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Review Series Introduction

Unraveling the Role of Autophagy in Cancer

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In this issue of *Autophagy*, experts have reviewed several topics related to the interrelationship between autophagy and cancer. Botti and colleagues discuss the signaling control of autophagy in the context of the biology of cancer cells.[1] Gozuacik and Kimchi review one specific family of proteins, the DAPk protein family, that is involved in both autophagic signaling, apoptosis, and tumor suppression.[2] Jin proposes a model for how autophagy might function as a tumor suppressor and anti-aging process, which involves mitochondrial quality control.[3] Finally, Kondo and Kondo present evidence that tumor cells can be killed by autophagy and speculate as to how autophagy modulation may be beneficial in cancer therapy.[4]

Several important themes emerge from these reviews. First, there is a remarkable degree of evidence to support the hypothesis that positive regulators of autophagy function as tumor suppressors, whereas (for the most part) negative regulators of autophagy function as oncogenes (Fig. 1). This evidence strongly suggests that autophagy is a bona fide mechanism of tumor suppression. Nonetheless, definitive proof is still lacking that autophagy is a mechanism involved in the tumor suppressor action of the autophagy sensors and effectors shown in Figure 1. In addition to autophagy, these autophagy sensors control a number of different cellular processes, including cell cycle control, cell growth control, cell proliferation, and apoptotic cell death. A priority will be to evaluate whether the tumor suppressor function of these autophagy sensors is impaired in cells lacking intact downstream autophagy execution machinery. If so, such findings will provide additional support for the concept that autophagy regulation is mechanistically linked to tumor suppression. Moreover, the autophagy effector Beclin 1 is not only part of a Class III PI3K complex, but is also the mammalian ortholog of yeast Atg6/Vps30 which is involved in both vacuolar protein sorting and autophagy. It is therefore possible that functions of Beclin 1 independent of autophagy may be involved in its tumor suppressor activity. Interestingly, in his review, Jin notes that other autophagy genes, including *LC3* (*ATG8* ortholog) and human *atg7*, like *beclin 1*, are frequently deleted in human cancers.[3] Therefore, it will be important to determine whether these genes (and other autophagy execution genes) also function as tumor suppressors.

The accompanying reviews identify several mechanisms by which autophagy may function in tumor suppression (Fig. 2). Jin proposes that autophagy suppresses cancer development by the selective degradation of damaged mitochondria, thereby decreasing the production of reactive oxygen species and the incidence of nuclear DNA mutations.[3] The work of Gozuacik and Kimchi suggests that autophagic cell death induced by DAPk family proteins may contribute to tumor suppression.[2] Botti et al. also discuss additional potential roles of autophagy in tumor suppression, including a role in cell growth control, tumor immunity, and inhibition of angiogenesis. Thus, a second important theme of these reviews is that there are numerous ways in which autophagy may suppress cancer development. However, it is still unknown which of the proposed mechanisms contribute to the putative tumor suppressor action of autophagy.

Even though the positive regulation of autophagy by tumor suppressor proteins strongly suggests that autophagy is a tumor suppressor pathway, a third important theme is that numerous uncertainties remain about the role of autophagy in cancer biology. Based upon known functions of autophagy, one can propose that this process may function either to prevent or to promote tumorigenesis (Fig. 2). All of the reviews in this series highlight potential tumor suppressor functions of autophagy. However, as discussed by Botti et al[1] and Kondo and Kondo,[4] it is also possible that autophagy may promote the survival of tumor cells, since autophagy genes promote cellular survival and prevent apoptosis during the stressful stimuli that tumor cells commonly confront, such as nutrient starvation, growth factor deprivation, and hypoxia. The relative balance of these pro-survival effects (and potentially oncogenic effects) versus the pro-death effects (and other potential tumor

suppressor effects) is not yet known. To complicate matters further, this balance may vary according to the type of tumor and the stage of the malignancy process.

