Autophagy Modulators

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Autophagy modulation is considered to be a promising programmed cell death mechanism to prevent and cure a great number of disorders and diseases. The crucial step in designing an effective therapeutic approach is to understand the correct and accurate causes of diseases and to understand whether autophagy plays a cytoprotective or cytotoxic/cytostatic role in the progression and prevention of disease. This knowledge will help scientists find approaches to manipulate tumor and pathologic cells in order to enhance cellular sensitivity to therapeutics and treat them. Although some conventional therapeutics suffer from poor solubility, bioavailability and controlled release mechanisms, it appears that novel nanoplatforms overcome these obstacles and have led to the design of a theranostic-controlled drug release system with high solubility and active targeting and stimuli-responsive potentials.

Keywords: autophagy ; mTOR ; AMPK ; Nanocarriers ; combination therapy ; cancer ; siRNA

1. Introduction

Autophagy—cell self-digestion machinery—is a substantial process which plays critical roles in many cellular processes and functions. The most important type of autophagy is macroautophagy (referred to as autophagy hereafter) [1][2][3][4][5]. This process targets the damaged cytoplasmic proteins or organelles with different complexity and size [6][7][8]. In the autophagy, double-membrane structures (termed phagophore or isolation membrane) capture the cargo, including aged-proteins, injured-organelles, and pathogens, and then elongate into enclosed double-membraned autophagosomes [9][10][11]. Subsequently, autophagosomes are fused with lysosomes by merging the outer membrane of autophagosome with lysosomal membrane, resulting in the formation of autolysosomes [12][13][14]. Finally, the cargo being delivered, together with the inner autophagosome membrane, is broken down inside autolysosomes. This process, like a thrifty source in the cell, leads to the recycling of biomolecules during starvation. Therefore, autophagy is considered to be a homeostatic mechanism to conserve cell survival during stress conditions via the degradation of damaged cellular components and the recycling of cellular constituents [15][16][17][18].

Triggering of autophagy is induced through multiple intracellular and extracellular stimuli including infection, proton concentration, starvation, metabolic perturbations and other chemical and physical stressors. It is noteworthy that deregulated autophagy leads to several disorders not only in healthy situations but also in transformed mammalian cells [19]. Furthermore, autophagy exhibits cytoprotective impacts on cells that make them a vital player in the adaptive responses to intrinsic or extrinsic impulses. There are only a limited number of cases where autophagy has been known as the bona fide cause of regulated cell death [18]. Autophagy inhibition through diverse mechanisms for example drug or genetic, resulting in enhanced in cell sensitivity to various stressors. In the importance of autophagy balance in cells, it should be said that not only permanent but also transient disturbance in autophagy leads to developmental and embryonic defects along with several pathological conditions.

As mentioned above, accurate protein homeostasis (proteostasis) and elimination of damaged or exacerbated intracellular compounds are crucial for the cell survival and its proper function. During starvation, autophagy is activated through multiple signaling pathways, such as mechanistic target of rapamycin (mTOR) pathway, one of the critical pathways involved in cell proliferation that inhibits autophagy [15][20]. Therefore, disturbances in autophagy, as the adverse effects of mTOR pathway, can create disorders. It is thought that autophagy has some protective and therapeutic roles in microbial infection, neurodegeneration, cardiovascular disorders and a dual role in cancer. Nevertheless, rapamycin promotes autophagy [21], and it seems that it may be prescribed as one of the choices in the treatment of the diseases which are caused by the inhibition of autophagy [22]. For example, in cancer cells, based on the different type and stage of cancer, nutrient availability, stress, immune system, and genetic context [23][24][25], autophagy will be induced and inhibited and this necessitates more investigations. There are several reports indicated that autophagy is inhibited at the onset of cancer in some parts through mTOR, Bcl2, damage-regulated autophagy modulator (DRAM) and PI3K activation and over-expression and P53 down-regulation. However, others believe that the level of cytoplasmic P53 not pool P53 leads to autophagy decrement at the basal level [7][26]. It is important to note that autophagy decrement at the just is sufficient for

the onset of cancer and does not guarantee tumor progression [8]. However, the over-expression of P62 derived from autophagy inhibition leads to tumor progression through the increasing of ROS, NFκB, NRF2 and DNA damage [27]. Moreover, it seems that autophagy is elevated in advanced cancers. An important point is related to the modulatory effect of autophagy on immune system where elevated autophagy in advanced cancers increases high-mobility group box 1 protein (HMGB1) release [28]. These events result in inducing anti-tumor T-cell responses through the activation of Toll-like receptors. Therefore, inhibition of autophagy by chemotherapeutic agents will lead to a decrease in HMGB1 release and anti-tumor response.

Autophagy activation has a dual role in cancers. From one side, autophagy activation in cancer cells promotes the efficacy of anti-cancer strategies especially in the case of a functional immune system. From the other side, it may promote cancer progression through the enhancement of cell survival. In other hands, if the association of autophagy with multidrug resistance (MDR) is fortified [15], autophagy can be undoubtedly considered as a promising target in oncotherapy [29]. In other words, since the up-regulation of ABC transporters involved in MDR is correlated with the level of microtubule-associated protein 1A/1B-light chain 3 (LC3) and Beclin1, autophagy is in good agreement with MDR [30]. Besides, there are the relationships with the over-expression of LC3 and other biomolecules and miRNAs such as HMGB1and miR-199a-5p involved in MDR [31][32].

