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An updated review on implications of autophagy and apoptosis in tumorgenesis; Possible alterations in autophagy through engineered nanomaterials and their importance in cancer therapy

Running title: Autophagy and Nanomaterials in Cancer Therapy

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Abstract

Most commonly recognized as a catabolic pathway, autophagy is a perplexing mechanism through which a living cell can free itself of excess cytoplasmic components, i.e., organelles, by means of certain membranous vesicles or lysosomes filled with degrading enzymes. Upon exposure to external insult or internal stimuli, the cell might opt to activate such pathway through which it can gain control over the maintenance of intracellular components, and thus, sustain homeostasis by intercepting the formation of unnecessary structures or elimination of the already present dysfunctional or inutile organelles. Despite such appropriateness, autophagy, might also be considered a frailty for the cell, as it has been said to have a rather complicated role in tumorigenesis. A merit in the early stages of tumor formation, autophagy appears to be salutary due to its tumor-suppressing effects. In fact, several investigations on tumorigenesis have reported diminished levels of autophagic activity in tumor cells, which might result in transition to malignancy. On the contrary, autophagy has been suggested to be a seemingly favorable mechanism to progressed malignancies, as it contributes to survival of such cells. Based on the recent literature, this mechanism might also be activated upon the entry of engineered nanomaterials inside a cell, supposedly protecting the host from foreign materials. Accordingly, there is a good chance that therapeutic interventions for modulating autophagy in malignant cells using nanoparticles may sensitize cancerous cells to certain treatment modalities, e.g., radiotherapy. In this review, we will discuss the signaling pathways involved in autophagy, and the significance of the mechanism itself in apoptosis and tumorigenesis, while shedding light on possible alterations in autophagy through engineered nanomaterials, and the their potential therapeutic applications in cancer.

KEYWORDS: autophagy, apoptosis, nanomaterials, cancer therapy

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Significance statement

Autophagy has been said to have a complicated role in tumorigenesis. In the early stages of tumor formation, autophagy appears to be salutary due to its tumor-suppressing effects. On the contrary, autophagy has been suggested to be a favorable mechanism to progressed malignancies. This mechanism might be affected upon the entry of nanomaterials inside a cell. Accordingly, therapeutic interventions for modulating autophagy using nanoparticles may sensitize cancerous cells to certain therapies.

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1 | Introduction

Several types of cell death determine the ultimate fate of a living organism. This phenomenon is an integral part of life as it maintains homeostasis by exterminating redundant cells that may otherwise become a liability. Through the never-ending course of evolution, various mechanisms of cell death have emerged that include apoptosis, necroptosis, and autophagy-dependent cell death (Su et al. 2015; Kang et al. 2011).

A self-digestive process, type II or autophagic cell death (Gozuacik and Kimchi 2004) is one such mechanism that regulates lysosomal degradation of superfluous or erroneous materials, e.g., damaged organelles and misfolded proteins (Choi 2012). Accordingly, autophagy is a regulatory process in which cytoplasmic vesicles with multiple membranes appear inside a cell, and start engulfing bulks of cytoplasmic organelles, only to disintegrate them from the cell. These so-called autophagic bodies are subsequently degraded by the lysosomal system of the very same cell. It is believed that autophagy is fundamentally different from the ordinary turnover cycle of organelles, as it assumes a broader scope in maintenance of cellular activity in conditions, which if not counteracted, might render the organism susceptible. During this process, the cell simply cannibalizes itself from the inside (Gozuacik and Kimchi 2004). On a basal level, autophagy contributes to maintaining homeostasis by mediating the turnover of proteins and organelles; however, it can be accelerated in response to stress as a survival mechanism (Choi 2012). Based on the molecular pathways associated with the biogenesis of autophagic vesicles or autophagosomes, autophagy can be classified as canonical and non-canonical. In this regard, autophagy-related or ATG genes are also categorized into two eponymous classes, of which more than 30 members have been discovered (Rebecca and Amaravadi 2016).

Once presumed to be a survival mechanism in yeasts under starvation, autophagy has now been recognized as a universal process involved in many cell types, particularly mammalian, that plays a major part in cellular function (Zhang et al. 2009). In fact, the phenomenon is so crucial that if defected, certain ailments may arise as a consequence, e.g., infection, aging, neurodegeneration, myopathy, Crohn's disease, and malignancies (Levine 2008). In spite of all the controversies around the footprint of autophagy in malignancy, it appears that the mechanism assumes an ambivalent approach in development of tumors, as despite being a tumor-suppressive process, autophagy might contribute to the survival of malignant cells (Rosenfeldt and Ryan 2009). Besides, tumor cells can exploit autophagy to gain resistance against several antitumor agents (Chen and Karantza-Wadsworth 2009). Due to rapid proliferation and altered metabolism, cancer cells are subject to more stress and have higher metabolic

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demands (White and DiPaola 2009), that might render them more dependent on autophagy as a survival mechanism (Amaravadi et al. 2011).

As of recent, several studies have reported certain correlations between autophagy and nanotechnological interventions. Pieces of evidence have recently suggested the significance of autophagy in development of adaptive reactions to nanomaterials. However, the nature of such reactions is yet to be elucidated, as they often happen to vary with physicochemical properties of nanomaterials that become up-taken by the cells to which they are introduced. In this regard, it can be asserted that autophagy grants the cell with cytoprotective effects in response to the uptake of foreign materials, which in this case are nanomaterials (Popp and Segatori 2015).

Nanoparticles (NPs) are now recognized as novel materials with a capacity to induce autophagy (Zhang et al. 2009). Different NPs such as Quantum Dots (QD), nanowires, and the more recently studied rare earth oxides can reportedly induce autophagy in cells derived from different tissues, e.g., mesenchymal stem cells, cervical cancer cells, etc. (Zhang et al. 2010b; Stern et al. 2008; Akbarzadeh et al. 2006; Mashayekhi et al. 2020). QDs were first documented to exert size-dependent autophagy-inducing effects on human mesenchymal stem cells in 1999 (Seleverstov et al. 2006). It was only a decade later that an investigation on QDs with different core materials revealed that these particles were able to induce autophagy in porcine kidney cells, further supporting the theory that autophagy might be a common cellular response to nanomaterials. Interestingly, the effects of cellular stress on autophagy determined by cell type and the kind of stimuli (Stern et al. 2008). Another study in 2011 implicated that iron oxide NPs could be utilized for treatment of tumors as they had the potential to mediate autophagy in malignant cells (Khan et al. 2012).

A well-founded understanding of mechanisms involved in the regulation of autophagy in malignancy and their response to nanomaterials might open a new pathway toward developing novel therapeutic interventions that can modulate this pathway either directly or indirectly. The present article will discuss the most recent advancements in understanding of autophagy in malignancy and the potential regulatory role of NPs in it.

2 | Autophagy; Involved Pathways

Autophagy, also known as Type II cell death (Gozuacik and Kimchi 2004), is a conserved catabolic process that can be considered as one of the main degradative pathways of unnecessary or dysfunctional cellular components, old or misfolded proteins, and superfluous or defected organelles in eukaryotic organisms (Kondo and Kondo 2006).

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Besides, autophagy has a crucial role in eliminating pathogens and engulfing apoptotic cells (Mathew et al. 2007). Microautophagy, macroautophagy, and chaperone-mediated autophagy are three known types of autophagy, of which macroautophagy is the primary type that occurs most frequently in eukaryotic cells (Li et al. 2017). In *Saccharomyces cerevisiae*, overlapping Atg (autophagy-related) genes, including Apg, Aut, and Cvt, have been found to be involved in the autophagic pathway (Gozuacik and Kimchi 2004). Factors such as nutrient deprivation, reactive oxygen species (ROS), hypoxia, drug stimuli, aggregated proteins, and damaged organelles mainly induce autophagy, causing cells to degrade macromolecules, including proteins, lipids, and carbohydrates, in order to synthesize essential cell components (Mei et al. 2014; Choi et al. 2013).

Basal autophagy brings about protein degradation and organelle turnover, being a vital factor in intracellular quality control and sustaining homeostasis. At the same time, it has been revealed that autophagy is also triggered in stressful conditions to maintain cell survival (Choi 2012). Upon receiving the signal from the cell, a cascade of reactions occur, that result in surrounding of cytoplasmic constituents by intracellular double-membraned structures to form the autophagosomes (Levine 2007; Zhang et al. 2009).

At first, cytoplasmic constituents are enwrapped by a membrane sac to form vesicles (Gozuacik and Kimchi 2004). These vesicles subsequently fuse with lysosomes. Following the release of lysosomal digestive enzymes into the lumen of the resulting autolysosomes, the internal contents are digested by lysosomal hydrolases. The degradation products are then recycled back to the cytosol, and reused by the cell to maintain energetic homeostasis and viability (Levine 2007; Zhang et al. 2009).

In normal cells and tissues, autophagy plays a complex and tissue-dependent role (Mizushima and Komatsu 2011). As a cellular housekeeper, autophagy maintains homeostasis by eliminating inessential proteins and non-functional organelles in normal physiological conditions (Anding and Baehrecke 2017; Mathew et al. 2009). In this regard, aberrant regulation of autophagy can lead to severe conditions, including neurological disease, infection, myopathy, inflammation, aging, and a variety of cancers (Yin et al. 2016; Choi 2012). To our knowledge, the process of autophagy depends on the continuous presence of ATP along with uninterrupted protein synthesis (Gozuacik and Kimchi 2004). Figure 1 represents involved signalling pathways.

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2.1 | Phosphatidylinositol 3-kinase (PI 3K) Complex

PI 3-kinase pathway is primarily involved in the autophagy process (Petiot et al. 2000). The pathway is of crucial importance for endocytic and phagocytic trafficking, and formation of autophagic vesicles (Burman and Ktistakis 2010; Mizushima et al. 2001; Simonsen and Tooze 2009). According to several studies, 3-methyladenine (3-MA); an autophagy inhibitor, and Wortmannin; a PI 3-kinase inhibitor, can inhibit the generation of autophagosome precursors in mouse embryonic stem cells (Mizushima et al. 2001).

2.2 | Tor Kinase and Apg Expression

Considered a gatekeeper against the triggering factors of autophagy (Liang 2010), Tor kinase plays a role in Akt signaling pathway by relaying growth factor-induced signals to the main pathway of autophagy. Accordingly, Tor kinase inhibitors, e.g., rapamycin, can induce autophagy in both yeast and mammalian cells (Díaz-Troya et al. 2008). Inhibition of Tor kinase pathway is thought to increase *Apg8* expression (Kirisako et al. 1999), which is an important gene in formation and expansion of autophagic vesicles (Gozuacik and Kimchi 2004). Phosphorylation of certain proteins in this pathway coincides with suppression of autophagy in mammalian cells (Blommaart et al. 1997).

2.3 | Ubiquitin-like systems

Formation of autophagic vesicles relies on two major ubiquitin-like conjugation systems. In the more predominant systems an E1-like enzyme called “Apg7” is conjugated with Apg12, and then translocated to an E2-like enzyme, Apg10 (Shintani et al. 1999). Next, a covalent linkage is formed between the C-terminal of Apg12 and the central part of the Apg5 protein (Mizushima et al. 1998). Nearly all Apg12 molecules in cells are conjugated with Apg5. In this case, Apg12/Apg5 conjugation is not affected by stimuli, that may otherwise induce autophagy (Gozuacik and Kimchi 2004).

3 | Apoptosis

Type I cell death or apoptosis is a cellular process characterized by the fragmentation of the cell into smaller membraned structures called an “apoptotic body”, that usually succeed alterations in the nucleic material, namely, condensation of chromatin and degradation of the DNA. The remaining components of the cell are then digested by phagocytes after heterophagocytosis (Gozuacik and Kimchi 2004).

