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Autophagy, Paradoxical Functions and Perspective in Cancer Treatment

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Abstract

Autophagy is known as a highly complicated bio-degradative mechanism which closely involves in the regulation of multiple physiological and pathological events such as embryonic development and neuro-degenerative diseases. Strikingly, recent research has highlighted the impact of autophagy on the progression of various kinds of malignancies. It functions as both pro-tumoral and tumor-inhibitory effects in a highly context dependent manner. It induces the autophagic cell death, which is termed as the typeII programmed cell death, in cancer cells. Additionally, through genetic or phamarological methods, the autophagic inducers were reported to efficiently attenuate the angiogenesis and as a result, block the metastasis. In contrast, as a essential regulator for exogeneous and endogeneous stresses, autophagy are proved to be the core response process relating to the chemotherapeutics, which greatly influences the efficacies of clinical treatment and the intensity of drug resistance. Herein, we summarized the current studies of the interaction between autophagy and malignant progression. We also emphasized on the application of the autophagic inhibitors or inducers in clinical practice. Finally, leading by the paradoxical and plastic features of autophagy and its key roles in cancer disease regulation, we made a perspective regarding to the reasonable strategy of autopahgy manipulation in the future cancer treatment.

Keywords: Autophagy; Programmed cell death; Drug resistance; Anti-cancer therapy

Autophagy and its Paradoxical Functions

Autophagy is a conserved cellular catabolic degradation process ubiquitously existing in most of the eukaryotic cells by which the macromolecules, long-lived proteins, ribosomes, and organelles can be degraded. It can be observed under both physiological and pathological conditions of cells. Autophagy process mainly refers to several sequential steps: a non-enclosed double membrane structure fall off from the ribosomeless region of rough endoplasmic reticulum; then this double membrane structure packages a modicum of the cytoplasm, aging organelles (such as mitochondria, endoplasmic reticulum and Golgi apparatus) and redundant biological macromolecular components to form autophagosomes; finally autophagosomes mature by fusing with lysosomes and the contents mentioned above could be lysosomally degraded. Depending on the transport way of the degradative content to lysosomes, mammalian autophagy can be divided into macroautophagy, micro-autophagy and chaperone-mediated autophagy ("autophagy" refers to "macroautophagy" in this manuscript). The original meaning of the term autophagy is "self-digestion", the autophagic digestion also provides raw material and energy for the construction and updating of organelles and meets the metabolic needs for cells. Hence, autophagy is considered as a recirculation system and an "alternative energy source" of cells. According to this, autophagy has been identified to be a self-rescue behavior responded to nutrient starvation, hypoxia and metabolic stress. However, if the continuous or excessive autophagy occurs, cell death may always ensue. Therefore, autophagy has also been considered as the third type of cell death in addition to apoptosis and necrosis [1]. As a common cell biological phenomenon, due to its confusing role and paradoxical functions, autophagy has drawn extraordinary attention comparing to the other types of programmed cell death (PCD) in recent studies The close correlation between autophagy and cancer disease was summarized in Figure 1. Depending on the cell context and type, autophagy tends to lead cells to different ending. In some fully transformed cancer cells, the defectiveness of autophagy appears to be positively correlated with carcinogenesis and malignant transformation [2-4]. For example, the BECN1 allelic is deficient in approximately 40% in human prostate [5], 50% in breast [6] and 75% in human ovarian cancer

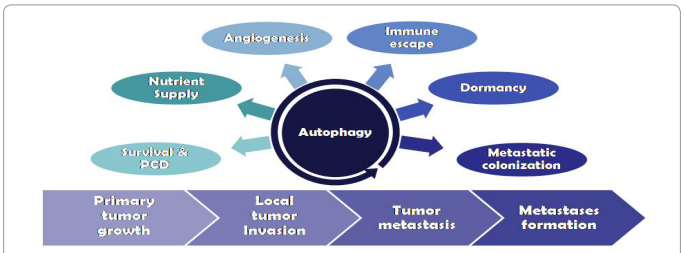

Figure 1: Close correlation between autophagy and cancer disease.

