Autophagy: A New Horizon in Cancer Research

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Abstract
Onco-physiology (cancer–autophagy interplay) became a focus of interest after awarding Yoshinori Ohsumi the Nobel Prize for Physiology or Medicine for his work elucidating the mechanism of autophagy. One of the interesting hot spots in the research work is the growing evidence of the fundamental role of autophagy in cancer. Autophagy is degradation process, intimately intertwined with cellular metabolism, stress, genetic instability and cellular death. Autophagy modulation could be a therapeutic rational for emerging cancer. We aim by this mini-review to precise the role of autophagy in carcinogenesis whether it is with or against.

Keywords: Autophagy; Cancer; Cell death

Introduction
Autophagy, the cell survival and health promoting machinery occurs normally at basal level that is enhanced in cellular stress. Autophagy in cancer research show complex dual interplay in cancer progression stages [1]. Autophagy represents a promoting protective and therapeutic strategy for cancer. Autophagy is claimed to have a complex dual role in carcinogenesis acting as double-edged sword, one edge is suppressing initiation and early stage of cancer while the other edge evokes tumor cell growth and tolerance to anticancer drugs under hypoxic conditions via supplying nutrients [2]. Inconsistent, up-regulated autophagic flux and autophagy block were evidenced to sensitize cancer cells to cell death indicating context dependent charterers of this machinery and that is why establishing autophagy-based cancer therapy is mandatory [3].

Literature Review

Autophagy machinery
Autophagy (Greek for “self-eating”) is a physiological housekeeping process. Autophagy copes the cell with the destructive events and together with apoptosis, establish homeostasis through preserving healthy functioning organelles, cytoplasm as well as genomic integrity, preventing cellular toxicity, waste products accumulation and supply essential substrates during starvation [4]. It is a highly conserved and regulated process occurs normally in low levels in all cells; however, it is enhanced in different stressful conditions [5]. This cyto-protective process sequesters, degrades, and recycles the intracellular proteins and organelles within autolysosomes. Three main types of autophagy are present according to the way of delivering the cargo into the lysosomes; Macroautophagy (known as autophagy), occurs by formation of a double-membrane vesicle (autophagosome) around targeted protein or organelles to fuses with the lysosomes forming (autolysosomes). Microautophagy occurs through direct engulfment of the cellular components via lysosomal membrane invagination. Chaperone mediated autophagy is a highly selective type depends on specific proteins called chaperone that translocate unfolded substrates but not aggregated proteins or organelles across the lysosome membrane [6].

Autophagy, autophagic cell death and cancer interplay
The cell survival supporting and death-promoting controversy roles of autophagy in carcinogenesis is still an area of intense research [7]. Growing evidence supports cell survival role for autophagy, paradoxically, cell death from excessive cellular consumption could be attributed exaggerated autophagy. This cell death pattern is associated with autophagy features is called autophagic cell death [8,9]. This occurs when cellular consumption during autophagy exceeds the cellular synthesis capacity.

Autophagy as tumor suppressor
Autophagy is health promoting machinery that prevents genome damage and chromosomal instability inducing tumorigenesis via preserving energy homeostasis and cellular quality control. It inhibits the damaging oxidative stress from accumulated unfolded protein or defective organelles. In cells with inactivated cycle check points, autophagy prevents early tumor cells formation and maturation rate suppression [10,11]. Normal cell undergoes senescence as a primary response to telomere depletion and stimulates tumor suppress pathway. However, with abnormality in cell cycle check-point, cells can get away senescence and proliferate despite shortening of telomere inducing tumorigenesis. Although the fast majority of cells undergo what is called replicative crisis and die few cells can skip and proliferate with neoplastic features such as chromosomal instability and abnormal genome with continuous telomere supply and absence of cell cycle check point control [12,13]. It was proved that autophagy is a final obstacle against carcinogenesis by inducing autophagic cell death during replicative crisis [14].

Autophagy as tumor promoter
The extensive evidence of mutually opposed roles of autophagy still needs explanation. However, the most conceivable clarification of the paradoxical role of autophagy as cancer cells survival support in various conditions such as following chemotherapy and radiation through supplying nutrients, essential substrates and energy to cancer cells during excessive metabolic and oxidative stress [15,16]. Several clinical trials investigated the efficacy of chemotherapy with autophagy inhibition or block on cancer cells [17-20]. Inhibition of autophagy...
using Hydroxychloroquine (a non-specific autophagy inhibitor) and more specific potent inhibitors and other autophagy-modulating agents may provide a therapeutic potential for progressive cancer in the future [20]. Autophagy inhibitors together with other drugs include angiogenesis, growth factor, and receptor inhibitors, organelle-damaging drugs or ER stress inducers might trigger cell death in cancer cells [20,21].

**Conclusion and Future Prospects**

In conclusion, depending on the type of tumor and its developmental stage, activation or inactivation of autophagy can contribute differently to tumorigenesis either promoter or suppressor (Figure 1). Autophagy might induce disparate effects according the stage of progression in tumors. This needs further experimental study on the cross talk between cancer at different stages and autophagy at molecular level.

**References**