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Apoptosis is usually mediated via two different cascades, the extrinsic and intrinsic pathways, that result in degradation of cellular organelles (Nagata 2018). The extrinsic apoptotic pathway involves membranous death receptors like CD95 (FAS), TRAIL receptors, and tumor necrosis factor (TNF) receptor (TNFR) family, which bind to specific ligands such as soluble TNF. Upstream to these receptors, there are several caspases, which function to mediate the process. Caspase-8 and caspase-10 activate the effector caspases known as caspase-3, 6, and 7, resulting in final-stage molecular degradation involved in apoptosis (Andreeff 2003). Mitochondria are the central part of the intrinsic pathway of apoptosis. Pro-apoptotic molecules such as Bad, Bax, Bak, Noxa, Bid, and PUMA constitute the intrinsic apoptotic pathways. In this case, Bak and Bax can dimerize, and therefore, permeabilize the outer membrane of mitochondria. As a result, cytochrome C is released into the cytosol and interacts with apoptotic protein activating factor-1 (Apaf-1), leading to the assembly of apoptosome. This multi-protein structure can activate caspase-9 and other effector caspases (Kang and Reynolds 2009).

4 | Autophagy and Apoptosis; Possible Links and Differences

The link between autophagy, apoptosis, and other types of cell death is an area of interest to researchers (Kang et al. 2011), especially in cancer research. Apoptosis one type of programmed cell death, that can be triggered by intra- or extracellular stimuli through activation of a cascade of proteases (Nagata 2018). On the other hand, autophagy or cellular "self-eating" is a mechanism in which a section of the cell is surrounded by an especial intracellular membrane, and its contents are then digested by lysosomal enzymes (Hurley and Young 2017). Autophagy is like a double-edged sword since it is oftenly induced as a response to stress to prevent cell death through ARHI (aplysia ras homolog I) dependent pathway. Nonetheless, in some special occasions, it can serve as a means of cell death (Fulda et al. 2010).

There are contradictive data on the interaction between autophagy and apoptosis. Several stressors can trigger autophagy, e.g., apoptosis-inducing chemotherapeutic agents (Verfaillie et al. 2010), dysfunction of cellular organelles (Anding and Baehrecke 2017), starvation (Li et al. 2013b), etc. Exposure to such stressors might activate autophagy, which can restore the cell to its normal status. But, in the long-term, the cell may undergo apoptosis. It can be concluded that unlike apoptosis, autophagy is a pathway toward survival of the cell, however, should there be prolonged exposure to stress, the cell may die by means of autophagic cell death (Shen et al. 2012). Figure 2 represents the link between autophagy and apoptosis.

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4.1 | Implications in cancer

Not only are autophagy and apoptosis independent, but also they have multiplex crosstalk with each other in physiological and pathological incidents like cancer. The tumor-suppressing function of apoptosis is supported by the recent evidence (Chao et al. 2006), however, autophagy is a rather different mechanism that serves as an intricate function in the onset and development of tumors (Sun et al. 2013). Unlike apoptosis, the function of autophagy in tumor cells is partly favorable, and partly unfavorable, hence, it can both instigate and halt tumor development (Eskelinen 2011). It has been argued that cancer cells benefit from autophagy, as it enables them to survive the exposure to several tumor microenvironment stressors such as hypoxia, starvation, and metabolic stresses (Dikic et al. 2010). Besides cancer, other diseases can also be occurred with this mechanism due to the abnormal balance between autophagy and apoptosis or linkage gene concept. For instance, *Atg5* deficiency can induce apoptosis as a result of stress to endoplasmic reticulum, and lead to cardiovascular diseases (Nishida et al. 2008).

5 | Can Autophagy Hinder or Aggravate Cancer?

Defects in autophagy contribute to the etiology of many diseases like cancer (Kondo and Kondo 2006). Most studies have indicated the ambivalent nature of autophagy in cancer (Fiaschi and Chiarugi 2012). Likewise, a remarkable body of published studies have pointed to the function of autophagy in tumor suppression (Mei et al. 2014). Accumulating evidence indicates that there might be a link between cancer and autophagy at two levels of cancer progression and cancer prevention. For example, inactivation of some autophagy genes has been shown to lead to increased tumorigenesis in mice (Ni et al. 2014). On the other hand, enforced expression of certain autophagy genes was reported to prevent formation of tumors (Levine 2007). It has also been noted that autophagy can be activated in response to chemotherapeutic drugs in cancer cells (Karantza and White 2007). Table 1 and Figure 3 represent correlation between autophagy and tumorigenesis.

A series of *in vitro* experiments showed that enhanced activity of beclin 1, an autophagy-inducing protein, might reduce the proliferation of cancer cells (Liang et al. 1999). It was also revealed that down-regulation of beclin 1 might promote the tumorigenicity of Hela cells (Wang et al. 2007b). In another study, scientists were able to show that beclin 1 overexpression by RNA interference methods reduced the proliferation and migration of cancer cells, introducing this protein as a potential target for cancer treatment modalities (Sun et al. 2011b). In 2011, scientists reported that induced autophagy by means of Docosahexaenoic acid could augment the apoptosis rate by affecting

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caspase-3 function in cancer cells (Jing et al. 2011). It was only two years later that another investigation confirmed the desirable effects of Kaempferol in treatment of cancer cells, which included arrestment of cell cycle and induction of autophagic cell death (Huang et al. 2013). Several years later, it was reported that a treatment regimen comprising beclin-1-derived protein hindered the proliferation of HER2-positive breast cancer cells (Vega-Rubín-de-Celis et al. 2018). It was also shown that most important autophagy-related genes like *beclin1*, *atg5*, *bif-1*, and *atg4c* had been lost in the genome of prostate, ovarian, and breast cancer cells (Maes et al. 2013). Allegedly, a combined therapy of autophagy targeting and radiotherapy might prove to be more effective than radiotherapy alone. Accordingly, down-regulation of *beclin-1*, *atg3*, *atg4b*, *atg4c*, *atg5*, and *atg12* could sensitize cancer cells to radiation (Apel et al. 2008). Recently, cisplatin-induced autophagy in ovarian cancer was inhibited by bortezomib, a proteasome inhibitor, to increase the efficacy of chemotherapy (Kao et al. 2014). Bufalin, in a similar way, causes autophagy-mediated cell death through ROS production and enhanced radiosensitivity in human colon cancer cells (Xie et al. 2011).

Thus, it can clearly be inferred that autophagy should not be considered a definitive solution, but rather, it should be regarded as a doubtful advantage with two sides, each of which have been well supported by several investigations. (Jiang et al. 2019). Through the removal of damaged DNA and organelles in the preliminary stages of tumorigenesis, autophagy acts as a protective mechanism to maintain the integrity of the cell, and prevent instigation of malignancy (Hönscheid et al. 2014). A pivotal mechanism for migration and invasion of tumor cells, epithelial-to-mesenchymal transition (EMT) can be counteracted by induction of autophagy, thus, hindering tumorigenesis (Lv et al. 2012; Catalano et al. 2015). However, as the tumors progress in stage, autophagy assumes a seemingly paradoxical role, by delivering essential nutrients to the tumor cells through degradation of unnecessary intracellular structures, resulting in the emergence of resistant tumor cells (Cheong 2015). 118. Therefore, development of an effective autophagy-based cancer therapy for the treatment of malignancies is a rather complicated task for clinicians (Jiang et al. 2019).

For centrally located tumor cells, autophagy can be an excellent option for cancer cells to survive and continue tumorigenesis. In this case, autophagy may function as a big barrier against most routine cancer therapies (Kimmelman and development 2011). Unlike the aforementioned data, dozens of studies have revealed that autophagy is another side of the sword that can help with the maintenance of tumor cells (Gong et al. 2013; Guo et al. 2016), as it contributes to their escape from the immune system (Noman et al. 2011). Table 2 summarizes the

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autophagic genes involved in cell death, invasion and tumor dormancy (Li et al. 2020; Fernández and López-Otín 2015; Poillet-Perez et al. 2015; Flynn et al. 2019; Maruyama and Noda 2018; Galluzzi et al. 2017; Broz et al. 2013; Capparelli et al. 2012; Liang et al. 2006; Maes et al. 2014; Liu et al. 2018c; Cubillos-Ruiz et al. 2017; Xie et al. 2015; Dimco et al. 2010; Schmitt et al. 2012; Aqbi et al. 2018a; Gundara et al. 2012; Murthy et al. 2014; El Andaloussi et al. 2017; Washington et al. 2015; Cusan et al. 2018; Mathew et al. 2009; Wu et al. 2012; Kang et al. 2009; Attar-Schneider et al. 2016; Liu et al. 2018b; Su et al. 2015; Vera-Ramirez et al. 2018; Wang et al. 2007a; King et al. 2011; Karch et al. 2017; Lindqvist and Vaux 2014; Wu et al. 2013; Tong et al. 2018; Richmond et al. 2015; Chen et al. 2018a; Criollo et al. 2009).

6 | Nanotechnology

A large number of studies have been conducted on wide-ranged applications of nanomaterials (NMs), only to discover their peculiarly unfavorable effects. In terms of cell function and molecular pathway, NMs often cause profound adverse biological effects (Setyawati et al. 2013a; Tay et al. 2013; Afzalipour et al. 2019; Shirvalilou et al. 2020; Kondori et al. 2020). Nanotechnology has multiple applications with a scientific impact; however, the underlying pathways in interaction of NMs with biological systems at a molecular level still remain to be elucidated. These controversies raise concerns for utilizing nanoscale particles in targeted cancer therapies (Warheit 2010; Setyawati et al. 2013b; Sheervalilou et al. 2020; Changizi et al. 2020; Sheervalilou et al. 2021b; Shakeri-Zadeh et al. 2020; Sheervalilou et al. 2021a; Shirvalilou et al. 2021; Kafshdooz et al. 2019).

7 | The Link between Autophagy and Nanotechnology

NPs have been widely used as beneficial research tools for modulating the process of autophagy. Autophagy abnormalities are associated with several disorders, including cancer, and cardiovascular, metabolic, and neurodegenerative diseases (Ghavami et al. 2014). Hence, NP-related autophagy modulations are suggested to be a state-of-the-art therapeutic intervention for treatment of such conditions. Induction of oxidative stress-dependent signaling (ER stress, mitochondrial damage, etc.), inhibition of Akt-mTOR signaling, and alteration of the expression of autophagy-related gene/protein stand amongst the primary mechanisms by which NMs modulate autophagic pathway (Wu et al. 2014). Table 3 and Figure 4 represent the link between autophagy and nanotechnology in cancer.

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7.1 | Can NMs Turn On or Turn Off Autophagy? Which One is Preferable for Killing Tumor Cells?

The paradoxical nature of autophagy can be turned into an advantage for development of cancer treatment modalities, as the mechanism is thought to be a driving factor of early survival and late cell death in tumor progression and cancer therapy (Singh et al. 2018). Thus, the role of NMs in cancer therapy enhancement is incontrovertible (Abed et al. 2019; Beik et al. 2019; Mirrahimi et al. 2019; Ghaznavi et al. 2018; Beik et al. 2017). In last decade, inhibition of autophagy introduced as a strategic mechanism in cancer therapy. A growing number of studies are being dedicated to delineating the link between NMs and autophagy to see if NMs are exploitable tools in cancer therapies (Wei and Le 2019). Since then, an expanding number of NMs ranging from soft NMs, liposomes and polymeric NPs to hard NMs such as Cerium dioxide (CeO2 NPs), Zinc oxide, iron oxide (IONPs), silver, gold (AuNPs), and titanium dioxide NPs, QDs, carbon nanotubes (CNTs), graphene oxide (GO), Silica NPs (SNPs), and fullerenes have shown to possess remarkable properties for modulating autophagy (Zheng et al. 2016; Yu et al. 2014b; Hussain et al. 2012). Chemical composition, morphology, and surface chemistry, as well as the size of NMs, determine whether a NP is likely to trigger autophagy under certain conditions. In other words, NPs can be considered as both inducer and inhibitor of autophagy in the target cell based on their size and morphology (Zhang et al. 2018; Popp and Segatori 2015).

Nevertheless, NP-mediated autophagy is associated with nanotoxicity (Sarkar et al. 2014). To boost the therapeutic efficacy and develop safer NMs, scientists investigated the variations of CNTs surface ligand and their impact in modulating the extent to which autophagy is triggered. They reported that the surface modification of CNTs might result in potential pharmaceutical autophagy modulators and biocompatible NMs (Wu et al. 2014).

