Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 5418 - 5434
Received 05 March 2021; Accepted 01 April 2021.

Treatment of Cancer by Induction of Autophagy

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Abstract

Autophagy is an adaptive evolutionary machine induced in all eukaryotic cells under different forms of cellular stimuli such as stress, amino acid, starvation and excessive loss in trophic factors and hormones to removes damaged organelles and proteins from cells and keep the cellular homeostasis. Since various diseases including cancer formed in response to dysregulation of autophagy, wide attention has been developed for understanding the ambiguous roles of autophagy in tumor suppression. Protein kinase A (PKA), 5'-AMP-activated protein kinase (AMPK) and mTOR complex 1 (mTORC1) are the main kinases that regulate this process. Targeting these kinases and other autophagy regulatory genes have been revealed an excellent result in the treatment of many resistance cancer cells such as breast and prostate cancer. This review will focus on the molecular mechanism, the main genes involved in the regulation of each step of autophagy, and how these genes have been targeted as a novel step in cancer therapy.

Introduction

Autophagy can be defined as a preserved catabolic machine that is participating in homeostasis in cells which was required to keep the normal cellular physiology under stressed circumstances [1]. Autophagic cell death (ACD) occurs as an adaptive process in all eukaryotic cells as a response to various forms of stimuli including stress, amino acid starvation, excessive falls in trophic factors and hormones [2], lipid malnourishment, and diminished intracellular cholesterol tracking [3]. All these stimuli can induce the function of autophagy and guide to diverse morphological consequences via different signaling pathways. Tumor cells can gain resistance to apoptosis via expressing anti-apoptotic proteins like B-cell lymphoma 2 (BCL-2) or by downregulating pro-apoptotic proteins. Defect in apoptosis has induced cancer and contribute in resistance to chemotherapy, this lead to alteration to

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another death pathway such as autophagy may allow more effective therapeutic role [4], so act as a tumor suppressor during the early and end-stage of cancer development, via destruction and elimination of carcinogens and cancerous cells, hence allowing the growth and development of normal cell[5,6]. It overcomes carcinogenic, infectious, degenerative, and deleterious agents to maintain the homeostasis of bodily systems and regulate healthy life processes; thus, its dysregulation is known to cause multiple human diseases[7,8] .There are three main forms of ACD, first one is macroautophagy (known as autophagy), second is microautophagy and the third is chaperone-mediated autophagy (CMA) [9,10].

Autophagy can be either selective or non-selectiveand specific for the substrate, organelles, protein aggregates, and intracellular pathogens whilst in nonspecific type, all materials are degraded by the lysosome in a nonspecific way[11] . Macroautophagy, definedas "autophagy", is the mainprocessin engulfment of great portions of cytoplasm and cellular contents into a double-membraned vacuole called the autophagosome, which fuses with lysosomes to form an autolysosome, degrades the autolysosomal contents, and recycles macromolecules touse again [12-14]. Microautophagy isa process by which lysosomes directly digest small volumes of cytosolic substrate[15,16]whilst CMA is stimulated by physiological stresses such as continued starvation and encompasses the heat shock cognate protein (HSC70; 71-kDa, also known as HSPA8) which contains a KFERQ-like pentapeptide sequence [17].