[7]. In addition, the decrease of BECN1 expression can also be observed in human brain tumors [8], hepatocellular carcinomas [9] and colon cancer [10]. In contrast, stably transfected BECN1 in MCF-7 cells, a human breast cancer cell line, leading to obviously autophagy activation and reducing the cellular tumorigenicity [5]. Besides the tumor suppression activity of autophagy, in the normal counterparts of the previously mentioned tumor cells and some other tumor cells, it becomes a protection mechanism against survival pressure (including hypoxia, acid microenvironment or damages induced by chemical treatment). In accordance with this, the occurrence, intensity and duration of autophagy have a significant effect on tumor disease progression. Especially, its pathological functional imbalance was the critical factor for the malignancy regulation. In line with this theory, the reestablishment of the physiological property and the maintenance of the "Yin and Yang" balanced phenotype of autophagy was a promising target

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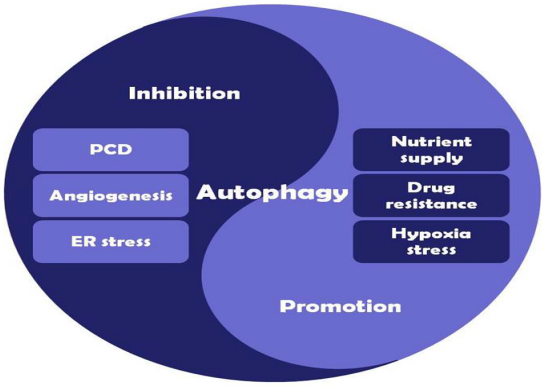

Figure 2: Balanced phenotype of autophagy.

in the future (Figure 2). It is the exact reason that autophagy intervention is becoming an attractive field in anti-cancer therapy. In order to clarify how targeting autophagy works as a novel anti-cancer therapy, the different autophagic responses caused by different treatment should be figured out first. The detailed information is shown in the section below.

Autophagy and Treatment Responses

Autophagy as a tumor promoting mechanism responds to anti-cancer therapy

Since autophagy is Janus in cells, it also plays a complex and contradictory role in clinical cancer therapy. It is widely known that tumor cells have the ability to initiate, proliferate and propagate in extremely harsh microenvironment, which are hypoxia, starvation, growth factor withdrawal and cytotoxicity caused by chemotherapy or radiation. Under this circumstance, autophagy seems to be the inevitable choice for cancerous cells to follow the rule of the "Survival of the Fittest". Autophagy facilitates the removal of misfolded or harmful proteins and damaged organelles, and, at the same time, functions as a back-up energy warehouse to provide extra energy to fight against anticancer therapy, thereby reducing the metabolic stress of tumor cells to the greatest extent. Studies show that a considerable anti-neoplastic therapies, including radiation therapy, chemotherapy and biological therapy, are capable of inducing autophagy in tumor cells. For instance, some commonly-used chemotherapy drugs, including doxorubicin, temozolomide, arsenic trioxide, rapamycin, etoposide, imatinib and some biological agents such as TNF-alpha, IFN-gamma, have been considered to have autophagy inductive effect and protect the survival of cancer cells. It has been revealed by Apel et al, that the occurrence of autophagy increased the resistance of HER2 positive breast cancers to the HER2 monoclonal antibody Trastuzumab. Whereas such Trastuzumab resistant cells regained the sensitivity after knocking-down of LC3 expression via shRNA [11]. Moreover Bellodi et al., proved that the inhibition of autophagy either by pharmacological inhibitors or RNA interference of autophagy genes potentiated CML cell death induced by Imatinib mesylate [12]. These evidences prove that the treatment induced autophagy in tumor cells increases their intrinsic resistance towards anti-cancer therapy and becomes the leading course of treatment failure as well as the assistant for tumor survival and growth. Besides, a dreadful problem in clinical cancer treatment is the frequent rapid relapse after the anti-cancer therapy even with longer dormancy [13,14] and the acquired resistance is one of the leading causes of this issue [15]. Presumably, autophagy is one of the core mechanisms to make cancer cells capable of surviving and eventual relapsing after cytotoxic treatment: due to the autophagic protective function, a few survived cells become the springhead of tumor relapse, which results in the colonization of the tolerate tumor cells against most cytotoxic chemotherapeutic drugs. Therefore, using the above anti-cancer agents while supplemented with autophagy inhibitor may be an efficient approach to reduce the occurrence of intrinsic or acquired drug resistance and eradicate cancer.