7.1.1 | Turn-on Effects of NMs

7.1.1.1 | Positive turn-on Effects: Pro-death Nature of Autophagy

Various NMs, including metallic-based NPs (Cordani and Somoza 2019) and light and heavy nanocrystals (Yu et al. 2009), can trigger autophagy. In 2005, scientists showed that nano-sized neodymium oxide (Nano Nd2O3) induced extensive autophagy in NCI-H460 human lung cancer cells (Chen et al. 2005). After that, NMs-related autophagy was generally believed to be a pro-death mechanism. The only way to acquire knowledge on the likelihood of such claims were to evaluate cell death while inhibiting autophagy. As a clarification, it was shown that both molecule inhibitors and *Atg5* gene knockdown dramatically reduced the rate of death in HeLa cells incubated with ZnO NPs,

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indicating that these NMs triggered pro-death autophagy (Hu et al. 2019). This was suggested to be a positive effect of NMs in cancer therapy through the regulation of oxidative stress and autophagy, which led to cell death. In this case, NMs served as cytotoxics and/or enhanced the efficiency of typical chemotherapies (Sun et al. 2014).

To enhance the efficiency of epidermal growth factor receptor (EGFR)-oriented triple-negative breast cancer (TNBC) therapy, scientists developed EGFR-targeted AuNPs to induce autophagy. In this case, autophagy induction rendered the cancer cells more susceptible to photothermal therapy (PTT) (Zhang et al. 2017b). They discovered that poly(lactic-co-glycolic acid) or PLGA-based NPs were able to trigger autophagy in tumor cells. In this modality, NPs were swallowed by autophagosomes before being delivered to degradative organelles (Zhang et al. 2014b). Modified PLGA-based NPs significantly enhanced the activity of autophagosomes compared with non-modified counterparts. In this study, induction of autophagy via docetaxel-containing NPs contributed to impaired intratumoral drug delivery (Liu et al. 2011).

In another study, redox-responsive nanohybrid GCMSNs were synthesized through GNPs attachment onto amine-functionalized MSNs. Compared to normal 3T3-L1 cells, GCMSNs induced higher oxidative stress-triggered autophagy in A549 lung cancer cells. Synergism, through the combination of chemotherapy and oxidative stress-induced autophagy via camptothecin-loaded nanohybrids, resulted in a superior nanocarrier system for highly effective cancer therapy (Lu et al. 2015). Despite that, autophagy-mediated cell death is still somehow challenging if the normal cells become involved as well. To address this issue, one should ascertain the selectivity of NP-based autophagy, as it must only be triggered in cancer cells.

The best targets for autophagy-mediated therapy are autophagy-deficient cancer cells. Lack of beclin-1 protein required for initiation of autophagosome formation in autophagy is a determining factor. Therefore, designing autophagy-inducing peptides engineered into polymeric NPs (P-Bec1) could significantly enhance autophagy-mediated cell death in these cells (Wang et al. 2015a).

NP-induced autophagy sometimes appears to be useful for cancer therapy, especially against drug-resistant variants, if it were coupled with autophagy-mediated chemosensitization. Fullerene c60, which induces autophagy in tumor cells, was reported to enhance the chemosensitization of both normal and drug-resistant cancer cells. Thus, the subsequent reduction in drug resistance may eventually establish novel therapeutic strategies for cancer treatment (Wei et al. 2010).

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7.1.1.2 | Negative turn-on Effect: Pro-survival Nature of Autophagy

To form a verdict on nano-related autophagy-inducing effect in cancer therapy from another perspective, it is appropriate to note the ineffectiveness of Chemo-PTT combination therapy approach in drug-resistant cancer. Turning on the pro-survival autophagy is thought to be a great solution to this issue. With a high absorption in the near-infrared (NIR) region, NMs can also induce pro-survival autophagy. The recent application of custom designed copper (Cu)-palladium (Pd) alloy tetrapod NPs in Chemo-PTT is considered a novel approach, that combines chemotherapy and PPT. Thanks to their unique structure, these NPs elicited an ideal photothermal conversion potential and induced pro-survival autophagic cell death. This achievement paved the way for application of custom-designed NPs as autophagy suppressing agents rather than the conventional therapeutic agents (Zhang et al. 2018). In contrast to the most noted autophagy-related cell death by NMs, nano-sized paramontroseite VO2 nanocrystals (P–VO2) were reported to induce cytoprotective autophagy in cultured HeLa cells (Zhou et al. 2013). Furthermore, several NMs were also reported to induce pro-survival autophagy (Zhang et al. 2019).

This increased level of protective autophagy (pro-survival autophagy) could hamper anti-cancer therapies. In such cases, autophagy might function as a cellular protector against NP-induced cytotoxicity in various tumor cell lines. Therefore, autophagy inhibitors have been widely used in company with drug-delivery NMs to improve the treatment efficiency. Hence, when deciding to modulate autophagy for enhancing treatment efficiency, one should consider whether the combined regimen enhances or dampens autophagic activity in tumor cells to accurately determine the modulation method (Høyer-Hansen and Jäättelä 2008; Das et al. 2019).

7.1.2 | Turn-off Effects of NMs

In addition to the above mechanisms, a number of studies suggest that NMs are capable of perturbing autophagic pathways by inhibiting Akt-mTOR signaling or altering the expression of autophagy-associated genes/proteins (Zhang et al. 2009; Liu et al. 2011; Li et al. 2009). Therefore, compared with the well-studied NMs that induce autophagy, inhibitory types are still rare. Citric acid-capped gold, REO, and IONPs have been known as blockers of autophagic activity; however, their mechanism of action and cellular targets are still ill-defined. In a recent study, custom designed titania-coated gold nano-bipyramids (NBP/TiO2) functioned as an innovative autophagy inhibitor for sensitizing U-87 MG brain tumor cells to proteasome inhibitor-induced cell death. Moreover, nanodiamonds (NDs) were recently shown to inhibit autophagy in oxygen-deprived tumors in a synergistic manner (Wan et al.

2018). In practical terms, high levels of autophagy under hypoxia is an adaptive strategy adopted by cancer cell for survival. Therefore, NDs-related autophagy inhibition, along with oxygen deprivation, may cause significant apoptosis in HeLa cells and MCF-7 cells (Chen et al. 2018b). In a similar study led by Sun, inhibition of autophagy resulted in sensitization of MDA-MB-231 cells to conventional chemotherapeutics (Sun et al. 2016).

NMs have the potential to either induce or inhibit the autophagic pathways. Still, more research on this topic needs to be conducted to delineate the link between NMs and autophagy.

8 | Effects of NMs on Tumor Dormancy; Focusing on Involved Signaling Pathways

NPs can influence the autophagic pathway in different ways; however, their role in the induction of tumor dormancy may hinder their practical applications. Autophagy plays a crucial role in preserving tumor cells in a prolonged state of arrest and senescence, that can be followed by apoptotic cell death (Polewska et al. 2013). That is to say, autophagy may be directly associated with tumor dormancy, as the senescent cells might recover their proliferative capability, giving rise to renewed tumor growth and metastasis (Gewirtz 2009). Nonetheless, PTT therapy has limited capacity for total eradication of tumor cells, as adjacent cells could be very well damaged by mild hyperthermia. In this case, heat shock proteins would naturally be recruited to repair the damaged cells, resulting in tumor relapse, and eventually, escape of tumor from dormancy (You et al. 2019).

Dormant tumor cells often gain drug resistance that protects them against chemotherapy (Aguirre-Ghiso 2007). In 2006, scientists established a link between the activation of the p38 signaling pathway and induction of tumor dormancy. They demonstrated how enhanced activation of PERK, an RNA-dependent protein kinase, compels dormant squamous carcinoma cells to develop drug resistance (Ranganathan et al. 2006). Several newly-designed NMs were reported to activate p38 signaling, therefore, induce drug resistance (Skuland et al. 2014; Eom and Choi 2010). These NMs are conjugated to drugs, and circumvent poor drug retention into the tumor cells for efficient targeting. However, either the induction or inhibition of autophagy could have profound impacts on drug resistance reversal (Panzarini and Dini 2014). One particular investigation, in 2018, adopted hyaluronic acid-based nanoparticles for targeting tumor stem cells, in order to decrease their drug resistance as a result of dormancy. In this work, the previously known antitumor agents (e.g., camptothecin, doxorubicin hydrochloride, or curcumin) were co-delivered to malignant stem cells via four multi-layered core-shell polymeric nanoparticles, that were synthesized from different chitosan-modified polymers (Wang and He 2018).

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There is another hypothesis that argues the strict connection between inflammation and senescence, highlighting the role of chronic inflammation in awakening of dormant tumor cells (Manjili 2017). Among cytokines, IFN-γ has been shown to leave anti-tumorigenic effects, that result in arresting of cell cycle and induction of dormancy in indolent tumor cells (Aqbi et al. 2018b). NMs featuring tailored chemical properties have been used for delivering IFN-γ to tumor cells (Mejías et al. 2011). Yet, the beneficial antitumor activity of this pleiotropic lymphokine might be autophagy-independent, since little has been reported regarding this matter. Most recently, scientists developed a novel chemo-Immuno strategy towards targeted delivery of agents with high antitumor and/or anti-fibrotic potency, celastrol and mitoxantrone. In their study, mitoxantrone-responsive nanocarriers successfully curtailed the proliferation of tumor cells and further suppressed tumor invasion. The affected tumor cells remained dormant long after co-treatment with both agents, causing a sustained progression-free survival of the mice affected with desmoplastic melanoma (Liu et al. 2018a).

Nanocarriers were also utilized for the efficient delivery of dormancy-associated miRNAs to tumor cells. To this end, a group scientists opted to prepare aminated polyglycerol dendritic nanocarriers for delivering miR-200c, miR-34a, and miR-93 into MG-63 and Saos-2 osteosarcoma tumor cells. Hence, using nanomaterial-mediated delivery of microRNAs associated with tumor-host interactions might be a useful strategy to induce a dormant-like state (Tiram et al. 2016).

9 | Autophagy Mediated Multiple Drug Resistance in Chemotherapy of Cancer Cells

Characterized by the gradual development of resistance to multiple chemotherapeutic agents with different mechanisms of action by tumor cells, multidrug resistance (MDR) is an undesirable outcome of chemotherapy that may occur in several instances (Holohan et al. 2013). A major culprit responsible for a significant proportion of cancer-associated mortality, MDR commonly results in the failure of treatment. A strikingly important challenge in cancer therapy, MDR, along with tumorigenesis, were previously thought to be correlated with disruptions in the regulation of autophagy. The idea came to fruition once several investigations reported potential involvement of autophagic pathways in the emergence of MDR (Kumar et al. 2012; Li Liu et al. 2020).

According to the recent findings, autophagy my affect MDR through a number of mechanisms as explained below (Li et al. 2017):

1) Autophagy can prompt MDR as a cytoprotective mechanism (Table 4a);

- Autophagy is positively correlated with development of MDR

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- Inhibition of autophagy may enhance the effectiveness of chemotherapy in cases with MDR

2) Autophagy, when resulting in cell death, can overcome MDR (Table 4b);

3) Autophagy triggers cell death in apoptosis-deficient MDR tumor cells

4) Autophagy accelerates chemosensitization

Induced by many cancer therapies, autophagy has been suggested to improve the survival of tumor cells, and facilitate the development of MDR (Kondo et al. 2005; Amaravadi et al. 2011; Levy et al. 2017; Smith and Macleod 2019). For example, resistance to enzalutamide was counteracted by inhibition of autophagy in an investigation on prostate cancer (Nguyen et al. 2014). Likewise, in one study, inhibition of autophagy in estrogen receptor-positive breast cancer resulted in sensitization of the resistant tumor cells to the cytotoxic effects of tamoxifen (Samaddar et al. 2008; Qadir et al. 2008). Autophagy was also reported to be activated in response to Imanitinib, used for the treatment of gastrointestinal stromal tumor (GIST). In this particular case, chloroquine (CQ) was adopted to overcome autophagy, and trigger apoptosis in tumor cells (Gupta et al. 2010). A growing body of evidence suggests that autophagy is induced in response to many types of cancer therapy, hence, the development of MDR (Galluzzi et al. 2017).

