft et al., 2009; van der Vaart et al., 2008). Microautophagy is dependent on GTP hydrolysis and on calcium (Uttenweiler and Mayer, 2008). However the molecular regulation of microautophagy remains to be unraveled. Bulk microautophagy does not seem to be dependent on Atg proteins, whereas selective forms of microautophagy require different sets of Atg proteins (Beau et al., 2008; Kraft et al., 2009; van der Vaart et al., 2008). Chaperone-mediated autophagy (CMA) is a selective form of autophagy that has so far only been described in mammalian cells (Cuervo, 2009). Substrates for CMA contain a KFERQ-related motif in their amino acid sequence. This motif is recognized by the cytosolic constitutive chaperone hsc70 (heat shock cognate of the Hsp70 family). This recognition allows the lysosomal delivery of CMA substrates to occur. The lysosomal membrane protein, LAMP-2A, serves as a receptor in the translocation of unfolded polypeptides across the lysosomal membrane. KFERQ-like motifs are found mainly in cytosolic proteins, and it is estimated that about 30% of cytosolic proteins contain this motif. CMA performs several general functions, such as the elimination of oxidazed proteins and the removal of misfolded proteins, and also provides amino acids during prolonged periods of starvation. It is interesting to note that cross-talk occurs between macroautophagy and CMA during starvation (Kaushik et al., 2008; Massey et al., 2006). When CMA is stimulated, macroautophagy is first induced and then declines. The molecular basis for this switch remains to

be identified. Prevention of the age-related decline of CMA is beneficial for the homeostasis of organs and function (Zhang and Cuervo, 2008). This observation is indicative of the potential importance of CMA and macroautophagy, as we discuss below, as possible anti-aging mechanisms. CMA is also involved in more specific functions, such as antigen presentation by MHC class II molecules, neurone survival, and kidney growth (Cuervo, 2009).

Molecular and cellular aspects of macroautophagy

Autophagosome formation. Autophagy is initiated by the formation of a double membrane-bound vacuole known as the autophagosome. The size of this vacuole can range from 300 to 900 nm. Autophagosomes are non-degradative vacuoles that sequester cytoplasmic material. The boundary membrane arises from a single membrane, known as the phagophore or isolation membrane (reviewed in Yang and Klionsky, 2010) (**Figure 1**). Once completed, autophagosomes receive inputs from the endocytic pathway, and thus acquire acidic and degradative capacities. These acidic and degradative vacuoles form single-membrane compartments known as amphisomes (reviewed in

Yang and Klionsky, 2010). The last stage of autophagy is the fusion of the amphisomes with lysosomes to degrade their autophagic cargoes and to recycle nutrients (to meet the metabolic demand) and membranes (to permit ongoing lysosomal function). Whereas the mobility of autophagic vacuoles is dependent on microtubules, fusion events between autophagic vacuoles and lysosomes seem to be independent of cytoskeletal elements. A long-standing question regarding autophagy was to identify the origin of the phagophore and to decipher the molecular basis of the biogenesis of autophagosomes. The discovery of *ATG* genes in yeast was a major milestone in our understanding of autophagy (Nakatogawa et al., 2009). More than 15 Atg proteins, plus class III PI3K or hVps34, are required to construct the autophagosome. These Atg proteins are hierarchically recruited at the PAS (Nakatogawa et al., 2009). The formation of the autophagosome is a multistep process that includes the biogenesis of the isolation membrane, followed by its elongation and closure. The process also requires the shuttling of Atg9, the only transmembrane Atg, between a peripheral site and the isolation membrane (Nakatogawa et al., 2009) (**Figure 2**).
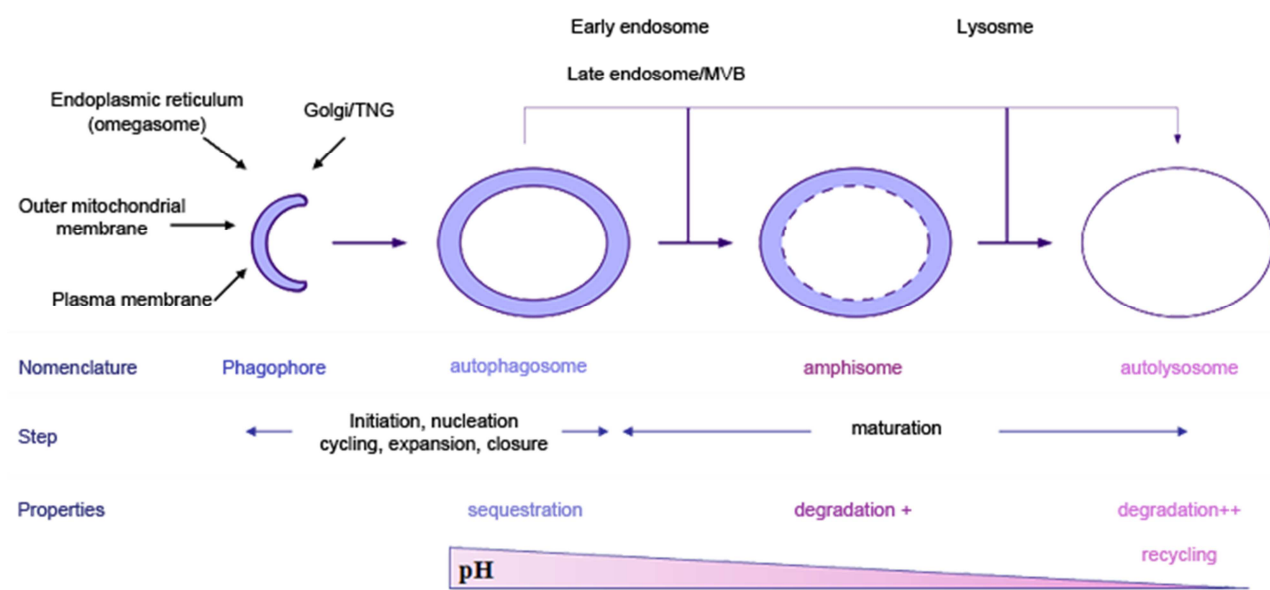

