Chinese Journal of Cancer

Editorial

Autophagy and apoptosis: rivals or mates?

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Abstract

Autophagy, a cellular process of "self-eating" by which intracellular components are degraded within the lysosome, is an evolutionarily conserved response to various stresses. Autophagy is associated with numerous patho-physiological conditions, and dysregulation of autophagy contributes to the pathogenesis of a variety of human diseases including cancer. Depending on context, activation of autophagy may promote either cell survival or death, two major events that determine pathological process of many illnesses. Importantly, the activity of autophagy is often associated with apoptosis, another critical cellular process determining cellular fate. A better understanding of biology of autophagy and its implication in human health and disorder, as well as the relationship between autophagy and apoptosis, has the potential of facilitating the development of autophagy-based therapeutic interventions for human diseases such as cancer.

Key words Autophagy, apoptosis, cancer, molecular regulation

Autophagy, originally defined as type II programmed cell death, can also act as a critical survival mechanism under stressful conditions, during which the degradation of intracellular proteins and organelles provides a source of amino acids and other nutrients[1]. During autophagy, intracellular components are delivered to lysosomes for degradation via three different mechanisms: macroautophagy, microautophagy, and chaperone-mediated autophagy. Autophagy plays a role in a variety of physiological and pathophysiological processes, including cellular homeostasis, survival, development, and differentiation, and is associated with human diseases[2,3]. To date, however, autophagy has been studied more in cancer than in other diseases. Autophagy acts as a tumor suppressor in early stages of cancer development but may also enable tumor cells to survive metabolic and therapeutic stresses and promote tumor progression[4,5]. Thus, the association between autophagy and cancer is complex, and autophagy appears to be a double-edged sword in cancer. At present, what specific autophagy-regulatory molecules and what specific autophagic mechanisms and pathways contribute to different stages of cancer (i.e., cancer initiation, development or progression) remain to be investigated and clarified.

As a variety of human cancers have been found to be associated with changes in the activity of autophagy, this cellular process is now considered a target for drug discovery, and modulation of autophagy by pharmacologic approaches has elicited a great deal of interests. However, despite the promise of targeting autophagy a new therapeutic mean, there remain some issues that need to be resolved before clinical modulation of autophagy in cancer can be achieved. For example, most of the current drugs described as modulators of autophagy do not directly or specifically regulate autophagy process but rather act on the pathways involved in activating or inhibiting this cellular process, raising a question of specificity. Also, in order to facilitate the discovery and development of the autophagy-targeted drugs, sensitive, effective, reliable and accurate high-throughput screening (HTS) assays would need to be established.

In recent years, tremendous progress has been made in understanding the regulation of apoptosis and autophagy and their roles in determining cell fate under various physiological and pathological conditions. During

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doi: 10.5732/cjc.013.10022

the past decade or so, there has been a remarkable elucidation of many molecular mechanisms and pathways critically involved in the regulation of autophagy and apoptosis (Figure 1). Although apoptosis is the primary form of programmed cell death used to control cell viability, cell death can also be associated with the presence of autophagic vacuoles, indicative of autophagic cell death. Autophagy-mediated cell death is purportedly linked to the apoptotic pathway through alterations in mitochondrial function. However, its actual role as a cell death effector remains incompletely understood.

This issue of *Chinese Journal of Cancer* (*Aizheng*) contains three reviews that focus on the relationship between autophagy, apoptosis, and cancer treatment and provides an overview of the associated regulatory signaling pathways. Liu *et al.*[6] discuss the targeting autophagic pathways as a new therapeutic strategy for cancer treatment and the approaches to developing novel small-molecule drugs that target autophagic pathways. Zhang *et al.*[7] summarize the current strategies of manipulating autophagy as a treatment for subtypes of acute myeloid leukemia. Fan *et al.*[8] give a comprehensive review on molecular mechanisms and pathways that regulate both the autophagic and apoptotic processes. These articles provide us with a better understanding of the complex interplay between autophagy and apoptosis—a necessary first step towards developing novel strategies to target autophagy for cancer prevention and treatment.