Disinhibition of autophagy is often suggested to be a consequence of low mTOR activity, and is most commonly observed with therapies that target mTOR, PI3K, or AKT (Amaravadi et al. 2011). Nonetheless, one cannot certainly predict the induction of autophagy, since the extent of induction may vary in conventional and non-conventional therapies. An increased p53 activity triggered by DNA damage, due to genotoxic therapeutics such as cisplatin, may partly explain the undesirable induction of autophagy in conventional treatments, that occur as a result of the increased activity of p53-dependent regulators of autophagy, e.g., DRAM1 (Crighton et al. 2006). Nevertheless, the exact role of p53 in this context is debatable, since this tumor-suppressing protein can also inhibit autophagy (Simon et al. 2017). 25. Known to stimulate the activity of autophagy-regulating genes, namely; ATG5, LC3, etc., the induction of ATF4 and FOXO transcription factors due to ER stress response and overproduction of ROS, respectively, may explain the activation of autophagy in these instances (Warr et al. 2013; Ranganathan et al. 2006). The dual pro-apoptotic/anti-apoptotic roles of autophagy largely depends on the characteristics of tumors. In the case of MDR cancer, exerts a protective effect on tumor cells by facilitating resistance to chemotherapeutic agents. Accordingly, inhibition of autophagy might be an effective strategy to sensitize MDR tumor cells to anticancer therapies. Nonetheless, more recent evidence suggests otherwise by pointing to the unappreciated

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potential of autophagy at sensitizing MDR tumor cells to anticancer agents, and reversing MDR. Should this be the case, autophagy will inspire development of promising therapeutic modalities to overcome MDR (Li et al. 2017). Table 4 represents the studies on the pro-survival and pro-death role of autophagy in MDR of chemotherapy (Updated from (Das et al. 2019; Li et al. 2017).

10 | Conclusion and Outlook

As of this date, the exact molecular pathways involved in modulation of autophagy, and their significance in tumor formation and progression are not clearly understood. Though, as scientists suggest, autophagy is not an immutable constituent, but a rather dynamic mechanism with quite a various behavior in cell biology. We ought to clarify that due to the double-edged nature of autophagy, this regulatory mechanism can either result in induction or suppression of tumorigenesis, depending on the type and stage of tumor. An increasing number of investigations have pointed to the impact of activated autophagy on the fate of tumor cells. From one point of view, autophagy might serve as an impeccable cellular shield against tumorigenesis, which can be adopted into therapeutic strategies. On the contrary, however, the exact same phenomenon might bring about further formation of tumors, with catastrophic consequences if provoked at will, namely; secondary metastasis and tumor relapse. Nevertheless, pharmacological modulation of autophagy has allegedly led to satisfactory results in limited research areas that could imply the potential of such interventions in development of novel therapeutics for cancer treatment. In this regard, scientists have less frequently discussed the potential effects of nanomaterials in mediation of autophagy.

As of recent, newly emerging technologies have provided us with such convenience for materialization of highly specialized nanoparticles for a variety of therapeutic purposes. Much to our dismay, however, the gross production of nanoparticles has led to an incontrovertible risk of exposure for people, prompting close studies of potentially harmful effects that might be conveyed through these tiny particles. Hopefully, an expansive array of information on the process of cellular uptake of nanoparticles has been gathered, indicating that the rate of cellular internalization is possible to be controlled based on physicochemical properties of nanoparticles, i.e., size, charge, and surface properties. It is anticipated that a thorough understanding of the functional interactions between autophagy and nanoparticles will tremendously impact the design of nanomaterials in such a way that development of tunable and safe nanomaterials will no longer be a far-fetched vision.

As for nanoparticles in this respect, several concerns still remain regarding the effect of different nanoparticles on the activation/suppression of autophagy, since it can very well lead to induction/inhibition of proliferation, differentiation, and invasiveness of tumor cells. According to many studies, nanomaterials can affect autophagy in malignant cells in such a way that can be adopted for development of therapeutic modalities for treatment of this malady. For instance, in a recent investigation (which is currently in press), we demonstrated the prominent role of gold nanoparticles applied through photothermal therapy in determining the destiny of tumor cells by means of regulating autophagy. In a similar fashion, in the present paper, we have sought to advise the scientists investigating in this particular fields of these concerns. That is to say, modulation of autophagy through nanomaterials is thought to be of therapeutic value for suppressing tumorigenesis in normal tissues, and initiation of alternative cell death in compromised cells that struggle to properly kill themselves, on top of which stand malignant cells. This type of intervention can be further complemented by combining with traditional antitumor regimens to achieve a higher level of efficacy.

The complex interaction of autophagy-related pathways with the immune cells is another factor that might determine the fate of a tumor cell. Better understanding of the molecular pathways underlying the immune escape in the recent years has accelerated the development of novel immunotherapies, that aim to target molecules that would otherwise counteract the desirable antitumor immune response. Recent investigations have also highlighted the regulatory effects of autophagy on immunity through modulation of cytokine release and the function of immune cells. In return, a number of cytokines and certain types of immune cells reciprocate by affecting the autophagy itself. Accordingly, autophagy can very well be adopted for development of novel therapeutic approaches when combined with tumor immunotherapy even nanobiotechnology.

An increasing research interest in autophagy and autophagy-related cell death is evidence enough to the significance of this matter. Since the mechanism is of both physiologic and pathologic prominence, it would be best if autophagy were approached from both academic and clinical aspects. One crucial task in this field is to identify new biomarkers and develop novel tests to precisely determine the dynamic processes of autophagy in real-life samples. It is expected that such efforts will help us better understand how autophagy is modulated within tumor cells, and ameliorate the design of clinical approaches aimed at targeting this mechanism. Prospective efforts should focus more on unraveling the genetic and physiologic grounds of autophagy, that would most likely improve the therapeutic value of our knowledge regarding this type of cell death.

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AUTHOR CONTRIBUTIONS

All authors contributed in different parts of the review study.

Participated in research design: Dr. Sheervalilou R, Dr. Ghaznavi H

Conducted experiments:-

Contributed new reagents or analytic tools:-

Performed data analysis:-

Wrote or contributed to the writing of the manuscript: Dr. Ghaznavi H, Dr. Shirvaliloo M, Dr. Zarebkohan A, Shams Z, Radnia F, Bahmanpour Z, Dr. Sargazi S, Dr. Saravani R, Dr. Shirvalilou S, Dr. Shahraki O, Shahraki S, Dr. Nazarlou Z, Dr. Sheervalilou R

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest.

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Table 1. Correlation between autophagy and tumorigenesis.

Cancer prevention								
In vitro	***In vivo***	**Autophagy related genes/ Signaling pathways**	**Autophagy related gene status in cancer**	**Techniques**	**Autophagy interaction with TSG**	**Autophagy interaction with oncogenes**	**Correlation**	**Ref**
MCF-7 cells	Nude mice	Mammalian: *Bec-1* Yeast: *apg6/vps 30*	Mono-allelically deletion of *Bec-1* in 40–75% of sporadic human BC	Gene-transfer techniques to induce *Bec-1*		*Bcl-2*	*Bec-1* activation: Inhibition of proliferation of MCF7 cells and clonogenicity, Inhibition of tumorigenesis in nude mice	Liang et al.[54] (1999) (Liang et al. 1999)
Hela cells	Athymic nude mouse (SPF) bearing-human cervical cancer	*Bec-1* (17q21)	*Bec-1* monoallelically deleted in BC	*Bec-1* silencing using RNA interference	*Cas-9*	-	siRNA against Bec-1 transfectants: Promoted cell proliferation, Less apoptosis *Bec-1*-expressing cells: Promoted the autophagy cell death, Regulation of the *Cas-9* expression, Inhibition of tumorigenesis in nude mice	Wang et al.[55] (2007) (Wang et al. 2007b)
CaSki Cells	-	*Bec-1*	*Bec-1* monoallelically deleted in BC	pcDNA3.1-Bec-1 and RNA interference vector pSUPER-Bec-1	-	*VEGF* and *MMP-9*	*Bec-1* overexpression: Decreased *VEGF* and *MMP-9*, Cell cycle arrest in the G0/G1 phase, Inhibited invasion and metastasis	Sun et al.[56] (2011) (Sun et al. 2011b)
HT-29 cells, Caco-2 cells	-	*LC3-II*, *Atg5*, *Bec-1*	-	Bufalin isolated from a TCM, siRNA transfection	-	-	bufalin activated autophagy through: LC3-II accumulation, Stimulation of autophagic flux, ROS generation, JNK activation, Increased expression of *ATG5* and *Bec-1*, autophagy-mediated cell death	Xie et al.[63] (2011) (Xie et al. 2011)
SiHa, A549	-	*LC3-I* p53/AMPK/mT	-	DHA treatment,	*p53*, *Cas-3*	-	DHA treatment: Cas-3-dependent apoptosis	Jing et al.[57]

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and MCF-7 cells		OR		GFP-LC3 expression vector			and autophagy induction, p53 loss, Increased active form of AMP-activated protein kinase and decreased the activity of mammalian target of rapamycin	(2011) (Jing et al. 2011)
SK-HEP-1 cells	-	*LC3-I, Bec-1, Atg,* AMPK and AKT signaling molecules	-	Kaempferol treatment, GFP-fluorescent LC3 assays	*Cas-3*	-	Kaempferol treatment: Autophagy induction, Increased protein level of p-AMPK, LC3-II, Atg 5, Atg 7, Atg 12 and Bec-1, Inhibited the levels of CDK1, cyclin B, p-AKT and p-mTOR, G_2/M arrest, Long-term cancer prevention	Huang et al.[58] (2013) (Huang et al. 2013)
HeLa, BT-474, SKBR3, MDA-MB-361 cells	C57/B6 Becn1 knock-in Becn1F121A mice, FVB/N-Tg (MMTV neu) 202 Mul/J strain	*Bec-1/BECN1*, *LC3-I*	Allelic loss of *Bec-1/BECN1* in HER-T positive BC	Genetically engineered mutation in Becn1, GFP-LC3 mice, Tat-Bec-1 treatment (autophagy-inducing peptide)	-	*HER-2*	Mice with a genetically engineered mutation in *BECN1*: Protected from HER2-driven mammary tumorigenesis, HER2 failed to inhibit autophagy Mice under treatment with Tat-Bec-1: Inhibition of tumor growth as effectively as a clinically used HER2 TKI, Disruption of HER2/Beclin-1 binding, Robust induction of autophagy	Vega et al.[59] (2018) (Vega-Rubín-de-Celis et al. 2018)
Cancer promotion								
In vitro	**In vivo**	**Autophagy related genes/ Signaling pathways**	**Autophagy related gene status in cancer**	**Techniques**	**Autophagy interaction TSG**	**Autophagy interaction with oncogenes**	**Correlation**	**Ref**
MDA-MB-231, HTB43, HTB35, A549 and SW707 cells	-	*Bec-1*, *atg3*, *atg4b*, *atg4c*, *atg5*, and *atg12*	Irradiation-induced accumulation of autophagosomes accompanied by strong mRNA induction of the Atg in tumor cells	Blockade of each Atg through specific target siRNAs, Radiation therapy	p53	-	Short-time inhibition of autophagy along with radiotherapy: Strongly diminished accumulation of autophagosomes, Sensitization of resistant carcinoma cells to therapy	Apel et al.[61] (2008) (Apel et al. 2008)