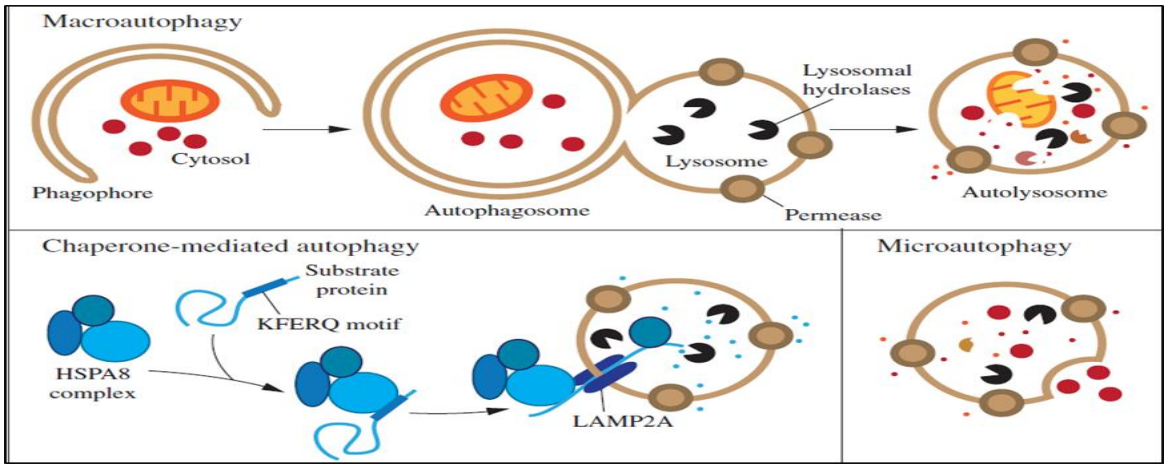

Figure 1. The types of autophagy in mammalian cells [18]

The major biological roles of cellular autophagy

Autophagy performed as an intracellular recycling system, so it has the main role in physiological and pathophysiological processes and the topmost of them are:

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- **Cellular homeostasis**

If any stimulus such as stress was absent, then the basal autophagy acts as a housekeeping process, keeping cellular homeostasis and control of cellular components by facilitating the clearance or turnover of long-lived or misfolded proteins, protein aggregates, and damaged organelles [19].

- **Nutrient stress**

Autophagy breakdowns molecules like DNA/RNA, in state of nutrient loss carbohydrates, proteins, and triglycerides. Therefore, nucleosides, amino acids, sugars, and free fatty acids are basic units to de novo synthesis of biomolecules and generation of ATP to power cellular roles by the tricarboxylic acid (TCA) cycle and other processes[20].

- **In hypoxic state**

Autophagy is induced to alleviate the stress caused by low levels of oxygen. Hypoxia-inducible factor-1α (HIF-1α), which is the primary transcription factor activated by oxygen deficiency, mediates this response by increasing the expression of BCL-2 interacting protein 3 (BNIP3), which induces autophagy by disrupting the Bcl-2/Beclin1 interaction [21].

- **Oxidative stress and mitochondrial damage**

Free radical creation in a substantial amount in the body can impair the organelles. Activation of the PERK-eIF2α-ATF4-CHOP pathway occurs as a response to oxidative stress and induces autophagy [22]. Increased reactive oxygen species (ROS) production can further induce mitogen-activated protein kinases (MAPKs) such as c-Jun N-terminal kinase1 (JNK1) [23], which in turn induce autophagy by phosphorylating Bcl-2. Phosphorylated Bcl-2 cannot form a complex with Beclin-1, so this permits Beclin-1 to contribute to the VPS34 complex production. The activity of the VPS34 complex is critical for the assembly of the pre-autophagosomal structure with autophagy induction [24, 25]. Autophagy can remove the damaged mitochondria for limiting ROS by their selective sequestration [26, 27].

Regulation and induction of autophagy

Several signal transduction pathways are involved in the regulation of autophagy as a response to different extra- and intracellular stimuli, as mentioned above. Hence the three main kinases that control autophagy are protein kinase A (PKA), 5'-AMP-activated protein kinase (AMPK) and mTOR complex

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1 (mTORC1). Mammalian target of rapamycin (mTOR) is a well-conserved serine/threonine kinase that functions as a nutrient/energy/redox sensor which controls protein synthesis [28] , it detects presence or absence of nutrients in the cell and hence regulates cell growth and division. In mammals, two complexes of mTOR, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2), have distinct localization and functions. In presence of nutrient and growth factors, mTORC1 inhibits autophagy by preventing activation of Unc-51-like autophagy-activating kinase-1 (ULK1) and Unc-51-like autophagy-activating kinase-2 (ULK2), by phosphorylating both ULK1 and ULK2 figure1 [29], however mTORC1 is targeted to the lysosome, by the Ragulator-Rag complex, which is crucial for mTORC1 initiation. lysosomes contain mTOR activators as Rheb. Stimulation of Rheb and in turn mTOR is kept in check by the TSC1/2 complex, which is a GTPase-activating protein (GAP) for Rheb. This function of TSC1/2 complex is controlled by protein kinase B (Akt), which phosphorylate and deactivates it to conserve an active mTORC1 [30]. Conversely, autophagy initiation, in the case of nutrient and energy stress, is mediated by the key energy sensor 5′ AMP activated protein kinase (AMPK). AMPK directly induce ULK1 by phosphorylation at Ser555 and Ser777 among other sites. It also activates the TSC1/2 complex, which negatively regulates mTOR [30, 31]. Thus, with evidence suggesting autophagy induction upon nutrient deprivation [32, 33], mTOR inhibition are in reverse relationship [34, 35].