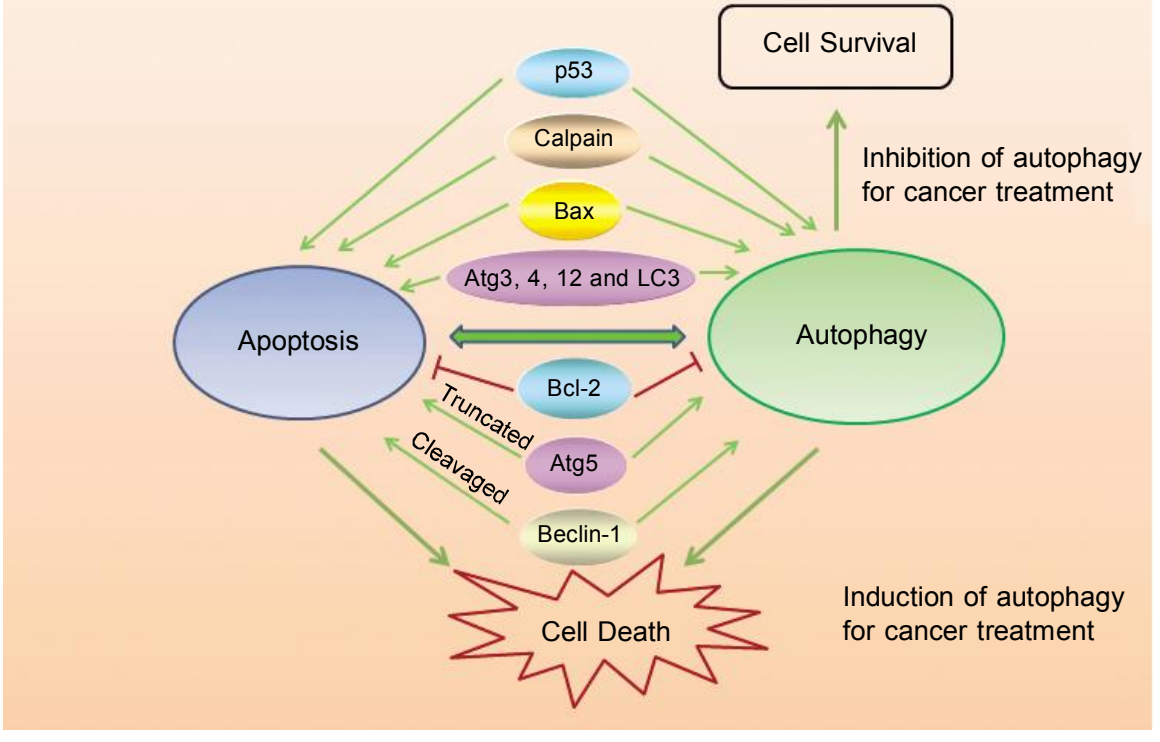

Figure 1. **Interrelationship between autophagy and apoptosis.** A number of molecules can affect both autophagy and apoptosis, and these molecules may act as switches between both cellular processes. Activation of the tumor suppressor p53 not only triggers apoptosis, but also may stimulate autophagy in a transcription-dependent fashion by activating the expression of the autophagy-inducing genes. Calpains, a family of Ca^{2+}-dependent cysteine proteases, are activated by several stimuli to trigger both apoptosis and autophagy. The Bcl-2 family anti-apoptotic proteins can interact with Beclin-1, thereby inhibiting Beclin-1–dependent autophagy; however, pro-apoptotic proteins disrupt the association between Beclin-1 and Bcl-2 and induce autophagy. Autophagy-related genes (Atgs), such as Atg3, Atg4, Atg12, and Atg8, have been reported to activate apoptosis by regulating specific signaling pathways. Truncated Atg5 activates apoptosis by interacting with Bcl-x_L. When cleaved by caspase-3, Beclin-1 loses its ability to promote autophagy but renders cells sensitive to apoptosis. Because autophagy can, paradoxically, promote cell survival or death, both autophagy-enhancing and -inhibiting agents may elicit beneficial effects in cancer treatment.

Received: 2013-01-29; revised: 2013-02-07;
accepted: 2013-02-10.

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