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IGR-Heu cell line, Heu171 cell clone, B16-F10 cells	C57BL/6 mice With B16-F10– engrafted tumors	*Bec-1*, *Atg5*, *p62/SQSTM1*, *pSrc*, *pSTAT3*, *HIF-1a*	Hypoxia-induced autophagy in tumor	Inhibition of autophagy by siRNA, HCQ treatment, TRP-2 180–188 peptide vaccination	-	-	Hypoxia-induced autophagy in tumor cells: Promoted tumor cell resistance to specific CTL lysis by a mechanism dependent on pSTAT3 Simultaneous inhibition of autophagy in tumor and stimulation of the immune system, HCQ treatment: Inhibited tumor growth in vivo significantly	Noman et al.[67] (2011) (Noman et al. 2011)
TOV112D, TOV21G, OV90, SKOV3, MDAH2774, and ES2	C57BL/6 mouse	*p62*	-	Bortezomib treatment, RNA interference	-	*ERK*	Bortezomib blocked the autophagic flux through: Inducing ERK phosphorylation, Suppressing cathepsins (B), Inhibiting protein degradation in lysosomes, Enhancing chemotherapy efficacy in ovarian cancer	Kao et al. [62] (2014) (Kao et al. 2014)

(Abbreviations; MCF7: human beast carcinoma cell line, Bec-1: Beclin 1, HeLa cells: cervical cancer cells, Cas-9: Caspase 9, TSG: tumor suppressor genes, Atg: autophagy-related genes, CaSki cells: Cervical Cancer Cells, DHA: Docosahexaenoic acid, LC3-I: microtubule-associated protein 1 light chain 3, SiHa cells: cancer cells harboring wild-type p53, Cas-3: Caspase 3, SiHa cells: Human cervical cancer, SK-HEP-1 cells: human hepatic cancer cells, Her-2: human epidermal growth factor receptor 2, BC: breast cancer, TKI: tyrosine kinase inhibitor, HIF-1a: hypoxia-inducible factor, pSrc: Src kinase, CTL: cytolytic T lymphocyte, B16-F10 cells: melanoma tumor cells, HCQ*: Hydroxychloroquine*, MDA-MB-231 cells: breast cancer cells, MDA-MB-361 cells: breast cancer cells HTB43 cells: pharyngeal cancer cells, HTB35 cells: cervical squamous cell carcinoma cells, A549 cells: lung cancer cells, SW707 cells: rectum carcinoma cells, IGR-Heu: lung carcinoma cell line, TRP-2 180–188 peptide: tyrosinase-related protein-2 peptide, TCM: bufalin isolated from a traditional Chinese medicine, HT-29: human colon cancer cells, Caco-2: human colon cancer cells, ROS: reactive oxygen species, JNK: c-Jun NH2-terminal kinase, siRNA: small interfering RNA, TOV112D: human ovarian cancer cell, TOV21G: human ovarian cancer cell, OV90: human ovarian cancer cell, SKOV3: human ovarian cancer cell, MDAH2774: human ovarian cancer cell, and ES2: human ovarian cancer cell)

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Table 2. The autophagic genes involved in cell death, invasion and tumor dormancy.

Autophagic genes involved in cell death (autophagic, apoptotic)				
Gene name	**Cellular Pathway**	**Effector**	**Consequences**	**Ref.**
Dormancy activation	P53 overexpression induced by Cdkn1b	Pentose phosphate pathway destruction, Increased ROS	Cell death, Dormancy induction by IFN-b	(Liu et al. 2018b)
FasL (CD95L or CD178), TRAIL and TNF-α activation	DISC formation	Cas-3, 6 and 7 activation, Bid change into tBid	Directly cell death, Mitochondria dependent apoptotic cell death	(Su et al. 2015)
Autophagy inhibition	ATG7 depletion	Accumulation of damaged mitochondria, Increase of ROS, Increase of apoptosis	Killing of dormant cells, Has no any effect on cell metastasis and proliferation	(Vera-Ramirez et al. 2018)
Autophagy activation	TMEM166 overexpression	High LC3II/LC3I Vacuolization Mitochondria membrane permeabilization	Autophagy and apoptosis regulator (autophagic and apoptotic cell death)	(Wang et al. 2007a)
IRGM	---------	negative regulation of IFN signaling	Autophagic cell death	(King et al. 2011)
Increase of Bax and Bak1	Inactivation of BaK1 and Bax	Intrinsic pathway (mito), indirectly affect on the autophagy	Increase cancer cell apoptosis	(Karch et al. 2017; Lindqvist and Vaux 2014)
DAPK1	----------	ARHI dependent	Tumor suppressor, Apoptotic cell death	(Wu et al. 2013; Tong et al. 2018)
PTEN	Autophagy activation	PI3K/Akt inhibitiom, PI3K/AKT/mTORC1 inhibition	Tumor suppressor	(Gundara et al. 2012)
PTEN	PTEN inhibitors	Tsc1 or Tsc2, p27 and Foxo3a	Escape from dormancy	(Richmond et al. 2015; Chen et al. 2018a)
PTEN	Apoptosis modulators activation	DRAM, DAPk and DRP-1, PTEN, E93 , Akt/PKB and mTOR)، Bcl-2 family proteins ،TRAIL and bec-1	Autophagy act as upstream control of apoptosis death	(Wang et al. 2007a)
Autophagy abortion	DRAM1 overexpression	By p53	Apoptotic death	(Criollo et al. 2009)
Autophagic genes involved in invasion (colonization, proliferation, tumor formation, promotion, metastasis)				
Gene name	**Cellular Pathway**	**Effector**	**Consequences**	**Ref.**
ATG5 and ATG7- RAS	Increased autophagy	Mitochondria activation	Tumor formation	(Li et al.

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				2020; Gundara et al. 2012)
Autophagy inhibition	Cas-3/ATG16L1 complex formation	Sustained intracellular stress and pathogen	Disease or tumor promotion	(Murthy et al. 2014)
Autophagy deficiency	ATG4D deficiency	Intracellular LC3-B/P62 accumulation, Autophagosome formation abortion	Disease and tumor promotion	(El Andaloussi et al. 2017)
Autophagy activation	ATG5/7 increased	----------	Increase in colonization	(Washington et al. 2015)
Autophagy activation	p27Kip1 coaded by CDKN1B	CDK-dependent kinase inhibitor	Tumor promotion	(Cusan et al. 2018)
Autophagy deactivation	ATG3/7/p62 targeting	Pfkfb3 normal expression	Tumor re-proliferation	(Flynn et al. 2019; Mathew et al. 2009)
STAT1 inhibition	p27 (CDKN1B), p21(CDKN1A) upregulation	Increase in IDO1 and Kyn receptors, Rb hypophosphorylation, suppress E2F transcription factor activity	Tumor dormancy, Increase in colony formation, Decrease in proliferation	(Wu et al. 2012)
ATG9B	Autophagy deregulation	----------	Tumorigenesis	(Li et al. 2020; Kang et al. 2009)
Autophagy manipulation	eIF4E/eIF4GI knockdown	Decrease in ERα, SMAD5, NF-kB, CyclinD1, c-MYC, and HIF1α	Decrease in EMT promoter, Increase in EMT inhibitors, Decrease in migration capability	(Attar-Schneider et al. 2016)
Autophagic genes involved in Dormancy (suppression, inhibition, resistance to anoikis, invasiveness and colonization, recurrence)				
Gene name	**Cellular Pathway**	**Effector**	**Consequences**	**Ref.**
Activation of Nix/ BNIP3L+ GABARAPL1+ GABARAP	Autophagy activation and Deletion of damaged Mitochondria	Increase ROS	Tumor suppression	(Poillet-Perez et al. 2015)
ATG5 and ATG7 deletion	Autophagy inhibition	Oxidative stress, Damaged Mitochondria	Tumor suppression	(Flynn et al. 2019)
ATG16L1, Bec-1 and LC3-II degradation	Autophagy deficiency	Oxidative stress Damaged Mitochondria, Inflammation (IL-1β و IL-18)	Tumor suppression	(Fernández and López-Otín 2015; Maruyama and Noda 2018)
High Atg4B	Autophagy inhibition	LC3-PE degradation, LC3 sequestration in cytosol	Tumor suppressive	(Galluzzi et al. 2017)
Autophagy activation	DNA damage	Atg4a and Atg4c/p53 contribution	Tumor suppression by p53-mediated apoptosis	(Broz et al. 2013)
Autophagy deficiency	ATG16L1 overexpression (non-specific organs)	----------	Tumor formation suppression	(Capparelli et al. 2012)
Autophagy deficiency	UVRAG upregulation	----------	Tumor suppression	(Liang et al.

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				2006)
Autophagy deficiency	ATG5 and ATG12 deficiency	Decreased of survival capacity to metabolic stress	Tumor suppression (Decrease in colonization and survival capability)	(Maes et al. 2014)
Dormancy activation	P53 overexpression induced by Cdkn1b	Pentose phosphate pathway destruction, Increased ROS	Cell death, Dormancy induction by IFN-b	(Liu et al. 2018c)
ER stress	K-RAS dependent Eif2ak3$^{-/-}$ MEFs	Decrease in VCIP and PDGFRB (angiogenic stabilizer)	Tumor suppression, ECM destruction, Vast hemorrhage	(Cubillos-Ruiz et al. 2017)
BBC3/ HSPA8(HSC70) complex formation	CMA	Cargo delivery to lysosome	Tumor protection by autophagy	(Xie et al. 2015)
IFN-γ/STAT1 activation	Downregulation of Cyclin E,A, D1,2,3	Downregulation of CDK4 and CDK6	Cell cycle arrest, Cancer cell dormancy	(Dimco et al. 2010; Schmitt et al. 2012)
Inherent ATG5 or autophagy KO	Intracellular inherent autophagy	Postpone of recurrence	Recurrence, chemotherapy desensitization, increase of dormancy frequency	(Aqbi et al. 2018a)
ER stress	EIF2AK3 suppression	Upregulation of FGF2 ،VEGF and IL-6, Downregulation of THBS1, CXCL14, and CXCL10	Suppression of angiogenesis and tumor promotion Tumor suppression	(Cubillos-Ruiz et al. 2017)

(Abbreviations; ATG5: autophagy-related gene5, Atg4B: autophagy-related gene4B, ATG7: autophagy-related gene7, Atg4a: autophagy-related gene4a, ATG12: autophagy-related gene12, Atg4c/p53: autophagy-related gene4c/Tumor Protein p53, ATG4D: autophagy-related gene4D, ATG5/7: autophagy-related genes5/7, ATG9B: autophagy-related gene9B, ATG3/7/p62: autophagy-related gene3/7/Sequestosome1, ATG7-RAS: autophagy-related gene7-Rat Sarcoma, ATG16L1: autophagy-related gene16L1, Akt/PKB: Protein Kinase B, ARHI: aplysia ras homolog I, Bid: BH3 Interacting Domain Death Agonist, Bax: BCL2 Associated X, Bak1: Bcl2 antagonist killer, Bcl-2: B-cell Lymphoma 2, bec-1: beclin-1, BBC3/HSPA8(HSC70): Bcl-2-binding component 3/Heat shock 70 kDa protein 8, Cas-3: caspase3,Cas-6: caspase6, Cas-7: caspase7, Cas-3/ATG16L1: caspase3/autophagy-related gene16L1, CDKN1B: Cyclin-dependent kinase1B, CD95L: CD95 ligand, CD178: Fas ligand or CD95L, c-MYC: Avian myelocytomatosis virus oncogene cellular homolog, CMA: Chaperon mediated autophagy, CDK4: cyclin-dependent kinease4, CDK6: cyclin-dependent kinease6, CXCL14: C-X-C motif chemokine 14, CXCL10: C-X-C motif chemokine 10, DISC:, DAPK1: Death-Associated Protein Kinase 1, DRAM: Damage-regulated Autophagy Modulator, DAPk: Death-Associated Protein Kinase, DRP-1:dynamin-related protein1, CDKN1B: cyclin-dependent kinease1B, CDKN1A: cyclin-dependent kinease1A, DNA: deoxynucleic acid, E93: transcription *factor E93*, E2F: Transcription Factors, eIF4E/eIF4GI: Eukaryotic translation initiation factor 4E/ Eukaryotic Translation Initiation Factor 4GI, ERα: Estrogen receptor alpha, EMT: epithelial-mesenchymal transition, ER: endoplasmic reticulum, Eif2ak3$^{-/-}$MEFs: Eukaryotic translation initiation factor 2-alpha kinase 3-/- Mouse Embryonic Fibroblasts, ECM: extra cellular matrix, EIF2AK3: Eukaryotic translation initiation factor 2-alpha kinase 3, FGF2: fibroblast growth factor 2, Foxo3a: Forkhead box O3, FasL: FasL or CD95L or CD178, GABARAPL1: Gamma-aminobutyric acid receptor-associated protein-like 1 precursor - Homo sapiens, GABARAP: Gamma-aminobutyric acid receptor-associated protein, HIF1α: Hypoxia-inducible factor 1 alpha, IFN-b: *interferon-beta*, IFN: *interferon*, IDO1: indoleamine 2,3-dioxygenase 1, IRGM: immunity-related GTPase M, IL-1β: Interleukin 1 beta, IL-6: Interleukin6, IL-18: Interleukin18, IFN-γ/STAT1: *interferon*-gamma/Signal transducer and activator of transcription1, Kyn: kynurenine, K-RAS: Ki-ras2 Kirsten rat sarcoma, KO: knocked out, LC3II/LC3I: microtubule-associated protein light chain 3II/ microtubule-associated protein light chain 3I, LC3-B/P62: microtubule-associated protein light chain