Autophagic cell death helps tumor suppression

The inhibition of tumor cells: Besides the survival promotion effects, as the programmed cell death type-II, autophagy plays a positive role in tumor inhibition. Emerging studies showed that in many kinds of tumor cells, especially in the advanced tumor, high drug-resistant tumors and tumors with high metastatic ability, there are mutations for apoptosis-related genes which are difficult to eradicate them through apoptosis. However, in those cells highly expressing Bcl-2 or Bcl-X_L, those lacking Bax or Bak, or those being long-term exposed to pan-caspase inhibitors, the defection of apoptosis does not protect these cells from being killed by cytotoxic treatment, instead, autophagic cell death is activated and the tumors are suppressed, especially supplemented by starvation, growth factor withdrawal and chemotherapy [16-19]. Notably, with autophagy alleviation or elimination by exposing these kinds of cells to autophagy inhibitors or silencing *ATG5*, *ATG7* and *BECN1*, cytotoxic-resistance recurs. In clinical treatment, cytosine arabinoside [18], rottlerin [17], staurosporine [19] and so on all exert tumor suppression effect by inducing autophagic cell death. Meanwhile, the anti-cancer capacity of autophagy can be verified from calorie restriction (CR) therapy. CR acts as a widely-accepted anti-cancer method effectively reducing the incidence of cancer [20]. From another perspective, CR is also a trigger to autophagy [21]. Therefore, it is reasonable to believe that autophagy, as a cell adaptive response, synergizes the incidence reduction effect of CR.

The tumor microenvironment regulation: More importantly, the influences of autophagy on tumor are not only confined to tumor growth in situ, but also affect tumor environment. Tumor associated angiogenesis is one of the typical process in tumor microenvironment. It is well known that angiogenesis is persistent activated in neoplastic diseases in order to provide necessary nutritionalsupport and material storage to tumor growth, invasion and distant metastasis [22]. Therefore, inhibition of angiogenesis is always an important anti-cancer therapy in clinic. In addition to the classic anti-angiogenic strategies, as represented by the VEGF inhibition, S Kumar proved that the magnolol induced autophagy led to the apoptosis-independent dysfunction of human umbilical vein endothelial cells (HUVEC) in vitro and vivo, which inhibited angiogenesis of colon cancer. Besides, the autophagic cell death induced by magnolol has negative regulatory effect with angiogenesis [23]. So it is foreseeable that anti-angiogenesis therapy combined with autophagy inducer is a practical treatment with great value and potential in clinic. In summary, the occurrence of autophagy and the efficacy of clinical cancer treatment are closely associated with each other and, more importantly, reinforce each other. On one hand, the treatment can induce autophagy; on the other hand, autophagy can also greatly affect the effectiveness of treatment. Indicated by this, either the induction or the inhibition of autophagy can be used as a efficient means of adjuvant therapy or combined therapy, which is therapeutically beneficial to patients worldwide.