Importantly, inhibition of autophagy may conquer resistance to kinase inhibitors in cancer cells. Notably, the positive impact of autophagy on cancer therapy is dependent to the stage of cancer and its progression and if mTOR inhibitor pharmaceuticals failed in cancer therapy owing to the acidic pH microenvironment of cancer cells [33]. All together findings emphasize the importance of engineerable drug delivery systems to improve the efficacy of autophagy modulators.

Although these findings highlight the fact that targeting autophagy is of importance in the treatment of pathological conditions, particularly cancer, there are several drawbacks associated with currently applied autophagy modulators. It is held that autophagy modulators suffer from low bioavailability restricting their therapeutic efficiency. Additionally, non-targeted delivery is another pitfall associated with autophagy modulators. On the other hand, nanocarriers have demonstrated great potential in delivery of autophagy modulators [34]. To date, several nanocarriers such as liposomes [35] [36], niosomes [37], micelles [38][39], carbon dots (CDs) [40] and polymeric ones [41][42] have been applied for delivery of drugs.

2. Nanocarriers as Autophagy Modulator: Challenging to Design Drug Delivery System

As mentioned earlier, liposomes have lipid nature, leading to the stimulation and formation of autophagic membranes which may be suitable to induce autophagy. However, it seems that they are not an appropriate candidate in autophagy inhibition. Gao et al. investigated the relationship between autophagy and cytotoxicity derived from polyethylenimine in MDCK (Madin-Darby canine kidney) and Chang liver cell lines [43]. They showed that inhibition of autophagy decreases the cytotoxicity induced by PEI, whereas autophagy induction enhances cell death, suggesting that autophagy is a key contributor for the enhancement of PEI cytotoxicity. Moreover, their results demonstrated that cytotoxicity derived from PEI-mediated autophagy acts through two steps: 1) early stage (3 h) with lysosome damage and 2) later stage (24 h) with mitochondrial damage. In another study, Li et al. investigated the effects of cationic PAMAM NPs on acute lung injury [44]. Their results demonstrated that cationic PAMAM NPs acts through Akt-TSC2-mTOR signaling pathway to induce autophagic cell death, resulting in the promotion of acute lung injury. It seems that autophagy inhibition is vital in generation of adverse effects of NPs. It is held that exposing to silica NPs is associated with development of pulmonary fibrosis. Investigation of molecular signaling pathways reveals that silica NPs are capable of inducing impairment in autophagy, resulting in apoptotic cell death in alveolar epithelial cells [45]. It appears that the aggregation of NPs after cell internalization negatively influences autophagy [46]. The modulatory effect of nanocarriers on autophagy can mediate their anti-inflammatory activity. Upconversion NPs encapsulating chlorin e6 effectively enhance the generation of ROS and subsequently, stimulate autophagy through PI3K/Akt/mTOR signaling pathway, resulting in down-regulation of pro-inflammatory factors (IL-12, TNF-α and iNOS) production [12]. Taking everything into account, NPs are able to regulate autophagy and this potential can be promisingly used in biomedical applications [47]. However, these nanoparticles could also trigger other organ toxicity tightly related with autophagy. For instance, ZnO NPs induce harmful impacts on gastrointestinal tract and autophagy stimulation is considered to be a potential candidate in ameliorating these toxic effects. [48].

In brief, it is worth mentioning that nanoparticles are able to induce or inhibit autophagic cell fates [192,335]. Therefore, autophagy nano-inhibitors should not be used for delivery of autophagy inducers and autophagy nano-inducers are not good options as nanocarriers for autophagy inhibitors.

3. Conclusions and Remarks

Nowadays, autophagy is the focus of attention owing to its homeostasis role in cells. Autophagy not only guarantees cell survival through the engulfment of damaged organelles and proteins and, thereby, its cargo biodegradation, but it also acts as a cell-assure valve, which leads to saving cellular power supplies. Considering the critical importance of the equilibrium of autophagy in cell, its disturbance leads to a great number of diseases and disorders. Therefore, an accurate understanding of the real causes of the diseases is important. Meantime, scientists are attempting to discover the underlying cause of the disease and find the effective remedies for them. However, the great majority of these molecules have poor bioavailability, mainly associated with their low solubility in water. However, it seems that nanotechnology may overcome these obstacles.

Autophagy has diverse check points, and medications can act through them to reverse the autophagy function. For example, it can modulate through the mTOR, AMPK, class III PI3K and MAPK signaling pathways. There are some conventional drugs to influence autophagy as an inducer or inhibitor including metformin, simvastatin, everolimus, temsirolimus, dactolizib, CQ etc. It is worth mentioning that there is controversy on the mechanism of autophagy in cancer progression and it seems that it is stage-dependent. In order to prove the finding, reference may be made to the protective potential of metformin in cancer, while it is not effective when the cancer is triggered and progressed. These reports delineate the promise of nanocarriers and combination therapy as a novel strategy to treat cancer and other pathological conditions through autophagy modulation.

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