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3-B/ Sequestosome1, LC3-PE: microtubule-associated protein light chain 3- phosphatidylethanolamine, Mito: Mitochondria, mTOR: mammalian target of rapamycin, NF-kB: nuclear factor kappa-light-chain-enhancer of activated B cells, Nix/BNIP3L: NIP-like protein X/ BCL2 Interacting Protein 3 Like, P53:tumor suppressor protein p53, PTEN: Phosphatase and tensin homolog, PI3K/Akt: Phosphatidylinositol-3-Kinase/Protein kinase B, PI3K/AKT/mTORC1: PI3K/Akt: Phosphatidylinositol-3-Kinase/Protein kinase B/mammalian target of rapamycin, p27: Cyclin-dependent kinase inhibitor 1B, p27Kip1: p27Kip1, Pfkfb3: 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase-3, p27: Cyclin-dependent kinase inhibitor 1B, p21: cyclin-dependent kinase inhibitor 1, PDGFRB: platelet derived growth factor receptor beta, ROS: reactive oxygen species, Rb: Retinoblastoma Protein, STAT1: Signal transducer and activator of transcription1, SMAD5: receptor-regulated SMAD, THBS1: thrombospondin 1, TRAIL: TNF-related apoptosis-inducing ligand, TNF-α: tumor necrosis factor-α, tBid Cdkn1b: truncated Bid Cyclin-dependent kinase inhibitor 1B, TMEM166: transmembrane protein 166, Tsc1: Tuberous sclerosis 1, Tsc2: Tuberous sclerosis 1, UVRAG: UV Radiation Resistance Associated, VCIP: vasoactive intestinal peptide, VEGF: Vascular endothelial growth factor**)**

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Table 3. Interaction between nanotechnology and autophagy in cancer.

I. Turn on effects of NMs; Pro-death nature of autophagy								
In vitro	***In/ex vivo***	**NPs**	**Size**	**Concentration**	**NPs treatment Effect**	**Mechanism**	**Approach**	**Ref**
NCI-H460 cells	-	Nano Nd2O3	Mean diameter : 80 nm	μM equivalent concentration range (40-45 μM)	Cytotoxic effects, Apoptosis induction, Autophagic cell death	Massive vacuolization induction, S-phase cell cycle arrest, Mild disruption of mitochondrial membrane integrity, Inhibition of proteasome activity	Therapy	(Chen et al. 2005)
-	-	nC60(Nd)	-	-	Induced autophagy and sensitized chemotherapeutic killing of tumor cells in both normal and drug-resistant cancers	Enhancing the cytotoxicity of chemotherapeutic agents and reducing drug resistance	Therapy	(Wei et al. 2010)
A549 cells, NCI-H1975 cells	Balb/c mice	f-SWCNTs	-	5% COOH-CNT	COOH-CNT; In vitro: Autophagy-induced cell death, In the presence of autophagy inhibitor (3MA), ATG6 or TSC2 siRNA: Increase in cell viability in vivo: Acute lung injury	*In vitro* (COOH-CNT): Formation of autophagosomes, LC3-II upregulation, Significant decrease in the phosphorylation of mTOR, mTOR's substrate S6 and Akt	Autophagy-blocking reagents as potential agents to remedy the ALI induced by NMs	(Liu et al. 2011)
A549 cells, IMR-90	-	IONPs	Size range: 30-65 nm, average size: 51.34 ± 14.71 nm	10-100 μg/ml	Selective autophagy-induced cell death	Autophagy correlated with ROS production and mitochondrial damage, AMPK/mTOR/PI3K/Akt pathway regulation by a significant reduction in phosphorylated mTOR, Akt, and p70S6K levels, Significant increase in phosphorylated APMK	Therapy	(Khan et al. 2012)
MCF-7 cells	Xenograft	PLGA NPs	100-150 nm in	*In vitro*: DOX: 0.25-25	Significant enhancement of therapy efficacy	Cancer cells captured PLGA NPs and	Clinical applicat	(Zhang et al.

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	SCID mice model		diameter	mg/mL, 3-MA: 10 mM, CQ: 30 mM, Drug free PLGA NPs: at the same NPs concentration, IC50: PLGA NPs: 38.27 ± 1.23, 3-MA: 6.7 ± 1.05, CQ:4.78 ±1.75 mg/mL *In vivo:* 10 mg DTX/kg, 20. 50 mg/kg CQ	through combined cholic acid conjugated DOX-PLGA NPs with autophagy inhibitors (3-MA and CQ)	degraded by auto-lysosomes	ion	2014b)
A549 cells, 3T3-L1	A549 lung cancer xenografted nude	GCMSNs: GNPs+ MSNs, CPT-loaded GCMSNs)	GNPs : 5 nm in diameter NMSNs: 200 nm	*In vitro:* 100 mg/mL *In vivo:* CPT-loaded GCMSN; CPT concentrations : 2.8, 5.6, 11.2 mM GCMSN: 1, 2 and 4 mg/mL	Growth inhibitory effect, Oxidative stress-triggered mitochondria-mediated autophagy	Up-taken GCMSNs: blocking pores and inciting production of ROS, mitochondrial dysfunction, oxidative stress-triggered mitochondria-mediated autophagy, GNPs: as an oxidative stress elicitor	Selective and effective cancer combined chemotherapy	(Lu et al. 2015)
MDA-MB-231 (cultured TNBC cells)	Female BALB/c nude mice with xenograft tumors	GNs, Anti-EGFR-GNs	10 nm × 40 nm	120 pM	Anti-EGFR-GNs-combined NIR-PTT: Autophagy-induced cell death	*in vitro:* Formation of a large number of autophagic vesicles, Significant increase in autophagy-specific proteins; LC3, p62, Bec-1, Atg5, Inhibition of AKT-mTOR signaling pathway *In vivo:* Increased LC3 and Bec-1 levels	Combined targeted therapy	(Zhang et al. 2017b)

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Dox-resistant MCF-7 cell line, MCF-7/ADR HeLa cells, 4T1 cells	4T1 tumor-bearing female BALB/c mice	ZON	Average size: 172 nm, = Zetapotential: −5.01 m	*In vitro:* 50 μg mL−1, 100 μg mL−1, *In vivo:* 2 mg kg^{-1}	Killed tumor cells, Enhanced tumor chemotherapy both normal and drug-resistant cancer cells, Overcame drug resistance	*In vitro:* Promoting Atg5-regulated autophagy flux, Accelerating zinc ion release, Accelerating the intracellular dissolution of ZONs, ROS generation *In vivo:* The antitumor therapeutic effect of co-treatment with ZONs or free DOX treatment	Adjunct chemotherapy	(Hu et al. 2019)
Pro-survival nature of autophagy								
In vitro	***In/Ex vivo***	**NPs**	**Size**	**Concentration**	**NPs treatment Effect**	**Mechanism**	**Approach**	**Ref**
HeLa cells	-	P-VO_2	-	-	Induced cyto-protective, rather than death-promoting, autophagy in cultured tumor cells	Up-regulation of HO-1 and protecting cells against death under stressful situations	Therapeutic applications	(Zhou et al. 2013)
4T1, MCF7/MDR cells	BALB/c mice, NOD/SCID, mice Human breast infiltrating ductal carcinoma specimens	Cu-Pd alloy TNP-1	TNPs: ~50 nm in length, SNP: 35 nm	*In vitro:* 0.5 mg mL−1 *In vivo:* 1.5 mg CuPd TNPs per kg	Induced pro-survival autophagy in tumor cells, Increased cell viability	Normal autophagy flux without impairment of lysosomal function	Autophagy-inspired chemo-PTT of drug-resistant tumor cells	(Zhang et al. 2018)
II. Turn off effects of NMs;								
HeLa cell, HEK293 cells	Tumor-bearing mice	NDs	Primary particle size: 10 nm, hydrodynamic size; in water: 191nm in cell culture:	20-50 μg/mL	Suppressed autophagic flux in cultured cells tumors	Selective induction of PCD in hypoxic cancer cells, Minimal impairment of lysosomal functions, Significant accumulation of in LC3-II and P62, Significant increase in protein levels of Cas-3	Targeted anti-angiogenic therapy	(Chen et al. 2018b)

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			289 nm					
Breast CSCs, ALDHhi, MDA-MB-231, MCF-7 cells	Orthotopic tumor murine model, ICR mice and female NOD/SCID mice	NPCQ, NPDOX, NPDTXL, NPDOX/CQ, NPDTXL/CQ	Similar diameter of about 110 nm	*In vitro:* 1-15 μg/mL, *In vivo:* 6.5, 1 and 2 mg/kg	Inhibited nanoparticle-mediated autophagy, Reduced "stemness" and increased susceptibility to chemotherapy drugs	Impairment of endosomal acidification, blocking endosome and autophagosome fusion with lysosomes, Increasing accumulation of LC3-II and p62	Effective therapy	(Sun et al. 2016)
U-87 MG cells	-	NBP/TiO2 nanostructures, CTAB-Capped Au NBPs, Au NBP/TiO2 Nanostructures	Lengths: 47 ±4, 95 ±5, 142 ±8 nm, Widths: 20 ±2, 33 ±2, 42 ±3 nm	30 or 60 μg Au mL-1	Inhibited Autophagic flux leading to cancer cell death	Significant autophagosome accumulation in cancer cells via blocking the autophagosome-lysosome fusion process, inhibiting lysosomal degradation, Reducing the mature cathepsin B, Inhibiting the proteolytic activity of cathepsin B, Inhibiting trypsin-like proteolytic activity, UPS inhibition, Synergistic loss of brain cancer cell viability by combination of Bortezomib and PTT	anticancer agent	(Wan et al. 2018)

(Abbreviations; NCI-H460 cells: non-small cell lung cancer cells, Nano Nd2O3: nano-sized neodymium oxide, μM: micromolar, NSCLC: non-small cell lung cancer, ZON: zinc oxide nanoparticles, ROS: reactive oxygen species, DOX: doxorubicin, Anti-EGFR-GNs: epidermal growth factor receptor-targeted gold nanorods, NIR-PTT: near infrared-photothermal therapy, TNBC: triple negative breast cancer, LC3: microtubule-associated protein light chain 3, Bec-1: beclin-1, Atg5: autophagy-related gene5, PLGA NPs: poly(lactic-co-glycolic acid, CQ: chloroquine, DOX: Docetaxel, f-SWCNTs: Functionalized single-walled carbon nanotubes, A549 cells: human lung adenocarcinoma, ALI: acute lung injury, NMs: nanomaterials, Cu-Pd alloy TNP-1: copper-palladium alloy tetrapod nanoparticles, Chemo-PTT: chemotherapy with photothermal therapy, 4T1: triple-negative, drug-resistant MCF7/MDR, SNP: spherical nanoparticle, TNP: tetrapod nanoparticles, GNPs: gold nanoparticles, MSNs: mesoporous silica nanoparticle, NMSNs: amino-functionalized MSNs, 3T3-L1: normal cells, CPT: camptothecin, ROS: reactive oxygen species, IONPs: iron oxide nanoparticles, IMR-90: normal human lung fibroblast cells, AMPK: AMP-activated protein kinase, nC60: water-dispersed nanoparticle solution of derivatized fullerene C60, P–$VO_{2:}$ nano-sized paramontroseite VO_2 nanocrystals, HO-1: heme oxygenase-1, NBP/TiO2: titania-coated gold nano-bipyramid nanostructures, UPS: ubiquitin–proteasome system, PPT: photothermal therapy, NDs: nanodiamonds, PCD: programmed cell death, Cas-3: caspase-3, CSC: cancer stem cells, HEK293: human embryonic kidney 293 cells)

