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The Role of Autophagy in Cell Survival and Cell Death

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ABSTRACT: *Autophagy targets portions of cytoplasm, damaged organelles and proteins for lysosomal degradation and has crucial roles in development and disease. This issue presents a series of specially commissioned articles that highlight recent developments and emerging themes in this area. Autophagy is a lysosome-based degradation process whose primary function is to degrade long-lived proteins and recycle cellular components. So far, 3 types of autophagy have been documented, including macroautophagy, microautophagy and chaperone-mediated autophagy. Autophagy has been shown to degrade cargo in selective and no-selective manners. In literature, the term "autophagy" usually indicates macroautophagy. Macroautophagy is characterized by the formation of double membrane vesicles termed autophagosomes.*

Keywords: Autophagy; Cell Survival; Cell death and Pathway

INTRODUCTION

Autophagy ('self-eating') is an essential process important for cell survival and homoeostasis. Although widely studied, there are still a number of questions about the mechanisms governing autophagy that need to be addressed. In recent years, autophagy has emerged as an important player in human disease, and therefore understanding its biological role and regulation has become the latest challenge for researchers. Autophagy is an important cellular process that serves as a companion pathway to the ubiquitin-proteasome system to degrade long-lived proteins and organelles to maintain cell homeostasis. Although initially characterized in yeast, autophagy is being realized as an important regulator of development and disease in mammals (Thomas *et al.*, 2014). Autophagy, a well-described cellular mechanism for lysosomal degradation of cytoplasmic content, has emerged as a tumour suppression pathway. Recent evidence indicates that the tumor suppressor function of autophagy is mediated by scavenging of damaged oxidative organelles; thereby preventing accumulation of toxic oxygen radicals that would cause genome instability paradoxically, however, in some cases autophagy can also promote the survival of cancer cells once tumours have developed. This is attributed to the ability of autophagy to promote cell survival under conditions of poor nutrient supply, as often faced by solid tumours and metastasising cancer cells. In addition, autophagy is frequently upregulated in tumours as a response to therapy and may protect tumours against therapy-induced apoptosis (Andreas *et al.*, 2009).

Autophagy plays an important role in cellular homeostasis by degrading excessive, damaged and/oraged proteins and organelles, and thus maintaining quality control of essential cellular components (Eskelinen and Saftig, 2008).

Defective autophagy has been implicated in the pathogenesis of diverse disease states, such as myopathy (Malicdan *et al.*, 2008), neuronal degeneration (inslow and Rubinsztein, 2008), microbial infection (Orvedahl and Levine, 2008), inflammatory bowel disease (Cadwell, 2008) and cancer (Jin and White, 2008). In addition to its basal function, autophagy is readily induced in response to nutrient deprivation (Komatsu, 2005), metabolic stress (Degenhardt *et al.*, 2006), endoplasmic reticulum (ER)-stress (Sakaki and Kaufman, 2008) and anticancer drugs (Gills *et al.*, 2007). The role of autophagy as an alternate energy source, and thus as a temporary survival mechanism, under stressful conditions is well recognized (Mizushima, 2005). The presence of autophagosomes in dying cells raises the possibility that autophagy may also play an active role in cell death (Baehrecke, 2005). However, in most occasions, it is unclear whether this is the case or autophagy is just a bystander merely representing the cell's desperate attempt to sustain survival upon severe stress and/or injury. The mechanism by which defective autophagy contributes to tumorigenesis is under intense investigation. Inactivation of apoptosis, and thus deregulation of cell death, is a frequent occurrence in tumor cells (Hanahan and Weinberg, 2000), indicating that aberrant cell survival and cell death drive cancer progression. Loss of a survival pathway, such as autophagy, might have then been expected to undermine tumorigenesis; however, the recognition of the essential autophagy regulator beclin1 as a haplo-insufficient tumor suppressor (Qu*et et al.*, 2003). Bif-1 (Bax-interacting factor-1), also known as SH3GLB1 or Endophillin B1, is a member of the endophilin B protein family, which contains an N-BAR domain and a C-terminal SH3 domain, but shares no significant homology with members of the Bcl-2 family. In normal cells, the mammalian target of rapamycin (mTOR) kinase, which is downstream of the nutrient-sensor PI3K, primarily regulates autophagy. In response to nutrient and growth factor availability, the PI3K/AKT/mTOR axis is activated leading to suppression of autophagy and stimulation of cell proliferation. To the contrary, starvation suppresses the PI3K pathway and de-represses autophagy, which can now take over as an alternate process for energy and amino acid generation to sustain cell survival, atleast temporarily. Regulation of autophagy in tumors is governed by similar principles, only in a much more complicated manner, given the frequently observed abnormal PI3K activation in cancer and the multitude of interactions between the PI3K/AKT/mTOR pathway and other cell signaling cascades, often also deregulated in tumor cells (Chen and Karantza-Wadsworth, 2009).

