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Signalling Networks in Focus

Core signaling pathways of survival/death in autophagy-related cancer networks

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ABSTRACT

Autophagy (macroautophagy), an evolutionarily conserved lysosomal degradation process, is implicated in a wide variety of pathological processes including cancer. Autophagy plays the Janus role in regulating several survival or death signaling pathways that may decide the fate of cancer cell. Accumulating evidence has revealed the core molecular machinery of autophagy in tumor initiation and progression; however, the intricate relationships between autophagy and cancer are still in its infancy. In this review, we summarize several key survival/death pathways such as mTOR subnetwork, Beclin 1 interactome, and p53 signaling that may play the crucial roles for the regulation of the autophagy-related cancer networks. Therefore, a better understanding of the relationships between autophagy and cancer may ultimately allow cancer biologists and clinicians to harness core autophagic pathways for the discovery of potential novel drug targets.

Signaling network facts

- Autophagy plays the Janus role for the regulation of pro-survival or pro-death signaling pathways in cancer.
- mTOR subnetwork, Beclin 1 interactome, and p53 signaling may interconnect with each other and thus integrating into the autophagy-related cancer networks.
- Targeting autophagy may be a promising avenue for the discovery of potential drug target for cancer therapeutics.

1. Introduction

Autophagy, a term from Greek "auto" (self) and "phagy" (to eat), refers to an evolutionarily conserved, multi-step lysosomal degradation process in which a cell degrades long-lived proteins and damaged organelles (Klionsky and Emr, 2000). Hitherto, at least three forms of autophagy have been identified, namely macroautophagy, microautophagy and chaperone-mediated autophagy that differ with respect to their modes of delivery to lysosome and physiological functions (Klionsky, 2007). Macroautophagy (hereafter autophagy) is the major regulated catabolic mechanism that involves the delivery of cytoplasmic cargo sequestered inside double-membrane vesicles to lysosome, highly regulated by a limited number of autophagy-related genes (ATGs) (Mizushima et al., 2008). Originally discovered in yeast, ATGs, playing the key roles in autophagosome formation and autophagy regulation, have astonishing numerous links with many human diseases, most notably cancer (Huang and Klionsky, 2007). In cancer cells, autophagy is a physiological mechanism that may serve as a means of temporary survival, and thus providing a means of recycling macromolecules (Kevin et al., 2010). On the contrary, if the cellular stress leads to continuous or excessively induced autophagy, cell death will ensue (Liang and Jung, 2010). These aforementioned paradoxical studies, however, are viewed as confusing because, depending on different cell- and tissue-specific, autophagy seems to regulate either pro-survival or pro-death pathways in cancer. In this review, we present several important well-characterized pathways of survival/death, including mTOR subnetwork, Beclin 1 interactome, and p53 signaling in the autophagy-related cancer networks, which, in turn, may uncover the complex interplay of autophagy and cancer.

2. Survival or death: the Janus role of autophagy in cancer

Autophagy plays the Janus role, acting as either guardian or executioner in cancer, dependent on different stages of cancer initiation and progression, or surrounding cellular environment. On one hand, autophagy is crucial for cell survival under extreme conditions through degradation of intracellular macromolecules, which provides the energy required for minimal cell functioning when nutrients are deprived or scarce (Dalby et al., 2010). Also, autophagy-mediated elimination of altered cytosolic constituents, such as aggregated proteins or damaged organelles, preserves cells

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from further damages, indicating that autophagy plays a protective role in early stages of cancer (Levine and Klionsky, 2004). On the other hand, autophagy plays a death-promoting role as type II programmed cell death (type II PCD), compared to apoptosis (type I PCD), as a *bona fide* tumor suppressor mechanism in cancer (Andrew, 2008; Liu et al., 2011).

However, a seeming paradox is that autophagy functions primarily in cancer cell survival, and yet also in cell death (Morselli et al., 2009; Levine and Kroemer, 2008). To alleviate this puzzle, two hypotheses have been put forward. One hypothesis suggests that the role of autophagy varies depending on different stages of tumor development. Autophagy limits tumor formation in the early stage, while favors tumor cell survival and invasion as soon as cancer has formed (Mathew et al., 2007). The other hypothesis indicates that autophagy regulates carcinogenesis in a cell- and tissue-specific manner (Gozuacik and Kimchi, 2004). At molecular level, autophagy plays the pro-survival or pro-death role by regulating some tumor suppressor genes including Beclin 1, ultraviolet irradiation resistance-associated gene (UVRAG), Bax-interacting factor-1 (Bif-1) and p53, or other oncogenes including B-cell lymphoma 2 (Bcl-2), Ras, Class I PI3K (PI3KI) and protein kinase B (Akt) in cancer (Morselli et al., 2009). As mentioned above, the core signaling pathways of survival/death would be integrated into the autophagy-related cancer networks that may ultimately determine the fate of cancer cell.