Figure 1. Schematic view of the autophagic pathway. Autophagy is initiated by the nucleation of an isolation membrane or phagophore. Several different membrane pools contribute to the formation of the phagophore. This membrane then elongates and closes on itself to form an autophagosome. In most cases, once the autophagosome has been formed it receives input from the endocytic pathway (early and late endosomes and multivesicular bodies-MVB). These steps are collectively termed maturation. The amphisomes that result from the fusion of autophagosomes with late endosomes/MVB are acidic and hydrolytic vacuoles.
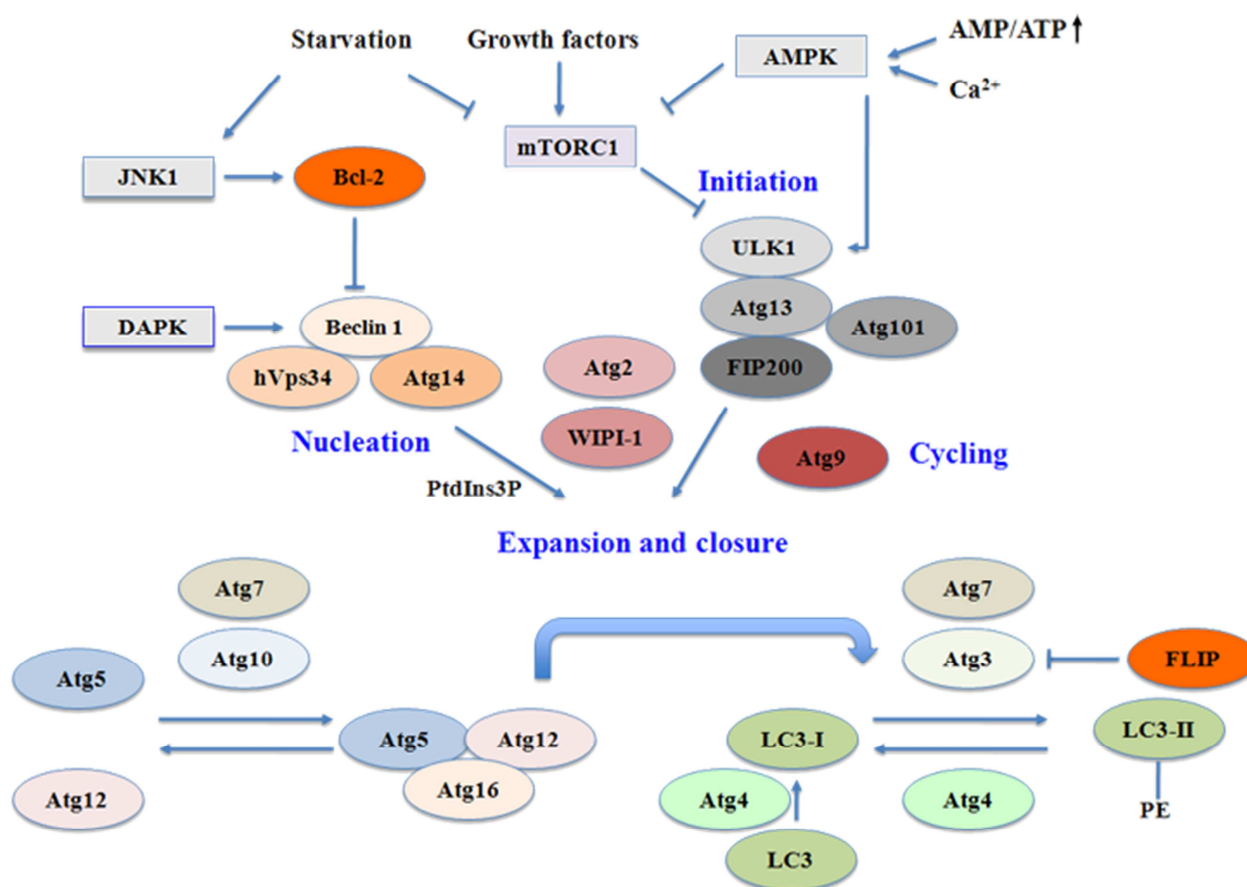
Figure 2. Regulation of autophagy and its relationship with signaling molecules and apoptotic mediators. In the presence of amino acids, growth factors and energy, the mTOR complex 1 (mTORC1) represses autophagy by inhibiting the kinase activity of ULK1. In contrast, in the absence of amino acids and growth factors, or in response to an increase in the AMP/ATP ratio (via activation of AMPK), mTORC1 is inhibited and autophagy is initiated by the ULK1 complex. In this complex, Atg13 and FIP200 are substrates for ULK1 kinase activity. We do not know whether ULK1 has any other substrates. During starvation, c-JUN N-terminal kinase 1 (JNK1) is activated. By phosphorylating Bcl-2, JNK1abolishes its inhibitory effect on the activity of the Beclin 1:hVps34:Atg14 complex. The phosphorylation of Beclin 1 by Death-associated protein kinase (DAPK) also triggers the dissociation of Bcl-2 from Beclin 1. Not shown in the Figure, BH3-containing proteins can dissociate the Beclin 1:Bcl-2 interaction by competing with the Beclin 1 BH3 domain independently of the modification of the phosphorylation status of the proteins in the complex. The activity of the Beclin 1:hVps34:Atg14 complex is important for the nucleation of the autophagosomal membrane. The functional relationship between the ULK1:Atg13:FIP200 (initiation) and Beclin 1:hVps34:Atg14 (nucleation) complexes remains to be determined. Production of PtdIns3P by hVps34 in the Beclin 1:hVps34:Atg14 complex allows the recruitment of WIPI-1 and Atg2 to occur. The expansion and closure of the autophagosomal membrane are dependent on the Atg12 and LC3 conjugation systems. The Atg12-Atg5 conjugate associated with Atg16 contributes to the stimulation of the conjugation of LC3-I to phosphatidylethanolamine (PE) to generate LC3-II. Expansion of the autophagosomal membrane is probably dependent on the supply of lipids by Atg9 that cycles between a peripheral pool and the growing isolation membrane or phagophore. The anti-apoptotic protein FLIP inhibits autophagy by interacting with Atg3. In this Figure, protein kinases with substrates in the autophagic machinery are boxed in rectangles. Mediators of apoptosis are boxed in orange. These mediators regulate autophagy at the nucleation step (Bcl-2 and DAPK) and at the expansion/closure step (FLIP).

Recently strong arguments have been advanced for the role of the endoplasmic reticulum (ER) in the initiation of autophagy (Axe et al., 2008; Hayashi-Nishino et al., 2009; Ylä-Anttila et al., 2009). The ULK1 complex (a complex composed of ULK1: the mammalian ortholog of yeast Atg1, FIP200: the mammalian ortholog of the yeast Atg13, Atg17, Atg101), and the PI3K complex (a complex composed of Beclin 1: the mammalian ortholog of yeast Atg6, Atg14, hVps34, hVps15 and AMBRA 1) congregate at the PAS to initiate autophagy in response to nutrient starvation. The kinase activity of ULK1 is controlled by the kinase mTOR in the mTORC1 complex sensitive to rapamycin (Hosokawa

et al., 2009). The protein Atg14 plays a key role in the ER targeting of the PI3K complex. How the ULK1 and PI3K complexes are coordinately regulated remains to be elucidated. The production of PtdIns3P by hVps34 recruits WIPI-1/2 (Atg18) and DFPC1, which are both PtdIns3P binding proteins. DFCP1 is located at the Golgi in resting cells, but in response to autophagy stimulation it is recruited to an ER structure known as the omegasome (Axe et al., 2008). The omegasome serves as a PAS to accommodate the two ubiquitin-like conjugation systems (Atg12-Atg5, Atg16 and LC3-II, the phosphatidylethanolamine containing LC3, the mammalian ortholog of the yeast Atg8) that act

sequentially to elongate the phagophore membrane and thus form the autophagosome (Nakatogawa et al., 2009). More recently it has been suggested that the mitochondrial outer membrane may be another source of the isolation membrane (Hailey et al., 2010). According to this scenario, the mitochondria-ER contact site provides the growing phagophore with lipids. The plasma membrane, through Atg16L1 decorated vesicles derived from coated pits, is also a source of membrane for the phagophore (Ravikumar et al., 2010a). Finally, Golgi apparatus and post-Golgi compartments containing Atg9 also contribute to the formation of the autophagosome membrane (Mari et al., 2010; Ohashi and Munro, 2010). Whatever the origin of the membrane, Atg proteins are retrieved from the autophagosome membrane after closure, with the exception of a fraction of LC3-II, which is transported into the lysosomal compartment (Yang and Klionsky, 2010). Following on from this discovery, several methods based on the analysis of the LC3 protein have been developed to monitor autophagy (Mizushima et al., 2010).