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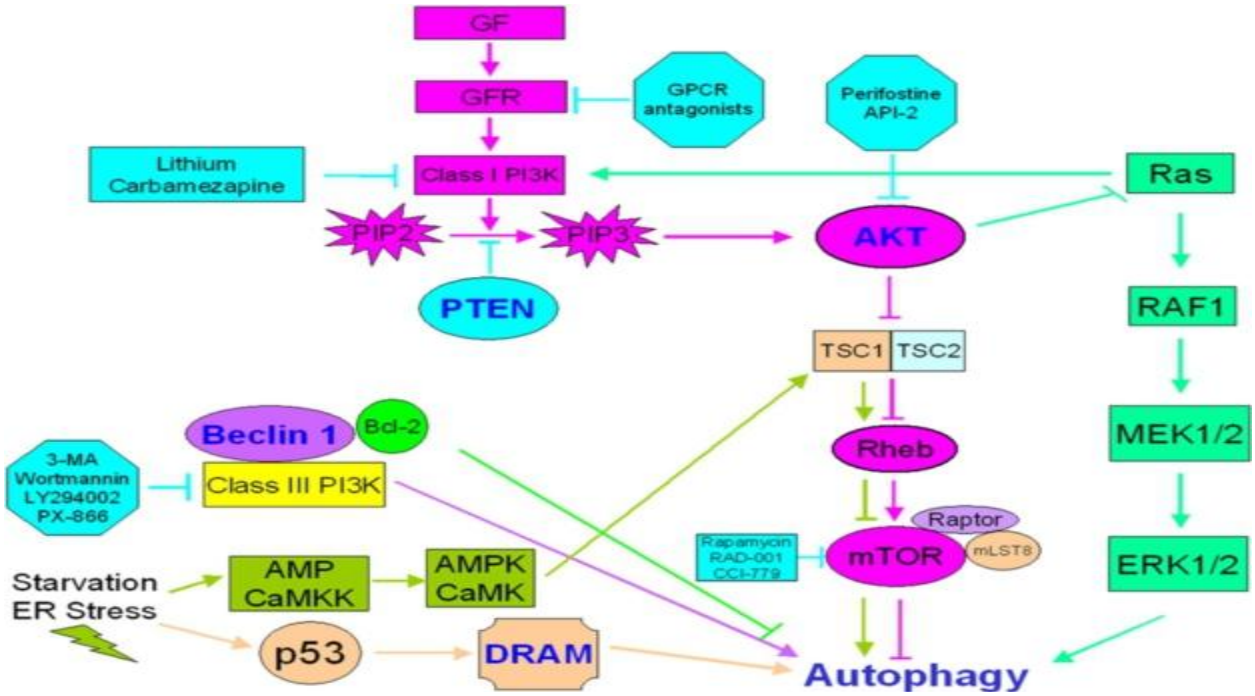