Finally, it is clear that many of these unresolved questions will need to be addressed before we can rationally design anti-cancer therapies to modulate autophagy. As Kondo and Kondo note in their review, there is now extensive evidence that diverse anticancer therapies promote autophagy and autophagic cell death.[4] Yet Kondo and Kondo[4] and Botti et al[1] also discuss the contrasting role of autophagy in cancer cell survival. Therefore, until further studies can help clarify when and how autophagy contributes to or prevents cancer, it may be premature to target autophagy in cancer therapy. Nonetheless, with the rapid rate of progress in the field, such an era may soon be at hand.

References

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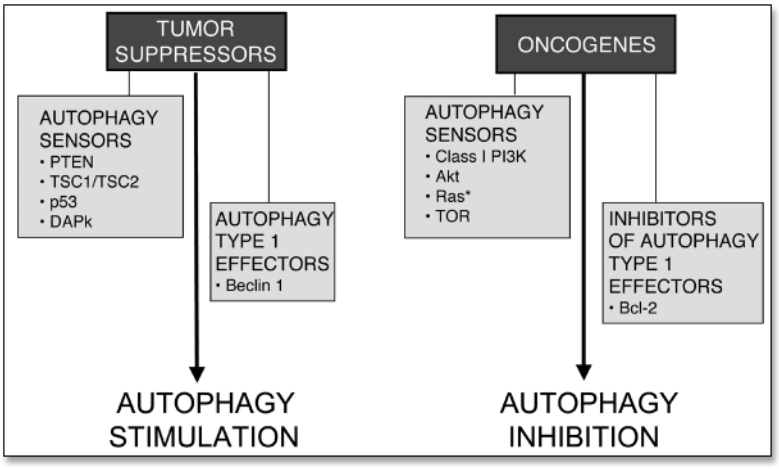

Figure 1. Dual control of autophagy and cancer. Shown are molecules that are involved in autophagy induction and tumor suppression (left side) and autophagy inhibition and oncogenesis (right side). These relationships form much of the basis for the hypothesis that autophagy is a tumor suppressor mechanism. *The oncoprotein Ras has been shown to both inhibit autophagy via activation of the class I PI3K pathway and stimulate autophagy via activation of the ERK1/2 pathway (see ref. 1).

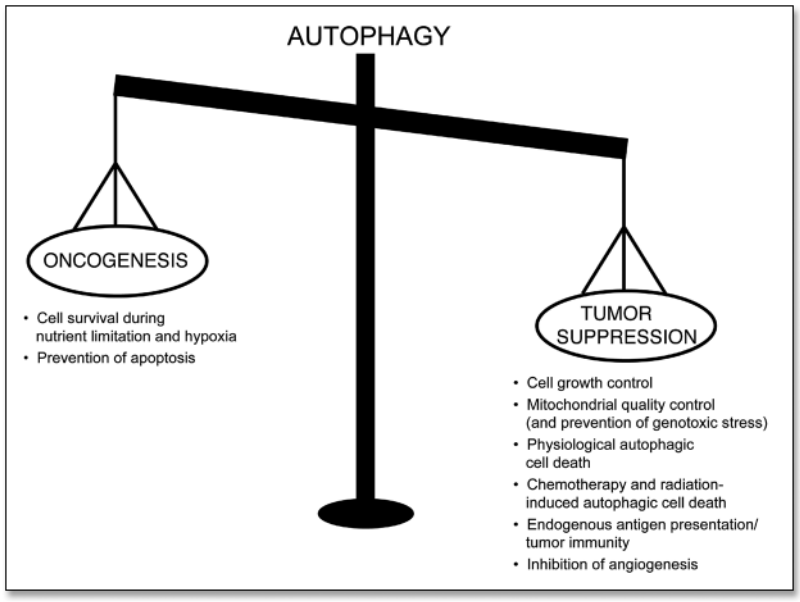

Figure 2. Dual effects of autophagy in cancer. Autophagy has been proposed to have oncogenic effects (shown on left side of balance) as well as tumor suppressor effects (shown on right side of balance). The net balance of these oncogenic and tumor suppressor effects is not known; however, in this schematic representation, the scale is deliberately tipped in favor of tumor suppression based upon the evidence depicted in Figure 1.