Targeting autophagy as a novel therapeutic strategy: Based on the double-sided, paradoxical and plastic characteristic of autophagy, the appropriate application of autophagy inducer or blocker to enhance its tumor suppression activity while inhibit its tumor promotion

function is the effective way to maximize the effectiveness of clinical treatment. In order to properly deal with this issue, we can start from the following aspects: First of all, we should analyze the specific biological characteristics of tumor cells and assess their molecular changes responding to the treatment of radiotherapy or chemotherapy. As mentioned in the previous section, apoptosis tends to be commonly defective in a number of tumor cell lines, particularly in advanced and high-metastatic tumor cells. For instance, pancreatic cancer cells fail to undergo apoptosis due to the endogenous resistance to mitochondria-initiated and death receptor apoptotic pathway and usually do not have response to most conventional cytotoxic therapies. Meanwhile, a variety of growth factor receptors are overexpressed in pancreatic cancer accompanied with p53 mutation [24]. Furthermore, breast cancer cell line MCF-7 is caspase 3-deficient and its expression is undetectable in 45%~75% of breast tumor cells [25,26], which means there is a higher threshold in those cells for therapy induced apoptosis. Such phenomenon suggests that using autophagy-inducing agents or therapeutic strategies are beneficial to treat these kinds of apoptosis-resistant cells. Secondly, assessing the autophagic consequences (including the presence or absence of autophagy occurrence and its sequential effect in cancer) caused by treatment is also crucial to maximize the autophagic influences positively. To achieve this goal, the identification of autophagy by using classic experimental methods (including electron microscopic observation of autophagosomes, sub-cellular localization of LC3 and the expression level analysis of key molecules in autophagy regulatory pathways) and the analysis of its role in tumor progression are necessary and crucial for the reasonable clinical treatment. Evidence showed that γ- ray radiation-induced autophagy increased the tolerance in the $CD133^{+}$glioblastoma and lung cancer cells, while the combination of autophagy inhibitor 3-MA and bafilomycin A1 recovered the sensitivity of those cells towards radiation [27,28]. In the opposite, autophagy induction leads to cell death in those tumor cells with highly expression of Tyrosine kinase growth factor receptor family accompanying with apoptosis defection [29]. Meanwhile, the intensity and the duration of autophagy are closely related to the cell functional outcome, so that autophagy is highly inducible and plastic. Based on these characters, looking for specific autophagy modulators, including the key regulatory genes or pharmacological agents, as well as the control methods on autophagy intensity are the feasible and valuable for the R&D of novel anti-cancer therapy. These therapeutic strategies can help enhance tumor-suppressing autophagy (good autophagy) or transform the tumor-promoting autophagy (bad autophagy) into good autophagy or other forms of cell death. There are literatures proved that tissue transglutaminase 2 (TG2) is overexpressed in more than 80% of pancreatic patients [17,30]. As an autophagy inhibitor, TG2 binds to important tumor-suppressing molecules Rb and p53 and involves in tumor growth and metastasis. While the down-regulation of TG2 through small interfering RNA inhibits tumor growth in pancreatic cancer bearing mice, which indicates that TG2 is a potential target to induce good autophagy. Moreover, it has been reported that doxorubicin predominantly induces apoptosis at high doses and autophagy at low doses. According to this, the combination of low dose doxorubicin with Bcl-2 siRNA treatment may be an potential therapy to promote autophagic response and to induce cell death [31].

Concluding Remarks

Overall, the role of autophagy and the detailed mechanisms underlying the autophagy regulation in tumor cells are not completely understood yet, however it should occurs to us that, autophagy is far more than "phagy". Autophagy is, for a long time, broadly defined as a "self-digesting" or "self-devouring" process, which is just a preliminary definition come from its functional behavior. Emerging studies have shown that, at least in the field of neoplastic diseases treatment, autophagy is not only about cell self-digestion, it profoundly impacts the functional outcome of cancer diseases by regulating the survival metabolism, oxidative stress, drug resistance, angiogenesis and so on in tumor cells. Therefore, it appears that modulation of autophagy may bring numbers of benefits. In order to achieve accurate regulation of autophagy which is consistent with the therapeutic target, we need to analyze the biological characteristics of the cells, and evaluate the induction effect of autophagy during chemotherapeutics, and perform directed regulation for the function of autophagy. Through the method of "experiments guide the treatment", the medical translation of the phenomenon of autophagy and truly effective guidance for clinical therapy of tumor will be achieved.

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