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Table 4. The studies on the pro-survival and pro-death role of autophagy in MDR of chemotherapy

a. The pro-survival role of autophagy in MDR of cancer				
Type of cancer	**Cell line**	**Intervention/Drug**	**Methods or Molecular Mechanism to study autophagy**	**Ref**
Gastric cancer	SGC7901 (Vincristine-resistant)	miR-23b-3p	siRNAs (Atg12, HMGB2), CQ	(An et al. 2015)
Esophageal cancer	Esophageal cancer cells (Drug-resistant)	5-FU	siRNAs (Beclin1, Atg7), 3-MA	(O'Donovan et al. 2011)
Breast cancer	MDA-MB-231 cells (Epirubicin-resistant)	Epirubicin	CQ	(Zhang et al. 2016)
	MCF-7 cells (Adriamycin-resistant)	Docetaxel	CQ	(Shi et al. 2015)
	MCF-7 cells (Adriamycin-resistant)	DOX	CQ	(Gao et al. 2017)
	MCF-7 cells MDA-MB-231 cells	Capsaicin	P38 and ERK	(Choi et al. 2010)
	SKBR3 cells	Trastuzumab	↑autophagic flux	(Vazquez-Martin et al. 2009)
	JIMT1 cells	Lapatinib, Gefitinib, Erlotinib, Trastuzumab	↑Atg12 transcripts	(Cufí et al. 2012)
	MCF-7 cells	Epirubicin	↑Bec1	(Sun et al. 2011a)
	BT549 cells MDA-MB-468 cells	Anthracycline	↑LAPTM4B	(Li et al. 2011)
	MCF-7 cells T47D cells MCF-7-HER2 cells	Tamoxifen	↑Atg5, Atg-7, and Bec1	(Qadir et al. 2008)
	MDA-MB-231 cells	Taxol group	mTOR pathway inhibition	(Notte et al. 2013)
	MDA-MB-231 cells MDA-MB-436 cells	Carboplatin	↑ATG7 by HSF1	(Desai et al. 2013)
	MCF-7 cells	Bortezomib	autophagy induction through ATF4	(Milani et al. 2009)
	MDA-MB-231 cells	DOX	eEF-2K induction	(Tekedereli et al. 2012)
	MCF-7 CSCs	Ginsenoside F2	Atg7 elevation	(Mai et al. 2012)
	MDA-MB-231 cells	Paclitaxel	↑autophagy, ↑clearance of damaged mitochondria	(Wen et al. 2015)
	MDA-MB-231 cells	Radiation	TAK1 activation	(Han et al. 2014)
	MCF-7 cells	CSTS203	↑Bec1 expression	(Wang et al. 2014a)
Prostate cancer	PC3 cells (PTEN-deficient)	Ursolic acid	siRNAs (Atg5, Bec1), 3-MA	(Shin et al. 2012)
	PC3 cells Rv1 cells	BITC	mTOR signalling inhibition	(Lin et al. 2013)
	LNCaP cells, PC-3 cells	Sulphoraphane	Mitochondria-derived ROS	(Naponelli et al. 2015)
	PC-3 cells	Ursolic acid	Inhibition of Akt/mTOR pathway	(Shin et al. 2012)

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	PC-3 cells	Piperlongumine	inhibition of Akt/mTOR pathway through ROS	(Makhov et al. 2014)
Ovarian cancer	ovarian cancer cells (Cisplatin-resistant)	FTY720	Baf A1, siRNAs (Bec1, LC3)	(Zhang et al. 2010a)
	ovarian carcinoma SKVCR (VCR-resistant)	Vincristine	CQ, 3-MA	(Liang et al. 2016)
	A2780	VP-128	↓AKT/mTOR pathway	(Brasseur et al. 2013)
	RMG-1 cells, OV90 cells, OV433 cells, OVCA420 cells, CAOV3 cells	Cisplatin	ERK pathway activation	(Wang and Wu 2014)
Cervical Cancer	HeLa cells	TAW	↑Bec1	(Zhang et al. 2015)
	Hela cells	Paclitaxel	ER stress-mediated	(Xu et al. 2015)
	Hela cells	Paclitaxel	Warburg effect-activated HIF1-α-mediated	(Peng et al. 2014)
Glioblastoma	glioma cell lines (PTEN-deficient)	PI-103	Baf A1, 3-MA, siRNA (Atg5)	(Fan et al. 2010)
	U251MG cells U87MG cells	Gambogic acid	Atg5, ↑Bec1	(Luo et al. 2012)
	U251 cells	ZD6474	PI3K/Akt/mTOR signalling inhibition	(Shen et al. 2013)
	T98G cells U251 cells	Cucurbitacin I	AMPK activation, ↓PI3K/Akt pathway	(Yuan et al. 2014)
	U87MG cells T98G cells U373 cells	Bevacizumab	↑(HIF-1α)/AMPK pathway	(Hu et al. 2012)
	C6 glioma cells	Caffeic acid phenethyl ester	AMPK and MAPKs pathway phosphorylation	(Yu et al. 2011)
	U251 cells	Cisplatin	↑autophagy through Chloride channel-3	(Su et al. 2013)
Leukemia	CML cells (Imatinib-resistant)	SAHA	CQ	(Carew et al. 2007)
	K562 cells	Perifosine	↑Atg5	(Tong et al. 2012)
	K562 cells	Daunorubicin	ERK activation	(Han et al. 2011)
	K562 cells, KU812 cells	Asparaginase	Akt/mTOR and ERK	(Song et al. 2015)
	Nalm-6 cells	Bortezomib	Bcl-2/Bec1 complex disruption	(Wang et al. 2015b)
Melanoma	melanoma cells (B-Raf inhibitor-resistant)	B-raf inhibitors	HCQ	(Ma et al. 2014)
Lung cancer	A549/DDP cells (Cisplatin-resistant)	Cisplatin	3-MA	(Ren et al. 2010)
	HCC827 cells, HCC4006 cells	Gefitinib	↑autophagic flux	(Sakuma et al. 2013)
	H23 cells, H1975 cells,	Erlotinib	LC3A activation	(Nihira et al. 2014)

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	A549 cells			
	A549 cells	Pterostilbene	ERK activation and both the AKT and JNK pathways inhibition	(Hsieh et al. 2014)
	H3122 cells	Crizotinib	AKT/mTOR pathways alteration	(Ji et al. 2014)
	A549 cells	Paclitaxel	↓miR-17-5p	(Chatterjee et al. 2014)
	A549 cells	Green tea extract	↑autophagic flux	(Izdebska et al. 2015)
	95D cells	Cucurbitacin E	AKT/mTOR pathway regulation through ROS	(Ma et al. 2016)
	A549 cells	Radiation	↓ROS under hypoxia	(Chen et al. 2017)
	A549 cells	Cisplatin	Hypoxia induction	(Wu et al. 2015; Lee et al. 2015)
Colorectal cancer	DLD-1 cells, HT-29 cells, Colon26 cells	Adiponectin	AMPKα and PPARα activation and of IGF-1/PI3K/Akt/mTOR pathway inhibition through Glucose deprivation	(Habeeb et al. 2011)
	HCT116 cells, SW620 cells, C26 cells	Gambogic acid	inhibition of Akt-mTOR signalling by ROS	(Zhang et al. 2014a)
	SW480 cells	NVP-BEZ235	PI3K/mTOR signalling inhibition	(Yang et al. 2016)
	HT-29 cells, RKO cells, Caco2 cells	PLX4032	AMPK activation	(Sueda et al. 2016)
	HT-29 cells	Huh7, HCT116	AMPK/Ulk1 signaling activation	(Min et al. 2014)
	RKO cells, HCT116 cells, SW480 cells	Aspirin	AMPK activation and mTOR inhibition independently	(Din et al. 2012)
	Huh7 cells, HCT116 cells	Atorvastatin	activation of p21 and ER stress via AMPK	(Makhov et al. 2014)
Hepatocellular carcinoma	MHCC97-L cells, PLC/PRF/5 cells, HepG2cells	Sorafenib	↑IRE1 pathway through ER stress signalling	(Shi et al. 2011)
	Huh7 cells, SMMC-7721 cells	Oxaliplatin	ROS modulation	(Ding et al. 2011)
	HepG2 cells	Capsaicin	ROS-STAT3-mediated	(Chen et al. 2016)
	SMMC-7721 cells, HepG2 cells	Ionizing radiation	Atg4B induction by Egr-1	(Peng et al. 2017)
Pancreatic cancer	PANC-1 cells, PaCa3 cells	Gemcitabine	mutant p53 nuclear stabilization	(Fiorini et al. 2015)
	PANC-1 cells	Bortezomib	AMPK-Ulk1 signalling activation	(Min et al. 2014)
	PANC-1 CSCs	Gemcitabine	OPN/NF-κB signaling induction	(Yang et al. 2015)
Head and neck cancer	OE19 cells, OE21 cells, OE33 cells, KYSE450 cells	Cisplatin, 5-Fu	Bec1, Atg7-mediated	(O'Donovan et al. 2011)

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	EC109 cells	Cisplatin	mTORC1 activity suppression	(Yu et al. 2014a)
	Hep-2	Cisplatin	↓Bec1	(Kang et al. 2012)
	HSC-3 cells, Ca9–22 cells	Safingol		(Masui et al. 2016)

b. The pro-death role of autophagy in MDR of cancer

Type of cancer	**Cell line**	**Intervention/Drug**	**Methods or Molecular Mechanism to study autophagy**	**Ref**
Breast cancer	MCF-7 cells (Tamoxifen-resistant)	SAHA	3-MA	(Lee et al. 2012)
	MCF-7 cells (Adriamycin-resistant)	Isoliquiritigenin	CQ, 3-MA	(Wang et al. 2014b)
	MCF-7 cell lines (Apoptosis-resistant)	Hernandezine	3-MA, Atg7-knockout	(Law et al. 2016)
	MDA-MB-231 cells	LYN-1604	cell death modulated by ULK1	(Zhang et al. 2017a)
Colorectal cancer	SW620 cells (Apoptosis-resistant)	Tanshinones	3-MA	(Hu et al. 2015)
Leukemia	leukemic K562 cells (Edelfosine-resistant)	Edelfosine lipid NPs	Starvation, Staurosporine	(Aznar et al. 2014)
Lung cancer	lung cancer cells (Multidrug-resistant)	GMI protein	CQ	(Chiu et al. 2015)
	A549 cell lines (Apoptosis-resistant)	Hernandezine	3-MA, Atg7-knockout	(Law et al. 2016)
	H460 cells (Cisplatin-resistant)	Cisplatin	Trifluoperazine, 3-MA	(Sirichanchuen et al. 2012)
	H460 cells (Apoptotic deficient)	RAD001	3-MA, siRNAs (Atg5, Bec1)	(Kim et al. 2008)
	H1299 cell lines (Apoptosis-resistant)	Hernandezine	Atg7-knockout, 3-MA	(Law et al. 2016)
	A549 cells, H1299 cells, H292 cells, H460 cells, HCC827 cells BEAS-2B	SBI0206965	Ulk1 inhibition	(Tang et al. 2017)
	NCI-H1299 cells NCI-H460 cells	PS VII	autophagy blocking by 3-MA via AMPK-ULK1	(Qian et al. 2020)
Bladder cancer	urothelial cancer cells (Cisplatin-resistant)	NVP-BEZ235	3-MA	(Li et al. 2013a)
Ovarian cancer	SKVCR cells (Multidrug-resistant)	p53 plasmids	3-MA	(Kong et al. 2012)
	ovarian cancer cells (Chemoresistant)	Quinacrine	Baf A1	(Khurana et al. 2015)
Cervical cancer	Hela cells (Apoptosis-resistant)	Hernandezine	Atg7-knockout, 3-MA	(Law et al. 2016)
Prostate cancer	PC3 cells (Apoptosis-resistant)	Hernandezine	Atg7-knockout, 3-MA	(Law et al. 2016)