Fig 1: **Autophagy regulation. Growth factor signaling activates the PI3K/AKT/mTOR axis resulting in autophagy inhibition. Consequently, G-protein coupled receptor (GPCR) It is essential for autophagy (termed Atg) have been identified in yeast, the molecular mechanism of how these Atg proteins control autophagosome formation in mammalian cells remains to be elucidated. Here, we demonstrate that Bif-1 (also known as Endophilin B1) interacts with Beclin 1 through UVRAG and acts as a positive mediator of the class III PI3-kinase (PI3KC3). In response to nutrition deprivation, Bif-1 localizes to autophagosomes where it colocalizes with Atg5, as well as LC3. Furthermore, loss of Bif-1 suppresses autophagosome formation, while the SH3 domain of Bif-1 is sufficient for binding to UVRAG, both the BAR and SH3 domains are required for Bif-1 to activate PI3KC3 and induce autophagosome formation. It also found that Bif-1 ablation prolongs cell survival under nutrient starvation. Moreover, knockout of Bif-1 significantly enhances the development of spontaneous tumors in mice. These findings suggest that Bif-1 joins the UVRAG-Beclin 1 complex as a potential activator of autophagy and tumor suppressor (Takahashi *et al.*, 2007).**

Autophagy and Cell Death

Autophagic cell death or type-II programmed cell death is distinct from apoptosis or type-I programmed cell death. However, the relationship between autophagy and apoptosis is actually probably more complex, because autophagy is not only able to collaborate with apoptosis to produce cell death but, as we have seen in the preceding section, it can also act as a survival mechanism. From the recent literature, it has become clear that prolonged autophagy in the absence of the central core of the apoptotic machinery (bax/Bak-/- cells) is a cell survival mechanism that delays cell death in hematopoietic cells when growth factors and nutrients are in short supply (Lum *et al.*, 2005) However, in the context of the same genetic background, embryonic fibroblasts utilize the autophagic machinery to die in response to apoptotic inducers (Shimizu, *et al.*, 2004). In this study we will review our understanding of the control of autophagy during cell death, and will point out similarities to and differences from the regulation of autophagy observed during cell survival.

Targeting the class-I PI3K and TOR pathways during programmed autophagy and autophagic cell death

In *Drosophila*, a marked increase in autophagy is observed at the end of the larval stage (Baehrecke, 2005). This developmental programmed autophagy is hormonally controlled by ecdysone, and is responsible for the elimination of organs, such as the fat body, during metamorphosis. The increase in autophagy of the fat body is caused by the inhibition of the class-I PI3K pathway by ecdysone (Rusten *et al.*, 2004). The inhibitory effect is observed when the ecdysone receptor is expressed. How ecdysone and its receptor inhibit the class-I PI3K pathway remains to be investigated. It is interesting to note that programmed autophagy does not depend on the feeding status, and inhibition of TOR signaling can further increase autophagy. This observation led the authors to suggest that dTOR may be only partially inhibited during programmed autophagy or possibly not involved at all. Overall, this study demonstrates the physiological significance of class-I PI3K during programmed autophagy. It also reveals the cross-talk between two signaling pathways involved in controlling autophagy, that is, the class-I PI3K and the ecdysone-receptor signaling. The antiestrogentamoxifen induces autophagy and cell death in MCF-7 cells (Bursch *et al.*, 1996). Tamoxifen stimulates autophagy by increasing the intracellular level of ceramide and abolishing the inhibitory effect of the class-I PI3K pathway on autophagy (Scarlatti*et al.*, 2004)—Unexpectedly, however, in a rat cardiomyocyte-derived cell line, the activation of class-I PI3K during glucose deprivation induces the accumulation of autophagic vacuoles and causes cell death (Aki*et al.*, 2004). A further degree of complexity is introduced by the observation that in glioma cells containing a Ras mutant (RasG12V) in which several signaling pathways, including the class-I PI3K pathway, were stimulated, autophagic cell death was induced(Chi*et al* 1999).In contrast, the expression of a Ras mutant that specifically activates class-I PI3K inhibits starvation-induced autophagy in transformed fibroblasts (Furuta *et al.*, 2004) which fits in with the inhibitory role of class-I PI3K on autophagy in other models.