3. Several core autophagic pathways in cancer

3.1. mTOR subnetwork

The mammalian target of rapamycin (mTOR), an evolutionarily conserved serine/threonine kinase, may serve as the main negative regulator of autophagy in cancer cells. mTOR forms two complexes in mammalian cells; of these, only mammalian target of rapamycin complex 1 (mTORC1) is sensitive to rapamycin; therefore, we focus on mTORC1 in autophagy (Loewith et al., 2002). There are three pivotal mTORC1 signaling pathways, including PI3KI-Akt and Ras-proto-oncogene serine/threonine-protein kinase (Raf-1)-Mitogen-activated protein kinase kinase 1/2 (MEK1/2)-extracellular signal-regulated kinases 1/2 (ERK1/2) pathways that activate mTORC1, as well as liver kinase B1 (LKB1)-AMP-activated protein kinase (AMPK) pathway that can inhibit mTORC1 (Jung et al., 2010). Subsequently, the three pathways may converge upstream of mTORC1 at the tuberous sclerosis protein 1/2 (TSC2/TSC1) complex, known as tumor suppressors. The TSC2/TSC1 complex suppresses mTORC1 by inactivating mTORC1-interacting protein, Ras homolog enriched in brain (Rheb). Upon PI3KI activation, Akt phosphorylation of TSC2 destabilizes TSC2 and disrupts its interaction with TSC1, thus abolishing the negative regulatory effect of TSC2/TSC1 complex on mTORC1 (Ma et al., 2005). In contrast, phosphorylation of TSC2 by AMPK increases its GTPase activity, stabilizes the TSC2/TSC1 complex, inactivates Rheb, and leads to inactivation of mTORC1; thereby triggering autophagy (Manning et al., 2002).

In mammals, two homologs of Atg1, uncoordinated 51-like kinase 1 (ULK1) and ULK2, Mammalian autophagy-related protein 13 (mAtg13) and the scaffold protein FAK-family interacting protein of 200 kDa (FIP200) have been identified. By phosphrylation of ULK and mAtg13 in a nutrient starvation-regulated manner, mTORC1 disrupts the binding of mAtg13 with ULK and destabilizes ULK, inhibiting the ULK-dependent phosphorylation of FIP200 and inducing autophagy (Corradetti et al., 2004; Ganley et al., 2009). Moreover, mTORC1 regulates autophagy by mediating protein translation and cell growth through 4E-BP1 and $p70^{S6K}$ phosphorylation. Phosphorylation of 4E-binding protein 1 (4E-BP1) leads to its detachment from eukaryotic translation initiation factor 4E (eIF4E) and upregulates cap-dependent translation (Jung et al., 2010). On the contrary, phosphoryaltion of $p70^{S6K}$ enhances its activity and facilitates its phosphorylatory role on the targets. $p70^{S6K}$ phosphorylates eukaryotic elongation factor 2 kinase (eEF2K) and thus relieving elongation factor 2 (eEF2) from the negative regulation of eEF2 kinase as well as inhibiting autophagy (Liu et al., 2010). Thus, mTOR subnetwork may occupy the central position in autophagic pathways of cancer (Fig. 1).

3.2. Beclin 1 interactome

Beclin 1, the mammalian homolog of Atg6, enhances autophagy by combining with PI3KIII in the initiating stage of autophagy. And, the tumor suppressor function of Beclin 1 is supported by identification of its mediators in tumorigenesis (Kang et al., 2011). UVRAG, a major Beclin 1 positive mediator, can interact with Beclin 1 by interacting with Beclin1. UVRAG markedly enhances PI3KIII lipid kinase activity; thus, facilitating autophagy. Through medi-

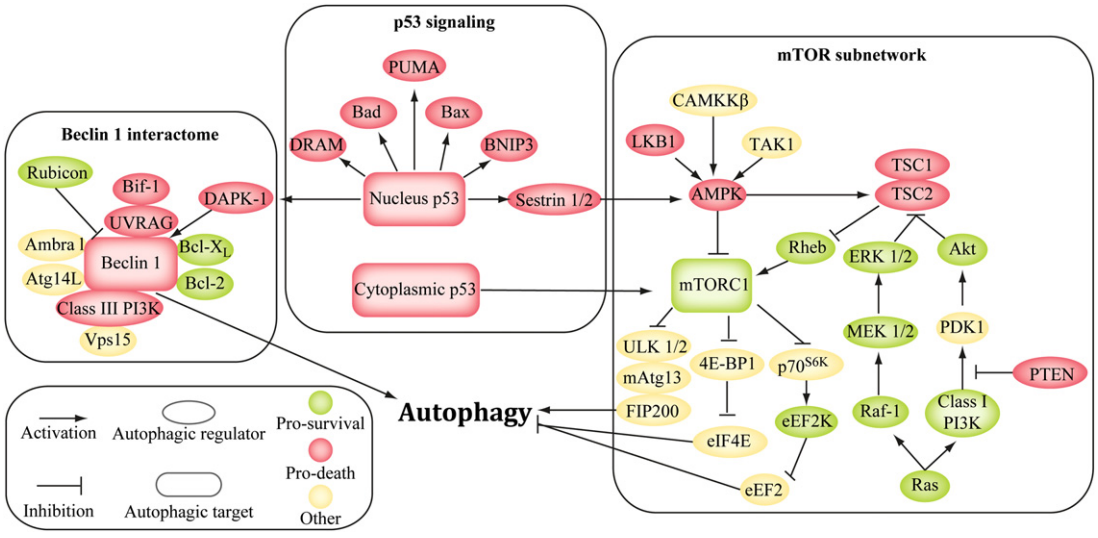

Fig. 1. Core signaling pathways in the autophagy-related cancer networks. In cancer cells, autophagy plays the Roman God Janus role for regulating pro-survival signaling pathways (indicated in green) or pro-death signaling pathways (indicated in green) implicated in mTOR subnetwork, Beclin 1 interactome and p53 signaling that may be further integrated into the autophagy-related cancer networks.