



Mini Review

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Autophagy: Dichotomy in the Host Response-Therapy in Cáncer



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Introduction

A hallmarik feature of autophagy, defined as an evolutionary catabolic lysosomal process, under a program core of 32 Atg proteins, each with a function in the multi step autophagosome formation, and a elegant and fine tuned regulatory mechanism; is the dichotomy in the host response in cell survival or cell death. As a protective and prosurvival mechanism contribute to maintain homeostasis [1,2], differentiation and normal tissue cell development, function like a housekeeping and control quality of any insult that threaten an organism. However, as an hyperactivated state (internal or external stimulus-insult) of self eating can cause serious damage cell/injury, that lastly kill the cell [3,4]. These two sides of the coin in which down stream signaling affects that for one side contribute to the elimination of waste disposal products of the metabolism but for other is a source of nutrients in tumor growth constitute the focus of current and intense research in cancer therapy.

Autophagy as Therapeutic Target in Cáncer

One aspect of serious concern for human health is that autophagy regulates diverse metabolic pathways that promote tumor proliferation and survival [5,6] which are closely associated with oncogenic activators and tumor suppressors. Autophagy has been implicated in cancer cell invasion, malignant transformation and cancer progression and even worse in metastasis [7,8]. The identification of potential targets that can be utilized to disrupt cancer development, novel methods to enhance targeted cancer therapies is key to understand the molecular networks integrating metabolic pathways [9,10]. More recent work have demonstrated that autophagy also facilitates cellular secretion, a novel function that should be taken in account for treatment and to understand its role in cancer progression [11,12]. From a therapeutic perspective, understanding whether, when and how

autophagy can be harnessed to kill cancer cells remains challenging and represent a new alternative target to treat tumor resistance [13]. In recent years, intense focus on the pathways linking autophagy and cancer that are relevant for target identification and on pharmaceuticals that can be utilized to improve cancer therapy by targeting the autophagic pathways, target apoptotic and autophagic activities, as well as epidermal growth factor receptor signaling pathway [14-16] cytochrome P450, CYP in mitochondria, vacuolar protein sorting 34 (VPS34), or another component important for the promotion of NK cells cytotoxicity, down regulation of PI3K γ mediated PI3K/AKT/mTOR/p70S6K/ULK [17,18].

The ideal treatment would be targeting autophagy in single-agent therapy to sensitize aggressive cancers that are dependent on autophagy for survival or in combination with therapeutic agents that induce autophagy as a resistance mechanism may be an effective therapeutic strategy to treat cancer [19]. Likewise the stimulation of autophagy in response to therapeutics can contextually favor or weaken chemoresistance and antitumor immunity. Furthermore, chemotherapy agents induce acute metabolic stress that cancer cells must overcome for their survival [20,21].

These metabolic stress cues in cancer cells, in first place, can activate and cause dependence on the self-cannibalization mechanism of macroautophagy (autophagy hereafter) for the lysosomal turnover and recycling of organelles and proteins for energy and stress survival [8]. Second, acute autophagy/activation in response to cancer therapy can potentially lead to refractory tumors resistant to conventional chemotherapy. For example, a specific form of autophagy that targets mitochondria (mitophagy) may also function to promote cell survival by the

clearance of damaged mitochondria that are potential sources of reactive oxygen species (ROS) [22].

Molecular mechanism underlying autophagy pathways by ROS and autophag in cancer cells responding to ROS producing agents, which are utilized as a therapeutic modality to kill cancer cells [23]. Furthermore, the molecular mechanism underlying autophagy pathways by ROS and autophag in cancer cells responding to ROS producing agents, which are utilized as a therapeutic modality to kill cancer cells [23]. By another hadn, the apoptotic neutrophils that have phagocytized TRAPs inhibited the proliferation and activation of CD4+T and CD8+ T cells in a cell contact-and ROS-dependent manner, representing a novel TRAP-mediated mechanism in neutrophils that potentially suppresses the anti-Tumor cell immunity and highlight TRAPs as an important target for future tumor immunotherapy [24-26].

How to Improve Anticancer Therapy. "Depending of the Circumstances"

Targeting for therapeutic approaches in cancer not only the apoptosis pathways but alternative pathways and this can represent an attractive strategy to improve anti-tumor therapy. For example, it has been showed that autophagy is critical to estrogen receptor positive (ER+) breast cancer cell survival and the development of anti estrogen resistance. Consequently, new approaches are warranted for targeting autophagy in breast cancer cells undergoing antiestrogen therapy. Moreover, anticancer therapy should take advantage of the modulatory capacity of pharmacologically active compounds, that can cause cells to switch from one cell death to another depending of the cellular setting. Since crosstalk has been demonstrated between the autophagy-and proteasome-mediated pathways of protein degradation. The proteasome inhibitor bortezomib affects autophagy and cell survival in antiestrogen-treated ER+ breast cancer cells [20,27]. This drug at clinically doses, induced a robust death response in ER+ antiestrogen-sensitive and antiestrogen-resistant breast cancer cells undergoing hormonal therapybortezomib inhibits prosurvival autophagy in addition to the known function in blocking the proteasome, and is cytotoxic to hormonally treated ER+ breast cancer cells [28]. Inhibition or activation of ER stress relates to autophagy, and how these associated pathways can serve dual functions to promote survival or cell death in cancer [20]. By combining a proteasome inhibitor like bortezomib with antiestrogen therapy may have therapeutic advantage in the managements of early stage of breast cancer or it lays out a spectrum of potential pharmacological agents and combinatorial approaches that target these pathways to enhance tumor cell kill [27]. In a similar way, triptolide-induce autophagy has a pro-death effect [29], requires autophagy-specific genes atg5 or beclin1, and is associated with the inactivation of the Protein kinase B (Akt)/mammalian target of Rapamycin/p70S6K pathway and the up-regulation of the Extracellular Signal-Related Kinase (ERK)1/2 pathway. Inhibition of autophagy in S2-013 and S2-VP10 cells results in cell death via the apoptotic

pathway whereas inhibition of both autophagy and apoptosis rescues cell death [30,31]. Quercetin (a dietary antioxidant), activated autophagy in pancreatic cancer cells by modulation of Akt-mTOR signaling and hypoxia-induced factor 1 alpha (HIF-1alpha) signaling [32-34]. Preliminary results by us, have found that *Bacillus thuringiensis* Cry toxins mediated-autophagy induction in human pneumocytes class II (A549), a potential cancer therapeutic capability that deserves further investigation either in-vivo and in-vitro [35-37].

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