Molecular mechanism of autophagy

- **Induction of autophagy-isolation membrane nucleation**

One of the initial events through the process of autophagy induction is the association of the ULK1 complex, comprising ULK1, Atg13, Atg101, and FIP200 [36] In this time, an isolation membrane known as the phagophore is formed by a membrane with contributions from various organelles, including the endoplasmic reticulum, Golgi apparatus, and mitochondria[37].The ULK1 complex translocates to the phagophore, promoting the association of the class III phosphoinositide 3-kinase (PI3K) complex, which comprises of Vps34, p150, Beclin-1, Atg14L, and Autophagy and Beclin1 Regulator 1 (AMBRA1) [50]. TheVps34/PI3K yields an autophagosome-specific pool of phosphatidylinositol3-phosphates (PI3Ps) that recruit downstream effectors, thereby driving the nucleation of the isolation membrane [38].

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- **Isolation membrane elongation and autophagosome completion**

After nucleation, the next step is the elongation of the isolation membrane; it involves two steps of Atg12–Atg5 conjugation and LC3 processing [36]. The Atg12–Atg5 conjugation is facilitated by E1 and E2 ligases, Atg7 and Atg10 [52]. Following that, the Atg12–Atg5 conjugate attach Atg16L and this complex aids in phagophore elongation by recruitment of LC3- II to the membrane [39]. The WD-repeat PtdIns(3)P effector protein I2 (WIPI2) family of the protein binds Atg16L, allowing the localization of the Atg12–Atg5–Atg16L complex to the autophagosomal membrane [40].

LC3 present in the cytoplasm is cleaved by cysteine protease Atg4 to generate a C-terminal-exposed glycine residue [41].Phosphatidylethanolamine (PE) is attached to the exposed glycine with the help of E1 and E2 ligases, Atg7 and Atg3, to produce lipidated LC3 on the autophagosomal membranes. Mammalian Atg8s like LC3 are present on the autophagosome throughout and after its formation. However LC3 has been studied as a marker for autophagosome [41].

- **Lysosomal fusion and degradation of cargo**

Following a completion of the autophagosome, it either directly merge with lysosomes to produce single-membrane autolysosomes or formerly fuse with late endosomes to form amphisomes and later fuse with lysosomes [42].The autophagosome-lysosome fusion is orchestrated by Rabs, soluble N-ethylmaleimide-sensitive factor attachment proteins (SNAREs), and tethers. Small G-protein Rab7, autophagosomal SNARE syntaxin17 (Stx17), and the membrane tethering complex HOPS are essential for autophagosome-lysosome fusion [43, 44]. Lysosomal function and acidification are also essential for autophagosome-lysosome fusion. Late-stage autophagy inhibitors BafilomycinA1 and Chloroquine (CQ) inhibit fusion by affecting acidification [45]. Autophagic flux by bafilomycin A1by inhibiting V-ATPase-dependent acidification, while Chloroquine is a lysosomotropic agent that prevents endosomal acidification [46]. Lysosome-associated membrane proteins 1 and 2 (LAMP1 and LAMP2), which protect the lysosomal membrane from self-digestion [47]. Lastly, the completion of the autophagic process requires degradation of cargo inside lysosomes by enzymes such as cathepsins,and the release of biomolecules in the cytosol for reuse[48].