The role of LC3 and of other members of the mammalian Atg8 family (GABARAPs) remains to be fully elucidated. However, a recent study shows that LC3s and GABARAPs are involved in different steps of autophagosome biogenesis (Weidberg et al., 2010). LC3s mediate the elongation of the autophagic membrane, and GABARAPs mediate a downstream event probably associated with the closure of the autophagosome membrane. Atg8 proteins induce membrane fusion, which is involved in autophagy (Nakatogawa et al., 2007; Weidberg et al., 2011a). However, the biogenesis of autophagosomes has also been shown to involve SNAREs in yeast and mammalian cells (Moreau et al., 2011; Nair et al., 2011). Atg8 proteins can also serve as a scaffold for recruiting proteins that may regulate events upstream and downstream of the formation of autophagosomes (Garcia-Marcos et al., 2011; Itoh et al., 2011; Mauvezin et al., 2010). Moreover, LC3 contributes to the selectivity shown by autophagy towards different cell structures, protein aggregates and microorganisms via the recognition of an LIR (LC3 Interacting Region) on target proteins such as P62 and NBR1 (Noda et al., 2008; Kraft et al., 2009; Weidberg et al., 2011b).

After their formation, autophagosomes can merge with endocytic compartments (early and late endosomes, multivesicular bodies can merge with autophagosomes) before fusing with the lysosomal compartment (Liou et al., 1997; Razi et al., 2009; Stromhaug and Seglen, 1993). The term "amphisome" (from the Greek roots, *amphi*: both and *soma*: body) has been coined by Per O. Seglen (reviewed in Fengsrud et al., 2004) for the vacuole that results from the fusion of an autophagosome with an endosome. The late stage of autophagy depends on molecules that regulate the maturation of autophagosomes, including their fusion with endosomes and lysosomes, as well as on the

acidification of the autophagic compartments, and the recycling of metabolites from the lysosomal compartment (**Figure 1**). These steps are of a fundamental importance for the flux (defined here as extending from the cargo sequestration step to that of its lysosomal degradation) of material through the autophagic pathway (Codogno and Meijer, 2005). Any blockade in the maturation of autophagosomes, fusion with the lysosomal compartment or impairment of the lysosomal function or biogenesis would result in an accumulation of autophagosomes that would inevitably slowdown or interrupt the autophagic flux (Eskelinen, 2005; Rubinsztein et al., 2009).

Maturation and degradation of autophagosomes

Rubicon and UVRAG. Rubicon and UVRAG (UV irradiation resistance associated gene) are two Beclin 1-binding proteins that regulate the maturation of autophagosomes and endocytic trafficking (Liang et al., 2006; Matsunaga et al., 2009; Zhong et al., 2009). These findings suggest that the Beclin 1: hVps34: UVRAG: Rubicon complex down-regulates these trafficking events, whereas the Beclin 1: hVps34: UVRAG complex upregulates the maturation of autophagosomes and the endocytic trafficking (Matsunaga et al., 2009; Zhong et al., 2009). Therefore, Beclin 1 regulates both the formation of autophagosomes (via its interaction with Atg14L) and the maturation of autophagosomes (via its interaction with UVRAG and Rubicon).

Rab proteins. Colombo and co-workers (Gutierrez et al., 2004), and Eskelinen and co-workers (Jager et al., 2004) have shown that Rab7 is required for autophagosome maturation. Autophagosome maturation is dependent on interactions with class C Vps proteins and UVRAG (Liang et al., 2008). This function of UVRAG is independent of its interaction with Beclin 1, and stimulates Rab7 GTPase activity and the fusion of autophagosomes with late endosomes/lysosomes. Interestingly, Rab11 is required for the fusion of autophagosomes and multivesicular bodies (MVB) during starvation-induced autophagy in the erythroleukemic cell line K562 (Fader et al., 2008). These findings suggest that specific membrane-bound compartment fusion processes during the maturation of autophagosomes engage different sets of Rab proteins, and possibly associated cohort proteins. Other Rab proteins such as Rab22 and Rab24 have subcellular locations compatible with a role in autophagy (Egami et al., 2005; Mesa et al., 2001; Olkkonen et al., 1993).

ESCRT and Hrs. The endosomal sorting complex required for transport (ESCRT) mediates the biogenesis of MVB and the sorting of proteins in the endocytic pathway (Raiborg and Stenmark, 2009). It has recently been demonstrated that the multisubunit complex ESCRT III is needed for autophagosomes to fuse with MVB and lysosomes to generate amphisomes and autolysosomes, respectively (Filimonenko et al., 2007; Lee et al., 2007; Rusten et al., 2007). ESCRT III

dysfunction associated with the autophagic pathway may have important implications in neurodegenerative diseases (such as frontotemporal dementia and amyotrophic lateral sclerosis) (Filimonenko et al., 2007; Lee et al., 2007). The Hrs protein (hepatocyte growth factor-regulated tyrosine kinase substrate) plays a major role in endosomal sorting upstream of ESCRT complexes (Raiborg and Stenmark, 2009). Hrs contains a FYVE domain that binds specifically to PtdIns3P, and facilitates the maturation of autophagosomes (Tamai et al., 2007). This raises the intriguing possibility that PtdIns3P may be required for the formation of the autophagosome and its maturation. However, the role of ESCRT proteins in autophagy remains to be elucidated. It is impossible to rule out the possibility that these proteins could be involved in the closing of autophagosomes (reviewed in Rusten and Stenmark, 2009).

SNAREs. Soluble N-ethylmaleimide-sensitive factor attachment protein receptors (SNAREs) are basic elements in intracellular membrane fusion (Gurkan et al., 2007; Rothman and Wieland, 1996). In yeast the vacuolar t-SNAREs Vam3 (Darsow et al., 1997) and Vti1 (Ishihara et al., 2001), are needed for complete fusion to occur between the autophagosome and the vacuole (the name given to the lysosome in yeast) in *S. cerevisiae*. The mammalian homologue of Vt1, Vti1b, may be involved in a late stage of autophagy, because the maturation of autophagic vacuoles is delayed in hepatocytes isolated from mice in which Vti1b has been deleted (Atlashkin et al., 2003). More recently, Colombo and colleagues (Fader et al., 2009) have reported that VAMP3 and VAMP7, two v-SNAREs, control the fusion between autophagosomes and MVB and fusion of amphisomes with lysosomes, respectively.

Endo/lysosomal membrane proteins. LAMPs (Lysosomal associated membrane proteins) are a family of heavily-glycosylated, endo/lysosomal transmembrane proteins (Eskelinen et al., 2003). Autophagic degradation has been shown to be impaired in hepatocytes isolated from LAMP-2 deficient mice (Tanaka et al., 2000). However, no defect in autophagy was observed in LAMP-2 deficient mouse fibroblasts (Eskelinen et al., 2004). A blockade in the later stage of autophagy only occurs in fibroblasts that are deficient for both LAMP-1 and LAMP-2. The differences in the autophagic activity observed between hepatocytes and fibroblasts may be responsible for the cell type-specific effects of LAMP-1 and LAMP-2 depletion (Eskelinen, 2005).

DRAM (Damage-regulated autophagy modulator) encodes a 238-amino acid protein which is conserved through evolution, but has no ortholog in yeast (Crighton et al., 2006). DRAM is a direct target of p53. The protein is a multispanning transmembrane protein present in the lysosome. DRAM may regulate late stages of autophagy, but surprisingly it also controls the formation of autophagosomes (Crighton et al., 2006).