Other signaling pathways stimulated by amino acids

In human colon cancer HT-29 cells, another amino-acid-dependent signaling pathway can control autophagy, in addition to the PI3K/mTOR pathway. Activation of Erk1/2 stimulates the GTPase-activating protein G alpha interacting protein (GAIP) and abolishes the inhibitory effect of trimeric Gi3 protein on autophagy (reviewed in Meijer and Codogno 2004). Amino acids, by stimulating the phosphorylation of Ser, inactivate the Erk1/2 mitogen-activated protein kinase (MAPK) Raf-1 and downregulateautophagy (Pattingre*et al.*, 2003). In contrast, in C2C12 myotubes, the inhibition of autophagy by amino acids is not accompanied by any changes in Erk1/2 phosphorylation. Differences in amino-acid signaling mechanisms and in the control of autophagy may exist, apparently depending on the cell type, and perhaps also on the degree of differentiation (Tassa *et al.*, 2003)

Other signaling pathways activated during autophagic cell death

The death-associated protein kinase (DAPK) family

DAPK and its related kinase death-associated related protein kinase-1 (DRP-1) are Ca^{2+}/calmodulin-regulated kinases, which act as positive effectors of cell death through caspase dependent apoptosis induced in response to various stimuli, such as interferon, TNF, and TGF and loss

of interaction with the extracellular matrix (Shohat *et al.*,2002). The phosphorylation of myosin-light chain mediates membrane blebbing during cell death. Expression of activated forms of DAP kinase and DRP-1 trigger autophagy and cell death independently of caspase activity in carcinoma cells with nonfunctional p53 (Inbal *et al.*, 2002). Moreover, the expression of a dominant-negative form of DRP-1 blocked the induction of autophagy and cell death in MCF-7 in response to tamoxifen treatment. It remains to be determined whether DRP-1 and ceramide act in the same signaling pathway, and contribute to tamoxifen-induced autophagy in MCF-7 cells. In this context, it is important to note that ceramide stimulated the expression of DAP kinase in neuronal cells (Pelled *et al.*, 2002). Interestingly, DRP-1 was found to be associated with the lumen of autophagosomes in HEK293 cells, suggesting that this kinase can phosphorylate some elements of the molecular machinery involved in the formation of autophagosomes (Inbal *et al.*, 2002). It is striking that DRP-1 also controls amino-acid-sensitive autophagy in MCF-7 cells. This suggests that similar control mechanisms operate during starvation-induced autophagy and autophagic cell death. It remains an open question as to whether autophagic cell death and starvation-induced autophagy are controlled by different domains of DRP-1, and subsequently by different signaling pathways.

TNF-related apoptosis-inducing factor (TRAIL) and the TRAIL receptor

It has been shown recently that both apoptosis and autophagy contribute to the formation of hollow acini-like structures in an *in-vitro* model of mammary gland morphogenesis.(Mills*et al.*, 2004) TRAIL-dependent autophagy was blocked in cells expressing either truncated TRAIL receptors or a dominant-negative form of the Fas-associated death domain protein (FADD), which is required to recruit the apoptosis initiator procaspase-.(Mills *et al.*,2004).Interestingly, the death domain of FADD can activate a cell death pathway involving both apoptosis and autophagy that is selectively inactivated at the earliest stages of epithelial cancer development(Thorburn *et al.*,2005)TNF, another member of the apoptosis-inducing family, stimulates autophagy and apoptosis in T-lymphoblastic leukemia cells(Jia, *et al.*, 1997) .Inhibition of autophagy by 3-MA protects these cells against death. In addition, TNF stimulates autophagic cell death independently of caspase activation.(Yanagisawa*et al.*, 2003)An analysis of gene expression in *Drosophila* suggests that the

TNF -like pathway is involved during autophagic cell death in salivary glands.(Gorski*et al.*, 2003). Recently, the interaction of Atg5 with the death domain of FADD has been shown to play a crucial role in interferon--induced cell death independently of detectable activation of caspase-8. (Pyo*et al.*, 2005). Elucidation of signaling events downstream of FADD in Atg5-induced cell death would contribute to a better understanding of the control of autophagic cell death.