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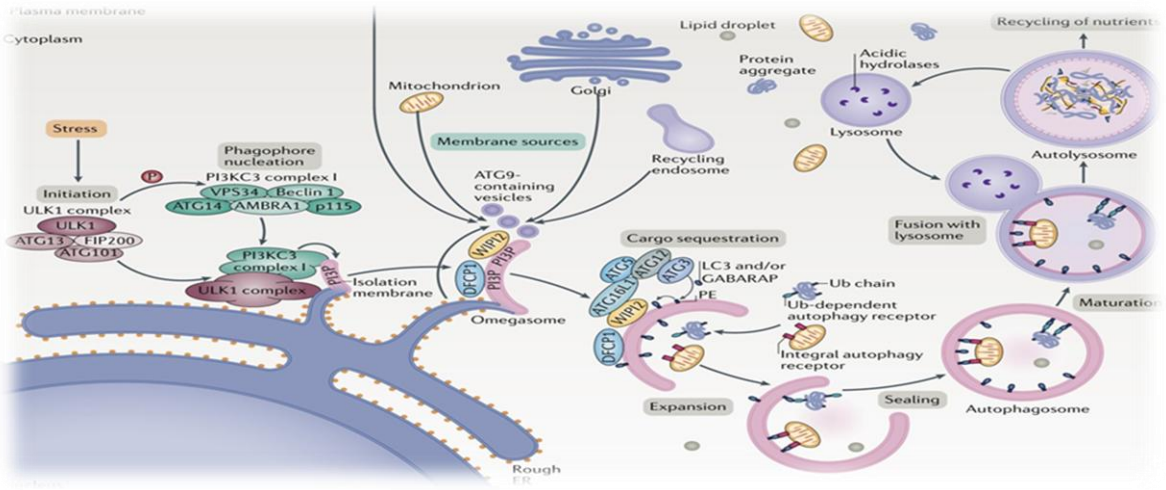

Figure.2.The main core machinery and signaling pathway regulation of autophagy[18].

Table 1: The major genes involved in autophagy and their regulation [18

Protein	Function	Mechanisms of regulation
Initiation and phagophore nucleation		
ULK1 and ATG1	ULK1 and ATG1 Serine/threonine kinase;	Stress and nutrients via mTORC1
FIP200	Component of ULK complex	ULK1 and miRNAs
ATG13	ULK1 and FIP200;	ULK1, mTORC1 and AMPK
ATG101	ULK complex; recruitment of downstream ATG proteins	ULK1
Beclin 1	Stimulates formation of PI3KC3–C1 and regulates the lipid kinase VPS34	Activation: AMPK , ULK1, MAPKAPK2, MAPKAPK3, DAPK and UVRAG; inhibition: BCL-2, AKT and EGFR
ATG14	PI3KC3–C1	PIPKIγI5 and mTORC1
ATG9	Delivery of membrane material to phagophore	ULK1 complex
WIPI2	PI3P- binding protein	TFEB and ZKSCAN3
Phagophore expansion		
ATG4	pro- ATG8s; deconjugation of lipidated LC3 and ATG8s	ULK1 and ROS
ATG7	E1-like enzyme; activation of ATG8; conjugation of ATG12 to ATG5	miRNAs
ATG3	E2-like enzyme; conjugation of activated ATG8s to membranal PE	miRNAs
ATG10	E2-like enzyme that conjugates ATG12 to ATG5	miRNAs
ATG12~ATG5–ATG16L	E3-like complex that couples ATG8s to PE	CSNK2
ATG9	Delivery of membrane material to the Phagophore	ULK1

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Cargo sequestration		
Ubiquitin	**Cargo labelling**	**PINK (phosphorylation**
Cardiolipin and ceramide	**Cargo labellingULK1, PKA , ATG4 and mTOR**	**Phosphorylation**
p62	**Autophagy receptor**	**ULK1 and TBK1**
OPTN	**Autophagy receptor**	**TBK1**
NBR1	**Autophagy receptor**	**TBK1**
NDP52	**Autophagy receptor**	**TBK1**
Membrane sealing		
LC3s and GABARAPs	**Unclear**	**Unclear ; might involve phosphorylation and acetylation events**
Autophagosome maturation		
ATG4	**Removal of ATG8s from the surface of the autophagosome**	**Unknown**
PE- conjugated LC3s and GABARAPs	**Linking the autophagosome to microtubulebased kinesin motor**	**Unclear ; might involve phosphorylation and acetylation events**

Role of autophagy in tumor-suppression

Many clinical trials have been shown the dual effect of autophagy on cancer. At early stages, autophagy usually acts as a tumor suppressor allowing cells to discard damaged cellular contents, decreasing ROS and DNA damage so exerting a cytoprotective effect. Therefore reducing the genomic defect that may progress to aberrant mutations by targeting genes involved in the regulation of autophagy machine has a protective role. Conversely, in more advanced stages of tumor development, ACD may aid cancer cells to persist in low-oxygen and low-nutrient situations, and acting as a tumor promoter [49].