This suggests the possibility of a new paradigm in which feedback signals from the lysosomes control the early stages of autophagy.

Microtubules. The destabilization of microtubules by either vinblastin (Høyvik et al., 1991) or nocodazole (Aplin et al., 1992) blocks the maturation of autophagosomes, whereas their stabilization by taxol increases the fusion between autophagic vacuoles and lysosomes (Yu and Marzella, 1986). More recent findings have confirmed the role of microtubules in the fusion with the acidic compartment (Jahreiss et al., 2008; Kochl et al., 2006; Webb et al., 2004). Autophagosomes move bidirectionally along microtubules. Their centripetal movement is dependent on the dynein motor (Kimura et al., 2008; Ravikumar et al., 2005). Two types of fusion have been documented (Jahreiss et al., 2008): **1.** Complete fusion of the autophagosome with the lysosome, **2.** Transfer of material from the autophagosome to the lysosomal compartment following a kiss-and-run fusion process in which two separate vesicles are maintained. However, fusion with lysosomes can be microtubule-independent during starvation-induced autophagy when autophagosomes are formed in the vicinity of lysosomes (Fass et al., 2006).

Acidification and degradation

ATPases. Vacuolar ATPases (v-ATPase) are ubiquitous, multi-subunit proteins located in the acidic compartment (Forgac, 2007). Inhibition of the activity of v-ATPase by bafilomycin A1 or concanamycin A blocks the lysosomal pumping of H+ and consequently inhibits lysosomal enzymes, which are active at low pH. It has been proposed that bafilomycin A1 blocks the late stages of autophagy by interfering with the fusion of autophagosomes with endosomes and lysosomes (Yamamoto et al., 1998) or preventing the lysosomal degradation of sequestered material (Fass et al., 2006; Mousavi et al., 2001). Overall, the resulting effect of the inhibition of v-ATPase is to interrupt the autophagic flux as determined by the lysosomal inhibition of autophagic cargo. Interestingly it has recently been demonstrated that a deficiency of vacuolar H+-ATPase homolog (VMA21), a chaperone that binds to the c" subunit of the v-ATPase in the ER and which is responsible for X-linked myopathy with excessive autophagy (XMEA), causes an accumulation of autophagic vacuoles and interrupts autophagy flux in striated muscle cells (Ramachandran et al., 2009).

ATPases associated with various cellular activity proteins (AAA ATPases) are a family of proteins broadly engaged in intracellular membrane fusion (White and Lauring, 2007). N-ethylmaleimide sensitive factor (NSF) is an AAA ATPase, which binds to SNARE complexes and utilizes ATP hydrolysis to disassemble them, thus facilitating SNARE recycling. In yeast mutants lacking sec18 (the yeast homolog of NSF), autophagosomes are formed, but dot not fuse with the vacuole (Ishihara et al., 2001). However, we

do not know whether the ATPase activity of NSF plays a role in the later stages of autophagy in mammalian cells. Nevertheless the activity of NSF is attenuated during starvation, which provides a possible explanation for the slow fusion between autophagosomes and lysosomes observed when autophagy is induced by starvation (Fass et al., 2006). Suppressor of K+ transport growth defect 1 (SKD1-Vps4), another AAA ATPase protein, is required for the maturation of autophagosomes (Nara et al., 2002) in mammalian cells. Vps4 controls the assembly of ESCRT complexes on the multivesicular membrane, and is involved in autophagosome maturation (Rusten et al., 2007) in *Drosophila*, and autophagosome fusion with the vacuole in yeast (Shirahama et al., 1997).

Degradation and lysosomal efflux. By virtue of lysosomal degradation autophagy contributes to regulating the metabolism of carbohydrates, lipids and proteins (Kotoulas et al., 2006; Kovsan et al., 2009; Mortimore and Pösö, 1987). Like acidification defects in the endo/lysosomal compartment, defects in the transport or the expression of lysosomal enzymes induce a blockade of autophagy, which is characterized by an accumulation of autophagic vacuoles (Koike et al., 2005; Yogalingam and Pendergast, 2008). The final stage of autophagy is the efflux of metabolites generated by the lysosomal degradation of macromolecules into the cytosol (reviewed in Lloyd, 1996). Atg22 has recently been identified as a permease that recycles amino acids from the vacuole in *S. cerevisiae* (Yang et al., 2006).

Cytoplasmic and nuclear regulation of mammalian autophagy

Several recent reviews have been dedicated to the regulation of autophagy by signaling pathways (Codogno and Meijer, 2005; He and Klionsky, 2009; Meijer and Codogno, 2009). In this section we would like to focus on signaling pathways with identified targets in the molecular machinery of autophagosome formation. We will also discuss the role of signaling pathways and transcription factors in the regulation of the expression of genes involved in controlling autophagy.

Cytoplasmic regulation

mTORC1 and mTORC2. Many signals, including growth factors, amino acids, glucose, and energy status, are integrated by the kinase mTOR (Kim et al., 2002). The induction of autophagy by the inhibition of TOR under conditions of starvation is conserved from yeast to mammals (Blommaart et al., 1995; Noda and Ohsumi, 1998). The mTOR pathway involves two functional complexes: mTORC1 and mTORC2. Both these complexes are involved in the regulation of autophagy **(Fig. 2)**. mTORC1, the rapamycin-sensitive mTOR complex 1, contains the mTOR catalytic subunit, raptor (regulatory associated protein of mTOR, a protein that acts as a scaffold for the mTOR-mediated

phosphorylation of mTOR substrates), GbL and PRAS40 (proline-rich Akt substrate of 40 kDa). The binding of FKBP12 to mTOR inhibits the mTOR-raptor interaction, suggesting a mechanism for rapamycin-specific inhibition of mTOR signaling (Oshiro et al., 2004). This mTOR-raptor interaction, and its regulation by nutrients and/or rapamycin are dependent on GbL (Kim et al., 2003). A major unanswered question about the stimulation of autophagy during starvation is how amino acids signal to mTOR (Meijer and Dubbelhuis, 2004). It has been suggested that hVps34 may have a role in the amino acid signaling to mTORC1 (Byfield et al., 2005; Nobukuni et al., 2005). Thus it appears that hVps34 acts both as a down-regulator of autophagy (acting as an amino acid sensor) and as an up-regulator (because it is a component of Beclin 1 complexes) of autophagy. However, recent observations in *Drosophila* and mammalian cells suggest that Rag GTPases (Ras-related small GTPases) activate TORC1 in response to amino acids by promoting its redistribution to a specific subcellular compartment, which contains the TORC1 activator Rheb (Ras homolog enriched in brain, a GTP-binding protein) (Kim et al., 2008a; Sancak et al., 2008). Moreover, the rate-limiting factor that enables essential amino acids to inhibit mTORC1 has been identified as L-glutamine (Nicklin et al., 2009). L-glutamine uptake is regulated by solute carrier family 1, member 5 (SLC1A5). Loss of SLC1A5 function activates autophagy, and inhibits cell growth. Thus, L-glutamine sensitivity is attributable to SLC7A5/SLC3A2, a bidirectional transporter that regulates the simultaneous efflux of L-glutamine out of cells and the transportation of L-leucine/essential amino acids into cells (Nicklin et al., 2009).

