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Apoptosis regulation by autophagy gene 5

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Contents

Abstract

Autophagy is a cellular process, in which cellular proteins and cytoplasmic organelles are degraded. It reflects the response of a cell to stress or starvation with the primary goal of cell survival. On the other hand, if the autophagic activity is too high, cell death happens, suggesting that this process requires a tight control. Autophagic cell death has often been observed under conditions, in which apoptosis is blocked. Recent studies suggest that autophagy may promote apoptosis and that Bcl-2 cannot block only apoptosis, but also autophagy and autophagic cell death. Here, we discuss recent findings regarding the interrelations between autophagy and apoptosis. In particular, we would like to draw the attention of the readers to Atg5, which exhibits, like Bcl-2, a dual function by modulating both autophagy and apoptosis.

Keywords: Apoptosis; Atg5; Autophagy; Bcl-2; Beclin 1; Calpain; Cancer

1. Introduction

Apoptosis is the most common form of physiologic cell death in multicellular organisms. It is morphologically characterized by cell shrinkage, chromatin condensation, and membrane blebbing [1]. The main biochemical features are activation of intracellular proteases (in particular caspases) and internucleosomal DNA fragmentation. In most cases, cells undergo apoptosis in the absence of inflammation. Apoptosis can be mediated by death receptors or cell stress (e.g., anticancer drugs, ultraviolet light, gamma-irradiation, growth factor deprivation). Mitochondria play a key role in pro-apoptotic pathways that release pro-apoptotic proteins (e.g., cytochrome *c*, Smac) under the control of proteins of the Bcl-2 family [2]. The released mitochondrial pro-apoptotic proteins lead to increased caspase activation [3].

Autophagy is a process in a cell that serves to degrade long-lived proteins and to recycle cellular components to ensure survival during starvation. It is further characterized by extensive intracellular membrane remodeling, engulfing portions of the cytoplasm in large double-membrane vesicles, called autophagosomes. Autophagosomes subsequently fuse

Abbreviations: Atg, autophagy gene; Bcl, B cell lymphoma; BH, Bcl-2 homology; LC3, microtubule-associated protein 1 light chain 3; mTOR, mammalian target of rapamycin; PE, phosphatidylethanolamine

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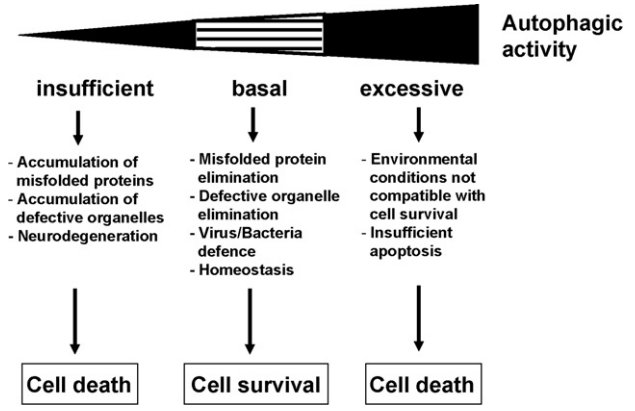

Fig. 1. Autophagy and its role in cell survival. Dysregulated autophagic activity can result in cell death.

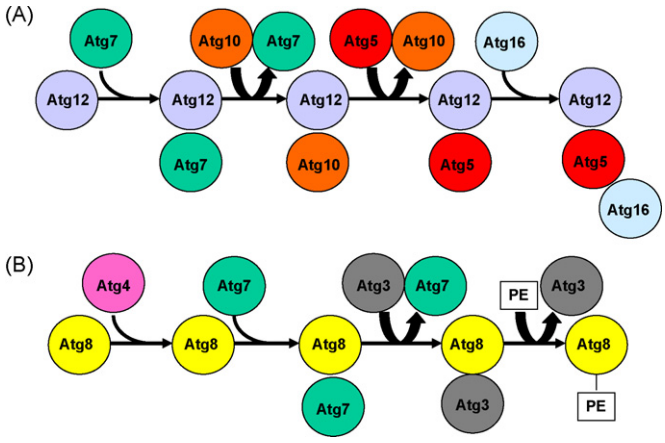

Fig. 2. The process of autophagosome formation involves two ubiquitin-like conjugation systems. (A) Atg12–Atg5 system and (B) Atg8–PE system.

with lysosomes, leading to degradation of their content [4]. Autophagy is controlled by autophagy genes (Atgs). Besides its central role during starvation [5,6], autophagy has been shown to play a role in tumor suppression [7,8], pathogen killing [9], antigen presentation [10], and the regulation of the lifespan of the whole organism [11].