The type of cancer also has a role in determining the effect of autophagy because the tumor cells' dependence on autophagy is extremely variable. Certain tumor models (like pancreatic cancer) exhibit an increase of autophagy levels in basal situations (extensive nutrient conditions), with autophagy having a role in the maintenance of tumor growth [50].

Impaired autophagy has been associatedwith genomic instability, tumor formation, and malignant transformation [51, 52]. The changes in gene expression in cancer tissue when compared to normal tissue

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have also shown a protective role of autophagy. For instance, mice having a monoallelic deletion of the autophagy-associated gene Beclin1 develop spontaneous tumors.

Allelic deletion of beclin1 had also seen in 40 to 75% of breast, ovarian, and prostate cancers [53,54]. As mention Beclin-1 induces autophagy by binding and stimulating Vps34 by a conserved domain which is essential for its tumor-suppressive activity [55]. Beclin-1, regulates these functions, by its regulators UVRAG and Bax-interacting factor-1 (Bif-1). Moreover, mice with a deficiency of Atg5 and Atg7 develop liver tumors owing to mitochondrial damage and oxidative stress, similarly, Atg7-deficient mice exhibit an accumulation of p62 and ubiquitinated protein aggregates in hepatocytes and neuron. Autophagy has also been implicated in benign hepatomas [56], and the inactivation of Beclin 1 and Atg5 was shown to increase the incidence of tumors in mice establishing that, defective autophagy can decrease the suppression of tumor [57].

UVRAG(UV Radiation Resistance-Associated Gene)-mediated activation of the Beclin1–PI(3)KC3complex excites autophagy and also suppresses the proliferation and tumorigenicity of human colon cancer cells, indicate UVRAG as an essential component of the Beclin1–PI(3)KC3 lipid kinasecomplex that is an important signaling checkpoint for autophagy[58].

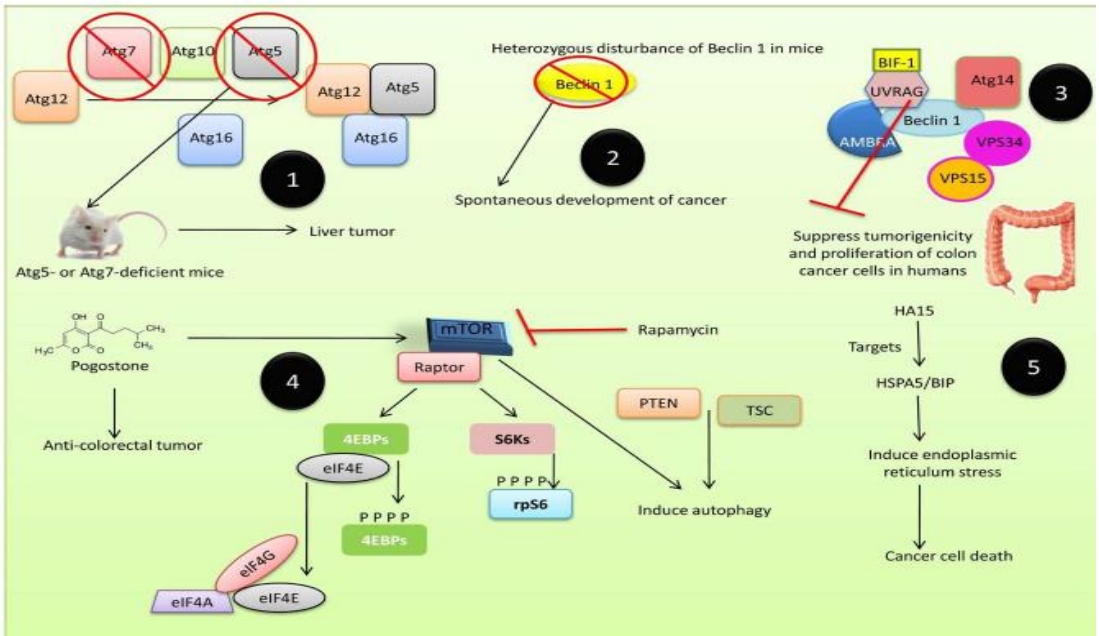

Figure3. Tumor suppression by autophagy [59]