The other mTOR complex, mTORC2, which is less sensitive to rapamycin, includes mTOR, rictor (rapamycin-insensitive companion of mTOR), GbL, SIN1 (SAPK-interacting protein 1) and PROTOR (protein observed with rictor) (Sarbassov et al., 2006). The mTORC2 complex phosphorylates the Ser[473] of Akt/PKB, thereby contributing to the activation of this important cell-survival kinase (Sarbassov et al., 2006). Phosphorylated Akt/PKB down-regulates the activity of the transcriptional factor Forkhead Box O3 (FoxO3). Interestingly, FoxO3 has been shown to stimulate autophagy in muscle cells by increasing the transcription of several genes involved in autophagy (see below) (Mammucari et al., 2007).

Signaling segments acting upstream of mTORC1 and mTORC2 that regulate autophagy have been discussed in recent reviews that the reader can consult for more information (Codogno and Meijer, 2005; Meijer and Codogno, 2009).

mTORC1 substrates and the regulation of autophagy. As discussed above,ULK1, Atg13 and FIP200 form a stable complex that signals to the autophagic machinery downstream of mTORC1. Importantly, mTORC1 is incorporated into the ULK1:Atg13:FIP200

complex via ULK1 in a nutrient-dependent manner. mTOR phosphorylates both ULK1 and Atg13. Under starvation conditions or in response to rapamycin treatment, mTORC1 dissociates from the ULK1 complex, resulting in the activation of ULK1. Activated ULK1 autophosphorylates, and also phosphorylates both Atg13 and FIP200 to initiate autophagy (Hosokawa et al., 2009). The location of phosphorylation sites, as well as the role played by other members of the ULK family, ULK2 and ULK3, remain to be determined. Once activated, mTORC1 favors cell growth by promoting translation via the phosphorylation of 70 kDa, polypeptide 1 ribosomal protein S6 kinase-1 (p70S6K), and phosphorylation of the inhibitor of translation initiation, 4E-BP1. Interestingly, Neufeld and coworkers showed that p70S6K is up-regulated during starvation-induced autophagy in the *Drosophila* fat body (Scott et al., 2004). Mammalian cells probably have a regulatory feedback pathway involving S6K that regulates autophagy (Klionsky et al., 2005). p70S6K is known to phosphorylate and inhibit IRS1 downstream of the insulin receptor (reviewed in Meijer and Codogno, 2009). This loop could provide a way to regulate the activity of mTORC1 during starvation-induced autophagy.

AMP-activated kinase (AMPK). Apart of being a sensor, mTOR can also sense changes in the cellular energy via AMPK. Activation of AMPK inhibits mTOR-dependent signaling, by interfering the activity of the GTPase Rheb, and protein synthesis (Meijer and Codogno, 2004). This is consistent with the switch off of ATP-dependent processes (Hardie, 2004) during period of energy crisis. In starved cells when AMP/ATP ratio increases, the binding of AMP to AMPK favors its activation by the AMPK kinase LKB1 (Corradetti et al., 2004; Shaw et al., 2004). Moreover, Ca^{2+}/calmodulin-dependent kinase kinase b (CaMKK-b) has been identified to be an AMPK kinase (Hawley et al., 2005; Woods et al., 2005). The activity of AMPK is required to induce autophagy in response to starvation in mammalian cells (Meley et al., 2006) and in yeast (Wang et al., 2001) in a TORC1-dependent manner. Moreover, induction autophagy is also dependent on the inhibition of mTORC1 by AMPK in non-starved cells in response to an increase in free cytosolic Ca^{2+} (Høyer-Hansen et al., 2007). In this setting, the activation of AMPK and stimulation of autophagy are dependent on CaMKK-b. Induction of autophagy through the activation of AMPK is probably extended to other settings such as hypoxia (Degenhardt et al., 2006; Laderoute et al., 2006). AMPK is probably a general regulator of autophagy upstream of mTOR (Høyer-Hansen and Jaattela, 2007; Meijer and Codogno, 2007). Another potential candidate of autophagy regulation downstream of AMPK is the Elongation factor-2 kinase (eEF-2 kinase) that controls the rate of peptide elongation (Hait et al., 2006). Activation of eEF-2 kinase increases autophagy while

slowing down protein translation (Wu et al., 2006). The activity of eEF-2 kinase is regulated by mTOR, S6K and AMPK (Browne et al., 2004; Browne and Proud, 2002). During periods of ATP depletion, AMPK is activated and eEF-2 kinase is phosphorylated (Browne et al., 2004) making a balance between inhibition of peptide elongation and induction of autophagy. How eEF-2 kinase impinges on the molecular machinery of autophagy remains to be investigated. Moreover, autophagy is activated by AMPK in a p53-dependent manner (Feng et al., 2005). But the cytoplasmic form of p53 has been shown to have an inhibitory effect on autophagy (Tasdemir et al., 2008).

Finally, AMPK also triggers the initiation of autophagosome formation by phosphorylating ULK1 (Egan et al., 2011; Kim et al., 2011) **(Figure 2)**.

Beclin 1:hVps34 complexes. As discussed in the preceding sections, the trimer Beclin 1:hVps34:hVps15 can interact with various different partners to control the formation and the maturation of autophagosomes. Recently, the anti-apoptotic protein Bcl-2, and anti-apoptotic members of the Bcl-2 family such as Bcl-X_L were shown to inhibit autophagy (Erlich et al., 2007; Maiuri et al., 2007; Pattingre et al., 2005). Bcl-2/Bcl-X_L binds Beclin 1 through a BH3 domain that mediates the docking of the latter to the BH3-binding groove. The constitutive Bcl-2/Bcl-X_L:Beclin 1 interaction is disrupted by signals that promote autophagy. Importantly, c-Jun N-terminal kinase 1 (JNK-1) phosphorylates 3 amino acids in the N-terminal loop of Bcl-2 to trigger its release from Beclin 1 (Wei et al., 2008) in response to starvation or ceramide treatment (Pattingre et al., 2009; Wei et al., 2008). In a reciprocal manner, the BH3 domain of Beclin 1 can be phosphorylated by death-associated protein kinase (DAPk), which has the effect of reducing its affinity for Bcl-X_L (Zalckvar et al., 2009). A second mechanism that leads to the dissociation of the complex involves the competitive displacement of BH3-domain Beclin 1 from Bcl-2/Bcl-X_L by other BH3-containing proteins with proapoptotic properties such BH3-only member of the Bcl-2 family (BAD), the pro-apoptotic member of the Bcl-2 family, Bax-, and BH3-mimetics (Luo and Rubinsztein, 2010; Maiuri et al., 2007). The role of the hypoxia-inducible BH3-only proteins BNIP3 and BNIP3L in the dissociation of the Beclin 1:Bcl-2 complex will be discussed in the next section. Overall these findings point to the central role of Beclin1:hVps34 complexes in the cross-talk between autophagy and apoptosis. Interestingly, a recent study reports that the anti-apoptotic protein FLIP, which blocks the activation of caspase 8 downstream of death receptors, is also an anti-autophagy molecule by blocking the formation of LC3-II via its interaction with Atg3 (Lee et al., 2009) **(Figure 2)**.