Jun N-terminal kinase (JNK)

Autophagic cell death has been observed in fibroblasts and monocytoid cells in response to the inhibition of caspase-.(Yu L *et al* 2004). The accumulation of autophagic vacuoles is dependent on receptor-interacting protein (RIP), a protein associated with the cytoplasmic domain of the death receptor, and on the activation of JNK and its upstream kinase, MKK7. In addition, RIP is a substrate for caspase-8, which cleaves and inactivates it. This study suggests that caspase-8 may also have a role in processes other than

apoptosis. Another interesting observation is the implication of c-Jun, a target of JNK, in the control of autophagic cell death, which suggests that transcriptional activity is required to induce cell death, and also that *de novo* protein synthesis is required under these conditions. This is supported by the observation that cell death is prevented in the presence of cycloheximide. However, the nature of the genes induced remains to be determined. Genome-wide scale investigations have shown that, during autophagic cell death in *Drosophila*, the expression of a large array of genes, including several ATG genes (ATG2, 4–7, and 12), is upregulated (Gorski *et al.*, 2003). Accumulation of ATGs has also been observed in mammalian cells undergoing autophagic cell death, and is dependent on the expression of proteins of the Bcl-2 family (Bcl-2 and Bc1-xL) (Shimizu *et al.*, 2004). An accumulation of Beclin 1 has been reported during tamoxifen-induced autophagy(Scarlatti *et al.*, 2004).The upregulation of ATG proteins is probably important in determining the amplitude of the autophagic response. The upregulation of Atg proteins is not a common trait during starvation-induced autophagy(Peng *et al.*, 2002).The initiation of autophagy may not in fact depend on protein synthesis (Abeliovich *et al.*, 2000).

Conclusions

Autophagy is an important cellular process that serves as a companion pathway to the ubiquitin-proteasome system to degrade long-lived proteins and organelles to maintain cell homeostasis. Although initially characterized in yeast, autophagy is being realized as an important regulator of development and disease in mammals . Autophagy, a well-described cellular mechanism for lysosomal degradation of cytoplasmic content, has emerged as a tumour suppression pathway.however, in some cases autophagy can also promote the survival of cancer cells once tumours have developed. This is attributed to the ability of autophagy to promote cell survival under conditions of poor nutrient supply, as often faced by solid tumours and metastasising cancer cells.The presence of autophagosomes in dying cells raises the possibility that autophagy may also play an active role in cell death. Autophagy plays an important role in cellular homeostasis by degrading excessive, damaged and/oraged proteins and organelles, and thus maintaining quality control of essential cellular components. Defective autophagy has been implicated in the pathogenesis of diverse disease states, such as myopathy , neuronal degeneration , microbial infection , inflammatory bowel disease and cancer ,.In this review our understanding of the control of autophagy during cell death, and will point out similarities to and differences from the regulation of autophagy observed during cell survival. Autophagy may play a variety of physiological roles in cancer progression at each stage in various cancers. Further investigations are required to clarify the biological role of autophagy related proteins so as to estimate their potential value in the diagnosis and treatment of cancer in addition to its ability to inhibit class-III PI3K, which is involved in the formation of autophagosomes, can also affect other signaling components, such as class-I PI3K and MAP kinases.The accumulation of autophagy gene products during cell death, and their relationship with members of the Bcl-2 family, is a promising track to explore in order to obtain a better understanding of how autophagy is controlled during cell death.

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