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The novel anti-cancer molecule HA15, which targets HSPA5/BIP, was shown to induce ER stress and increase the unfolded protein response, resulting in cancer cell death via autophagy [60]. Protein kinase, mTOR, has been also implicated in cancer in another way since its substrates (eukaryotic initiation factor 4E (eIF4E)-binding proteins (4E-BPs) and ribosomal S6 kinases (S6Ks) 1 and 2) stimulate cycle progression of a cell [61] so rapamycin [62], phosphatase and tensin homolog (PTEN) are tumor suppressor genes can induce autophagy by mTOR, inhibition [63,64]. The widely used medicinal herb pogostone which used in the gastrointestinal disease revealed an anti-colorectal tumor activity by inducing autophagy and apoptosis via the PI3K/Akt/mTOR axis [65].Besides, the novel anti-cancer molecule HA15, which targets HSPA5/BIP, was shown to induce ER stress and increase the unfolded protein response, resulting in cancer cell death via autophagy and apoptosis [66].

Role of autophagy in immune response activation

It has been shown that autophagy induce tumor cells immunogenicity, being contribute in tumor antigenprocessing leading to activation of the effector T cells. Therefor several new approaches aiming at autophagy induction could act as adjuvantto increase the antitumor immune response. For example,tumor autophagosome-derived vaccines have been found to stimulate the cytotoxic immune cells and, consequently, antitumor effect in mice[67].

Novel anti-cancercompounds (autophagy inducer)

1. mTOR Inhibitors

mTOR inhibitor can induce autophagy by various mechanisms which makes it appropriate for combined therapies [68] Temsirolimus or cell cycle inhibitor-779 (CCI779), has shown to inhibit tumor growth in vitro in adenoid cystic carcinoma [69] Everolimus (or RAD001), developed for oral administration, has shown to induce cell cycle arrest through autophagy-mediated degradation of cyclin D1 in breast cancer cells[70].mTOR inhibitors may act by completion with ATP, blocking phosphorylation of target proteins, causing a more inhibition of mTOR[71].

2. BH3 Mimetics

Gossypol is a BH3 mimetic isolated from cotton that has a great affinity for Bcl-2, Bcl-XL, Mcl-1, and Bcl-w. Obatoclax (GX15-070) is another BH3 mimetic that has shown autophagic-mediated

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necroptosis in oral squamous cell carcinoma rhabdomyosarcoma cells and acute lymphoblastic leukemia cells [72].

3. Natural compound

Cannabinoids have shown potent anticancer effects related to autophagy [73] by mTORC1 inhibition and autolysosome permeabilization with the subsequent release of cathepsins and posterior induction of apoptosis [74,75] JWH-015 is a synthetic cannabinoid CB2 receptor-selective agonist that has shown to inhibit tumor growth through inhibition of Akt/mTORC1-pathway through AMPK activation [76]. Resveratrol has been shown to inhibit cell proliferation in breast cancer stem-like cells via suppressing the Wnt/b-catenin signaling pathway [77]. δ-Tocotrienol have vitamin E that has shown cytotoxic effects against prostate cancer cells in vitro through autophagy activation via ER stress [78]

Curcumin induces autophagy, depending on the concentration and duration of the treatment [79]. The combination of Vitamin D with radiation promoted cytotoxic autophagy in breast tumor cells [80, 81]. Resveratrol and curcumin caused cell death in several human tumor cell lines through apoptosis and autophagy[82, 83].

Conclusion

Currently, autophagy was received wide attention and become an excellent novel target that many clinical trials have been developed. It is a complex pathway fall under the control of several internal regulations, so understanding this and the main genes responsible for regulation are the cornerstone. The dual role of autophagy in cancer therapy may be a great challenge in anticancer drug discovery. There are broad agreements with the cytoprotective effect of autophagy inducers, particularly in the early stages. On the other hand, it induces tumor cells resistant to chemotherapy, contributing to tumorigenesis and progression in advanced stages. However which autophagy upregulation or downregulation was the target, depending on many factors such as cancer type, the stage, and the genetic background. Many issues should be studied intensely such as the diagnosis and markers, hoping autophagy modulation become reality in the medicine for the treatment of cancer.

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