Inositol 1,4,5-trisphosphate (IP₃) receptor. Autophagy can also be induced via an mTOR-independent pathway by lowering *myo*-inositol 1,4,5-trisphosphate (IP₃) levels (Sarkar et al., 2005). This effect can be

achieved pharmacologically with drugs such as lithium or L-690 330, which disrupt the metabolism of inositol by inhibiting inositol monophosphatase (IMP). Rubinsztein and coworkers found that L-type Ca2+ channel antagonists, the K+ATP channel opener, and Gi signaling activators all induce autophagy (Williams et al., 2008). These drugs reveal a cyclical mTOR-independent pathway regulating autophagy, in which cAMP regulates IP_3 levels, influencing calpain activity, which completes the cycle by cleaving and activating Gs alpha, which regulates cAMP levels. These data also suggest that insults that elevate intracytosolic Ca2+ (such as excitotoxicity) inhibit autophagy, thus retarding the clearance of aggregate-prone proteins. Both genetic and pharmacological inhibition of the IP_3 receptor (IP_3R) strongly stimulate autophagy. Kroemer and coworkers have shown that the IP_3R antagonist xestospongin B induces autophagy by disrupting a molecular complex formed between the IP_3R and Beclin 1, an interaction that is regulated by Bcl-2 (Vicencio et al., 2009). The IP_3R is known to be located in the membranes of the ER as well as in ER-mitochondrial contact sites, and IP_3R blockade triggers the autophagy of both ER and mitochondria, as observed in starvation-induced autophagy. ER stressors, such as tunicamycin and thapsigargin, also induce autophagy of the ER and, to a lesser extent, of mitochondria. Autophagy triggered by starvation or IP_3R blockade is inhibited by Bcl-2, and Bcl-X_L located at the ER, but not at the mitochondrial outer membrane (Pattingre et al., 2005; Vicencio et al., 2009). In contrast, ER stress-induced autophagy is not inhibited by Bcl-2 or Bcl-X_L. Autophagy promoted by IP_3R inhibition cannot be attributed to a modulation of steady-state Ca2+ levels in the ER or in the cytosol (Vicencio et al., 2009).

Other cytoplasmic autophagy regulation mechanisms.
The function of Atg proteins in autophagy can be regulated not only by protein-protein interactions and phosphorylation, but also by oxidation, acetylation, and proteolytic cleavage. Elazar and colleagues (Scherz-Shouval et al., 2007) have reported that the oxidation of a cysteine residue near the catalytic site of Atg4A and Atg4B is required during starvation-induced autophagy. During starvation, the deacetylation of Atg5, Atg7, LC3 and Atg12 is important to stimulate autophagy. The acetylation is dependent on the activity of p300 (Lee and Finkel, 2009), and the deacetylation is probably under the control of the histone deacetylase sirtuin 1 (Lee et al., 2008). Atg5, Atg7 and Beclin 1 are substrates for calpains (Kim et al., 2008b; Xia et al., 2010; Yousefi et al., 2006), and Atg4D and Beclin 1 are substrates for caspases (Betin and Lane, 2009; Cho et al., 2009; Luo and Rubinsztein, 2010). The cleavage of Beclin 1 by caspase 3, and that of Atg5 by calpain 1 inhibit autophagy (Luo and Rubinsztein, 2010; Xia et al., 2010). The cleavage of Atg proteins by caspases and calpains has been proposed as a possible additional mechanism modulating autophagy. Interestingly, the

truncated form of Atg5 generated by calpain 1 cleavage is translocated into the mitochondria and induces apoptosis (Yousefi et al., 2006).

Nuclear regulation of autophagy

JNK/c-Jun. The sphingolipid ceramides have been shown to increase the expression of Beclin 1 in human cancer cell lines (Scarlatti et al., 2004). In cancer cell lines exposed to ceramide, Li et al. have observed activation of JNK and increased phosphorylation of c-Jun (Li et al., 2009). They also showed that c-Jun controls the transcription of *Becn1* (we have adopted this nomenclature for the gene encoding Beclin 1), and the induction of autophagic cell death in response to ceramide. Activation of JNK, resulting in the upregulation of Beclin 1 expression, has also been reported in the autophagic cell death of human colon cancer cells induced by the stimulation of the human death receptor 5 (Park et al., 2009).

NF-κB. The NF-κB transcription factor, which plays a plethoric role in inflammation, immunity and cancer (Karin, 2006), has also been implicated in regulating autophagy. A conserved NF-κB binding site has recently been unveiled in the promoter of the murine and human gene that encodes Beclin 1 (Copetti et al., 2009). The authors have shown that p65/RelA, a member of the NF-κB family, upregulates the expression of Beclin 1 and stimulates autophagy in several cellular systems. Autophagy stimulation has also been observed after the activation of NF-κB during the heat shock response (Nivon et al., 2009). However, in contrast to this stimulatory role of NF-κB in the regulation of autophagy, the inhibition of NF-κB favors TNFα-dependent and starvation-dependent autophagy (Djavaheri-Mergny et al., 2006; Fabre et al., 2007). Moreover, Schlottmann et al. reported that activation of NF-κB prevents autophagy in macrophages by downregulating the expression of Atg5 and Beclin 1 (Schlottmann et al., 2008).

E2F1. E2F transcription factors are known to be involved in cellular proliferation, but also in DNA repair, differentiation and development (DeGregori and Johnson, 2006). E2F1 has been shown to bind to the promoter of *Becn1*, although an effect of E2F1 on Beclin 1 expression remains to be demonstrated (Weinmann et al., 2001). More recently, the activation of E2F1 has been shown to induce autophagy by upregulating the expression of the autophagy genes *Map1lc3*, *Ulk1*, *Atg5* and *Dram* (we have adopted the nomenclature *Map1lc3* for the gene encoding LC3) (Polager et al., 2008). The E2F1-mediated induction of *Map1lc3*, *Ulk1* and *Dram* is direct (interaction with the promoter), whereas the up-regulation of the expression of *Atg5* is indirect.

HIF-1. HIF-1 (hypoxia-inducible factor-1) is a transcription factor, which regulates the transcription of hundred of genes in response to hypoxia (Manalo et al., 2005). Recently Zhang et al have demonstrated that hypoxia-induced mitochondrial autophagy via HIF-1

mediated induction of *Bnip3* (Zhang et al., 2008). In a similar way, Bellot et al. have shown that hypoxia-induced autophagy is mediated by HIF-1, which induces the expression of BNIP3 and BNIP3L (Bellot et al., 2009). BNIP3 and BNIP3L play important roles in the induction of autophagy by disrupting the interaction of Beclin 1 with Bcl-2 via their BH3 domain. HIF-1 could also regulate the expression of Beclin 1 and Atg5, probably indirectly although according to a recent report the silencing of HIF-1 in cultured chondrocytes was associated with a reduced level of Beclin 1 (Bohensky et al., 2007).