The involvement of autophagy in programmed cell death has been controversial. Autophagy is considered to be a survival mechanism. However, changes in autophagic activity can result in cell death (Fig. 1). Some, but not all, cancers have reduced autophagic activity [7,8]. This may explain, why anticancer drugs, which increase autophagic activity, can induce both efficacy and drug resistance [12]. Moreover, since many human cancers exhibit mutations in pro-autophagy genes, sufficient autophagic activity might be important for tumor suppression [13]. On the other hand, autophagy enhances the survival of tumor cells under conditions of nutrient shortage and/or metabolic stress [14]. Taken together, the molecular mechanisms regulating cell survival and cell death within the process of autophagy are currently not understood.

2. Atg12–Atg5 and Atg8 (LC3)–PE conjugation systems

As mentioned above, autophagy is regulated by Atgs, which are mostly involved in the process of autophagosome formation and generate two ubiquitin-like conjugation systems: (1) the Atg12–Atg5 and (2) the Atg8 (LC3)–phosphatidylethanolamine (PE) systems (Fig. 2). Atg12 covalently links to Atg5. The mode of conjugation of Atg12 to Atg5 is similar to that of ubiquitination, since Atg12 is first activated by Atg7 (=ubiquitin-activating enzyme E1) and then transferred to Atg10 (=ubiquitin-activating enzyme E2) before it binds to Atg5 [15].

LC3 (microtubule-associated protein 1 light chain 3) is the mammalian orthologue of Atg8. In the process of autophagy, LC3 is cleaved by Atg4, resulting in the cytosolic form LC3-I, which is, similar to Atg12, first activated by Atg7, but then transferred to Atg3 and subsequently, interacts as LC3-II with PE. This results in the integration of LC3 into the membranes of pre-autophagosomes and phagosomes. Interestingly, this process is Atg5 dependent [16]. The Atg8–PE complex can be visualized as clusters using immunofluorescence microscopy, and this phenomenon is considered as being a proof for increased autophagic activity [17,18]. The complex is removed from the membranes prior to fusion with lysosomes [19].

3. Atg5: a molecular switch factor between autophagy and apoptosis

Besides promoting autophagy, Atg5 may also play a role in a pro-apoptotic pathway. Therefore, although Atg5 might initially be involved in a survival process, it may later promote cell death. We noticed that overexpression of Atg5 increased the cell's susceptibility to undergo apoptosis following stimulation with several death triggers, including anticancer drugs [20]. The death stimulation resulted in calpain activation, leading to Atg5 cleavage. Truncated Atg5 induced cytochrome *c* release and apoptosis, both was blocked by high levels of Bcl-2. Therefore, Atg5 may serve as a molecular switch between autophagy and apoptosis (Fig. 3). However, it remains unclear, how truncated Atg5 can trigger

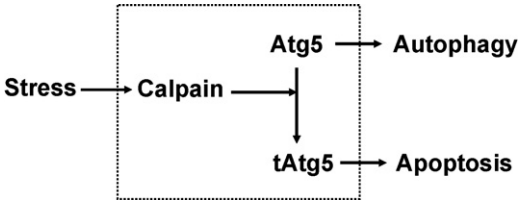

Fig. 3. Atg5 promotes autophagy. Upon calpain activation (often the consequence of cellular stress), Atg5 is cleaved at Thr 193 and the resulting 24 kDa N-terminal fragment (truncated Atg5) mediates apoptosis. Therefore, Atg5 represents a molecular switch between autophagy and apoptosis.