FoxO proteins. Three members of the FoxO family of transcription factors, FoxO1, FoxO3, and FoxO4 are regulated by Akt phosphorylation in response to growth factor and insulin stimulation. FoxO proteins are phosphorylated by Akt, which renders them inactive in the presence of growth factors. When Akt is repressed, FoxO proteins are translocated into the nucleus, bind to DNA, and transactivate its target genes (Salih and Brunet, 2008). Several studies of protein degradation during muscle atrophy show that FoxO3 can induce the expression of multiple autophagy genes, including *Map1lc3, Atg12, Becn1, Atg4b, Ulk1, Pik3c3* (we have adopted the nomenclature *Pik3c3* for the gene encoding hVps34), *Bnip3/Bnip3l,* and *Gabarapl1* (Mammucari et al., 2007; Zhao et al., 2007), and then upregulates autophagy. FoxO3 can bind directly to the promoter region of some of these genes, such as *Map1lc3, Atg12, Gabarapl1* and *Bnip3/Bnip3l.* Expression of a constitutive form of FoxO3 induces autophagy in adult mouse skeletal muscle. Recently another member of the FoxO protein family, FoxO1, has been shown to regulate the expression of key autophagy genes, *Pik3c3, Atg12,* and *Gabarapl1* in hepatocytes in an insulin-dependent manner (Liu et al., 2009).

p53. p53 is a pivotal factor involved in regulating cell death and survival, and in regulating metabolism (Vousden and Prives, 2009). When p53 is activated by cellular stress, p53 accumulates in the cell nucleus, where it transactivates several autophagy-modulating genes including *Dram* (damage-regulated autophagy modulator) and *Tigar* (TP53-induced glycolysis and apoptosis regulator). DRAM stimulates the accumulation of autophagosomes, probably by regulating autophagosome-lysosome fusion to generate autophagolysosomes (Crighton et al., 2006). TIGAR, through its fructose 2, 6-bisphosphatase function, can modulate the glycolytic pathway and indirectly contribute to the fall in the intracellular level of ROS (Bensaad et al., 2006). Recently, the same group showed that TIGAR can also modulate the intracellular ROS level in response to nutrient starvation or metabolic stress, and consequently inhibit autophagy via an mTOR-independent pathway (Bensaad et al., 2009). So, while DRAM and TIGAR are both transactivated by p53, DRAM promotes autophagy whereas TIGAR inhibits autophagy. The complexity of the autophagic response to p53 is further increased by the ability of cytoplasmic p53 to limit autophagy (Tasdemir et al., 2008).

Transcription factor EB (TFEB). Recently the bHLH-leucine zipper transcription factor TFEB has been shown to control lysosomal biogenesis and function. TFEB is a master gene in the gene regulatory network CLEAR (CLEAR: Coordinated Lysosomal Enhancement And Regulation) that binds to CLEAR target sites in the promoter of lysosomal genes and increases lysosomal biogenesis (Sardiello et al., 2009). TFEB not only controls the expression of lysosomal proteins, it also regulates the autophagy transcription program during starvation (Settembre et al., 2011). TFEB is retained in the cytosol because it phosphorylates MAP kinase (ERK2). The reduction of TFEB phosphorylation during starvation triggers its nuclear transport where it activates a transcription program that activates the biogensesis of lysosomes and stimulates autophagy. TFEB has a broad range of activities, because it controls the activity of genes involved in various different steps of autophagy, including autophagosome formation (*Map1lc3, Wipi*), cargo recognition (*Sqstm1,*) and autophagosome fusion with the lysosomal compartment (*Uvrag, Vps11, Vps18*). The fact that autophagy and lysosomal formation are both coordinated by TFEB offers a possible therapeutic target that could be used to boost the autophagic pathway when appropriate.

Other regulators of Atg genes expression. Recently the phosphorylation of eIF2α by PERK has been shown to be essential for the conversion of LC3-I to LC3-II during ER-stress induced by the polyQ72 or dysferlin L1341P mutant (Fujita et al., 2007; Kouroku et al., 2007). In polyQ72 loaded mammalian cells, the phosphorylation of eIF2α upregulates the expression of Atg12 (Kouroku et al., 2007). During the unfolded protein response, triggered by hypoxia, the transcription factors ATF4 and CHOP, which are regulated by PERK, increase the expression *Map1lc3b and Atg5,* respectively (Rouschop et al., 2010). Glyceraldehyde-3-phosphate dehydrogenase (GAPDH), a multifunctional enzyme known to play a role in glycolysis as well as having other less well-understood roles such as transcriptional coactivation, has also been shown to upregulate the transcription of *Atg12* to protect cells against caspase-independent cell death (Colell et al., 2007).

Beclin 1 is one of the essential components involved in autophagosome formation, and its level usually increases during autophagy. For example, in HBV (hepatitis B virus)-infected hepatocytes, the HBV x protein increases autophagy by upregulating the expression of Beclin 1 (Tang et al., 2009). In human monocytes and human myeloid leukemia cells, vitamin D3 has been shown to induce autophagy by upregulating both Beclin 1 and Atg5 (Wang et al., 2008; Yuk et al., 2009). The transcription factor implicated has not been identified, but it has been
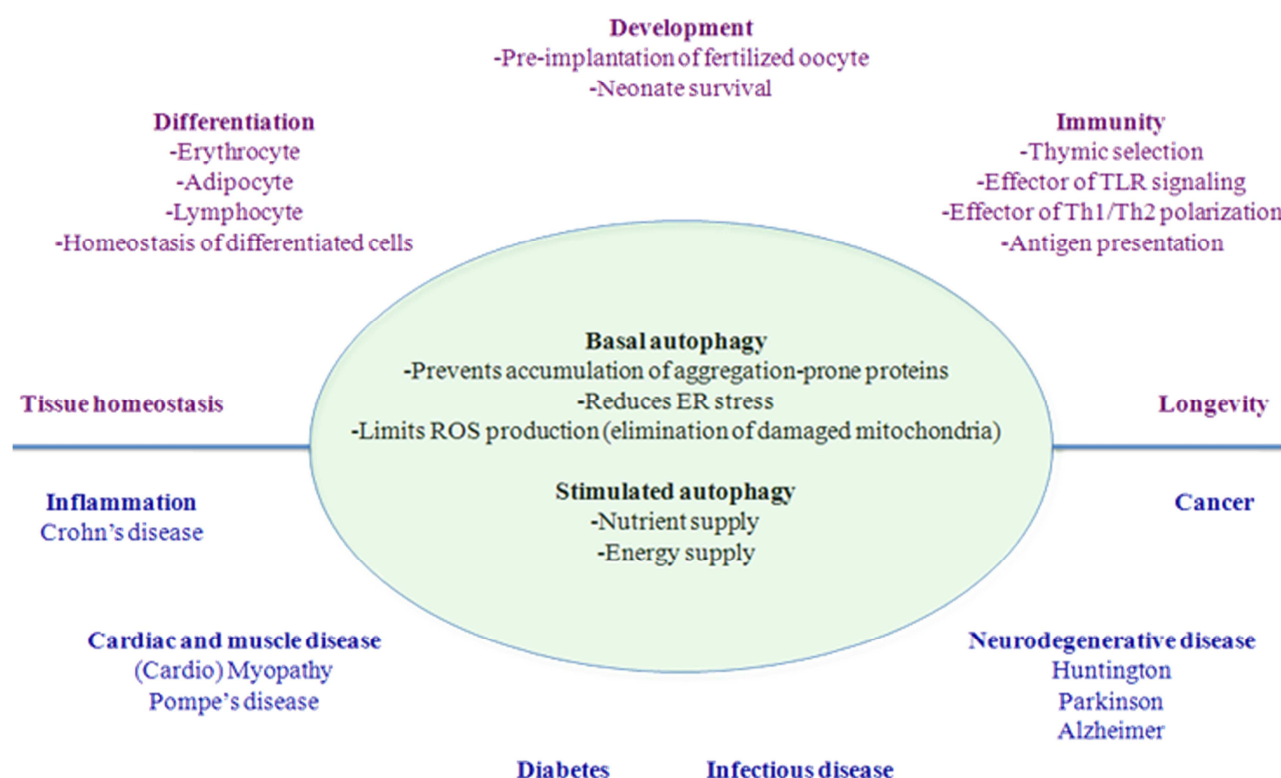
Figure 3. Physiological and pathological roles of autophagy. The physiological role of basal autophagy is to clean the cytoplasm of damaged organelles and protein aggregates. This function is essential for cell fitness by limiting the accumulation of ROS. The stimulation of autophagy during periods of starvation plays a major role in many tissues, but with some exceptions, such as the brain, in providing nutrients for cell metabolism, for the biosynthesis of macromolecules, and to maintain the level of ATP. Autophagy is involved in an early stage of development (pre-implantation of the fertilized oocyte), and differentiation. Autophagy declines during aging, and the restoration of autophagy extends life span in various species. Autophagy contributes to both innate and adaptive immunity. Defective autophagy is observed in many human diseases, and its stimulation is beneficial in most cases. Autophagy plays a more complex role in cancer, because it can be a tumor suppressor mechanism, but can also become a cytoprotective mechanism in tumors, where it contributes to cell survival in a context of metabolic stress and in response to cancer treatments.

shown that in human monocytes the effect of Vitamin D3 is mediated via cathelicidin.

Very recently, Zhu et al. (Zhu et al., 2009) observed for the first time the regulation of autophagy by miRNA. They showed that miR-30a targets Beclin 1 mRNA, and down-regulates the expression of Beclin 1.

Autophagy in physiology

Autophagosome formation occurs at a basal rate in most cells and controls the quality of the cytoplasm by initiating the elimination of protein aggregates and of damaged organelles (Ravikumar et al., 2010b) **(Figure 3)**. This autophagy-dependent quality control is also important to limit the production of ROS.

Stimulation of autophagy during periods of starvation is an evolutionarily-conserved response to stress in eukaryotes (Yang and Klionsky, 2010). Under starvation conditions, the degradation of proteins and lipids allows the cell to adapt its metabolism and meet its energy needs **(Figure 3)**.

The stimulation of autophagy plays a major role at birth to maintain energy levels in various tissues after the maternal nutrient supply via the placenta ceases (Kuma et al., 2004). Moreover, starvation-induced autophagy

is cytoprotective by blocking the induction of apoptosis upstream of mitochondrial events (Boya et al., 2005).

Autophagy is essential during development and differentiation. The pre-implantation period after oocyte fertilization is dependent on autophagic degradation of components of the oocyte cytoplasm (Tsukamoto et al., 2008). Autophagy remodeling of the cytoplasm is involved during the differentiation of erythrocytes, lymphocytes and adipocytes (Ravikumar et al., 2010b). Autophagy is crucial for the homeostasis of immune cells, and contributes to the regulation of self-tolerance (Nedjic et al., 2008).

The pioneering work of Bergamini and colleagues in the field of autophagy (Yang and Klionsky, 2010) suggested that its stimulation during calorie restriction may contribute to extending lifespan in the rat. Recent data have shown that the induction of autophagy increases longevity in a large panel of species (Eisenberg et al., 2009). The antiaging effect of autophagy probably depends, at least in part, on its quality control function that limits the accumulation of aggregation-prone protein and damaged mitochondria. Calorie restriction stimulates autophagy via the activation of the deacetylase sirtuin-1 (Morselli et al.,

2010). Targets of sirtuin-1 include Atg proteins 5, 7 and 8. In several cell lines, deacetylation of these Atg proteins is necessary for autophagy to be stimulated by nutrient deprivation (Lee et al., 2008). It would be interesting to investigate whether this regulation of autophagy is conserved in tissues that preferentially use fatty acids as oxidizable substrates during starvation, where a high level of acetyl-CoA is to be expected.

Autophagy and pathology

As mentioned above, basal autophagy is important as a housekeeping process to prevent the deposition of aggregation-prone proteins in the cytoplasm (**Figure 3**). Several neurodegenerative diseases, including Huntington's, Alzheimer's and Parkinson's diseases, are characterized by the accumulation of such protein aggregates in the brain (Ravikumar et al., 2010b). As a protective measure, the stimulation of autophagy limits the accumulation of toxic products and protects neurons against degeneration. The important pathological role of autophagy in aggregation-prone protein disease is strengthened by a recent study showing that a drug that enhances autophagy promotes the degradation of mutant, aggregation-prone α1-antitrypsin in the liver, and consequently reduces hepatic fibrosis (Hidvegi et al., 2010). Autophagy is involved in the clearance of aggregation-prone proteins in muscle diseases, including limb girdle muscular dystrophy type 2B, Miyoshi myopathy, and sporadic inclusion body myositis. Blockade of the autophagic pathway leads to the cardiomyopathy and myopathy of Danon disease (Ravikumar et al., 2010b). Autophagy is also involved in muscle atrophy but it is unclear whether autophagy has a beneficial effect by promoting survival during catabolic conditions, or a detrimental effect by causing atrophy. In the heart, basal autophagy is necessary to maintain cellular homeostasis and is upregulated in response to stress in hypertensive heart disease, heart failure, cardiac hypertrophy, and ischemia-reperfusion (Nakai et al., 2007).

In the pancreas, autophagy is required to maintain the architecture and function of pancreatic β-cells (Ebato et al., 2008). Defective hepatic autophagy probably makes a major contribution to insulin resistance and to predisposition to type-2 diabetes and obesity (Yang et al., 2010).

In infectious diseases, autophagy is involved in the elimination of intracellular pathogens (bacteria, viruses and parasites), and thus contributes to the innate immunity (Levine and Deretic, 2007; Virgin and Levine, 2009). Autophagy acts as an effector of Toll-like receptor (TLR) signaling. TLR ligands induce autophagy to promote the delivery of infecting pathogens to the lysosomes (Levine and Deretic, 2007). Autophagy contributes to adaptive immunity by generating antigenic peptides that are exposed on the cell surface in association with MHCAtg16L1 class II for presentation to CD4-positive T cells, or by promoting the development and survival of B and T

cells (Paludan et al., 2005; Pua et al., 2007). Recently polymorphisms of the genes that encode and IRGM, two autophagy genes essential for the elimination of intracellular pathogens, have been associated with Croh's disease, a chronic inflammatory bowel disease (Virgin and Levine, 2009).

Cancer is frequently associated with defects in autophagy, but the role of autophagy in cancer is clearly complex, because autophagy is also required in the later stages of tumor progression to enable tumor cells to cope with metabolic stress (caused by limited supplies of oxygen and nutrients) (Levine, 2007). The link between autophagy and cancer is further strengthened by the fact that several of the proteins involved in regulating autophagy are known to be tumor suppressor genes or oncoproteins (Morselli et al., 2009). Several of the functions of autophagy, such as the elimination of defective organelles, which reduces oxidative stress and prevents DNA damage, also contribute to its tumor suppressor role (Mathew et al., 2009; Mathew et al., 2007). Remarkably, autophagy facilitates effective glucose uptake and glycolytic flux in Ras-transformed cells (Lock et al., 2011). Moreover, the loss of autophagy in Ras-transformed cells is associated with reduced oxygen consumption and lower levels of the tricarboxylic acid (TCA) intermediate (Guo et al., 2011). The high basal level of autophagy observed in tumors with Ras mutation is required for cancer cell survival (Yang et al., 2011). In these tumors, autophagy certainly constitutes an Achilles heel that could be used in the fight against cancer. More generally, inhibiting autophagy is a challenging concept; because in many tumors autophagy is a stress response to anti-cancer treatments (Kondo et al., 2005).

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