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Hepatocellular carcinoma	HepG2 cells (Apoptosis-resistant)	Hernandezine	Atg7-knockout, 3-MA	(Law et al. 2016)
	Hep3B cells (Apoptosis-resistant)	Hernandezine	Atg7-knockout, 3-MA	(Law et al. 2016)
Gastric cancer	SGC7901 (Drug-resistant)	HTCC-MNPs	3-MA	(Li et al. 2016)

Abbreviations; ATG: Autophagy-related genes, Baf A1: bafilomycin A1, Bec1: Beclin1, BITC: Benzyl isothiocyanate, CML: chronic myelogenous leukemia, CQ: Chloroquine, CSCs: cancer stem cells, DOX: Doxorubicin, DRAM: Damage-regulated autophagy modulator, Egr-1: early growth response factor, ERK: Extracellular signal-regulated kinase, FTY720: 2-amino-2-[2-(4-octylphenyl)]-1,3-propanediol hydrochloride, GMI: Ganoderma microsporum immunomodulatory, HCQ: Hydroxychloroquine, HMGB2*:* high-mobility group box2, HTCC-MNPs, *N*-[(2-hydroxy-3-trimethylammonium)propyl] chitosan chloride/alginate-encapsulated Fe3O4 magnetic nanoparticle, JNK: c-Jun N-terminal kinase, LAMP: Lysosomal-associated membrane protein, LAPTM4B: lysosomal-associated transmembrane protein, LC3: protein1 light chain3, mTOR: Mammalian target of rapamycin, NPs: nanoparticles, OPN: osteopontin, PP2: 4-amino-5-(4-chloro-phenyl)-7-(*t*-butyl)pyrazolo[3,4-*d*]pyrimidine, PS VII: Paris saponin VII's, PTEN: phosphatase and tensin homologue, Rab: Ras-related protein, SAHA: suberoylanilide hydroxamic acid, siRNA: small interfering RNA, TAK1: transforming growth factor-activated kinase1, TAW: 8-p Hdroxybenzoyl tovarol , TMZ: Temozolomide, Ulk: UNC-51-like kinase, UPR: Unfolded protein response, VCR: vincristine resistance, Vps: Vacuolar protein sorting, 3-MA: 3-methyladenine, 5-FU: 5-fluorouracil

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Legends

Figure 1. Mechanisms involved in autophagy. Stressors such as starvation and infection can induce autophagy. Upon nutrient deficiency in the environment, autophagy is usually triggered in *S. cerevisiae* to provide the prerequisite amino acids and macromolecules for the survival of the microorganism. A nutrient sensor, TOR protein kinase is the primary molecule responsible for the regulation of autophagy inside the cell, which has been mostly investigated in fungal cells, particularly yeasts (Gozuacik and Kimchi 2004). When nutrients are amply available, TOR protein kinase prompts phosphorylation of Apg13, the affinity of which for Apg1 significantly decreases upon hyperphosphorylation, resulting in reduced Apg1 kinase activity (Kamada et al. 2000; Scott et al. 2000) and concomitant activation of the Cvt pathway. Administration of rapamycin or inaccessibility to nutrients, in contrast, lead to inhibition of TOR protein kinase, and subsequent dephosphorylation of Apg13. The resulting increase in the activity of Apg1, thus, prompts autophagy (Gozuacik and Kimchi 2004). In this circumstance , autophagy is mediated through macroautophagy and mitophagy (Popp and Segatori 2015). In the former, the PI3K/Akt and MAPK/ERK1/2 pathways become initiated, and are then succeeded by inhibition of mTOR and activation of beclin-1/Atg6. Mitophagy, however, is triggered following mitochondrial damage and the activity of ubiquitin-like conjugation systems. Further down the cascade, an interaction between p62 and LC3-II results in cargo delivery to autophagic membranes or phagophores. Fusion of the phagophores surrounding the cargo material results in formation of autophagosomes, structures that subsequently bud into lysosomes to form autophagolysosomes or degradation center. ROS can induce autophagy through several different mechanisms; nuclear PTEN, the PI3K pathway and LKB1/AMPK. Rapamycin acts as an mTOR inhibitor (Popp and Segatori 2015; Díaz-Troya et al. 2008). Rubicon, 3-MA and choloroquine function to inhibit autophagy (Zhang et al. 2014b; Rebecca and Amaravadi 2016). Activation of p53 leads to up-regulation of DRAM and sestrin 1/2, that ultimately accelerates autophagy. p70S6 kinase (p70S6K) might be a good option for controlling of autophagy downstream to mTOR (Gozuacik and Kimchi 2004).

(Abbreviations; 3-MA: 3-Methyladenine, ALFY: Autophagy-linked FYVE Protein, AMPK: AMP-activated Protein Kinase, Atg5/6/7/10/12/13/16L1: Autophagy-related Gene5/6/7/10/12/13/16L1, Ambra: Activating Molecule in Beclin 1-regulated Autophagy, Beclin1: a Mammalian Homolog of Yeast Atg6 Encoded by the BECN1 Gene, BNIP3: BCL2 and Adenovirus E1B 19 kDa-interacting Protein 3, BNIP3L/NIX: BNIP3-like, CVT: Cytoplasm Vacuole Targeting, DRAM: Damage-regulated Autophagy Modulator, FIP200: Focal Adhesion Kinase Family Interacting Protein of 200 kDa, GBL: Gamma-Butyrolactone, HMGB1: High Mobility Group Box Protein 1, LKB1:

Liver Kinase B1, LC3-II/I: Microtubule-associated Proteins Light Chains, LIR: LC3-interacting Region, MEK1/MEK2: MAPK Kinase, MAPK/ERK: Mitogen-activated Protein Kinase/Extracellular Signal-regulated Kinases, mTOR: The Mammalian Target of Rapamycin, NBR1: Neighbor of BRCA1, PI3K-I/Akt: Phosphatidylinositol 3-kinases-I/ Protein Kinase B, PTEN: Phosphatase and Tensin Homolog, PRAS40: The Proline-rich Akt Substrate of 40 kDa, p70S6K: Ribosomal Protein S6 Kinase Beta-1, P150: a Mammalian Homolog of Yeast Vps15, PI3K-III: Phosphatidylinositol 3-kinases-III, P53: Tumor Protein p53, PARL: Presenilin-associated Rhomboid-like Protein, PINK/PARKIN: Mitophagy Regulators, ROS: Reactive Oxygen Species, Ras: Rat Sarcoma, Raf: Rapidly Accelerated Fibrosarcoma, RAPTOR: Regulatory-associated Protein of mTOR, SQSTM1/P62: Sequestosome-1, ULK1: Unc-51-like Kinase 1, ub: *Ubiquitin)*

Figure 2. Correlation of apoptosis and autophagy. Oxidative stress, pathogens and cell death signals can induce autophagy or apoptosis through either dependent or independent pathways. (modified from (Gozuacik and Kimchi 2004))

Figure 3. Autophagy in tumor cells. Oncogene products (blue) inhibit autophagy, whereas tumor suppressors (green) accelerate autophagy, except for cytoplasmic p53, however. Growth factor signaling through activation of the PI3K/Akt/mTOR axis leads to inhibition of autophagy. On the contrary, class III PI3K activates autophagy. Low levels of cellular energy with an increased AMP/ATP ratio activate the LKB1-AMPK-mTOR pathway, that ultimately results in up-regulation of autophagy. p53 is a complex regulatory factor in the process of autophagy, as nuclear p53 activated by genotoxic or oncogenic stress positively regulates autophagy by inhibiting mTOR in an activated AMPK- and TSC1/TSC2-dependent manner. In contrast, cytoplasmic p53 has a negative regulatory effect on autophagy. Autophagy can also be induced by the cell death-associated protein kinase (DAPK) and the death associated related protein kinase 1 (DRP1) 51. (Modified from (Choi 2012))

(Abbreviations; Akt: Protein Kinase B, AMPK: AMP-activated Protein Kinase, Beclin1: a Mammalian Homolog of Yeast Atg6 Encoded by the BECN1 Gene, Bcl2: B-cell Lymphoma 2, Bnip3: BCL2 and Adenovirus E1B 19 kDa-Interacting Protein 3, Bad: Bcl2-associated Death, Bax: BCL2 Associated X, DAPK/DRP1: Cytosolic Protein, DRAM: Damage-regulated Autophagy Modulator, E2F1: Transcription Factors, ERK1/2: Extracellular Signal-regulated Kinases1/2, Foxo3A: Forkhead Box Class O 3a, LKB1: Liver Kinase B1, IRS: Insulin Receptor Substrate, MEK1/2: MAPK Kinase1/2, mTOR: The Mammalian Target of Rapamycin, mLST8: The Mammalian Lethal with Sec13 Protein 8, PI3K-I: Phosphatidylinositol 3-kinases-I, PTEN: Phosphatase and Tensin Homolog, PRAS40: The Proline-rich Akt Substrate of 40 kDa, PI3K-III: Phosphatidylinositol 3-kinases-III, P53: Tumor Protein p53, Puma: The p53 Upregulated Modulator of Apoptosis, P21: cyclin-dependent Kinase Inhibitor 1A, P27: Cyclin-dependent Kinase Inhibitor 1B, P16: CDKN2A, Ras: Rat Sarcoma, Raf1: Rapidly Accelerated Fibrosarcoma, Rheb: Ras Homolog Enriched in Brain, Raptor: Regulatory-associated Protein of mTOR, RB: Retinoblastoma, Sestrin: Cysteine Sulfinic Acid Reductase, TSC1/2: Tuberous Sclerosis Proteins 1/2 ,TAK1: TGF-beta-activated Protein Kinase 1)

Figure 4. Mechanisms involved in nanomaterial-regulated activation of autophagy. Nanomaterials may induce autophagy through different mechanisms, including; enhanced formation of autophagosomes, induction of oxidative

stress, and instigation of lysosomal damage. Based on the nature of the nanomaterial, activation of autophagy might result in enhanced clearance or blockage of autophagic flux. Upon their release into the cytoplasm, nanomaterials may also impair the cytoskeleton integrity and function, leading to autophagosome dysfunction and blockage of autophagic flux. Else, nanomaterials can also enhance the formation and functioning of lysosomes and autophagosomes and induce autophagy.

(Abbreviations; AMPK: AMP-activated Protein Kinase, Atg: Autophagy-related Gene, Bcl2: B-cell Lymphoma 2, Beclin1: a Mammalian Homolog of Yeast Atg6 Encoded by the BECN1 Gene, Cas3/9: Caspase3/9, EGFR: Epidermal Growth Factor Receptor, HER2: Human Epidermal Growth Factor Receptor 2 , HO-1: *Heme Oxygenase-1*, LC3-I: Microtubule-associated Proteins Light Chain, MEK: MAPK Kinase, ERK: Extracellular Signal-regulated Kinases, mTOR: The Mammalian Target of Rapamycin, MMP9: Matrix Metallopeptidase 9, NF-kB: Nuclear Factor Kappa-light-chain-enhancer of Activated B Cells, Ras: Rat Sarcoma, Raf: Rapidly Accelerated Fibrosarcoma, P62: Sequestosome 1, P38: Mitogen-activated Protein, PI3K: Phosphatidylinositol 3-kinases-III, P53: Tumor Protein p53, TLRs: Toll-like Receptors, TRIF: TIR-domain-containing Adapter-inducing Interferon-β, VEGF: Vascular Endothelial Growth Factor)

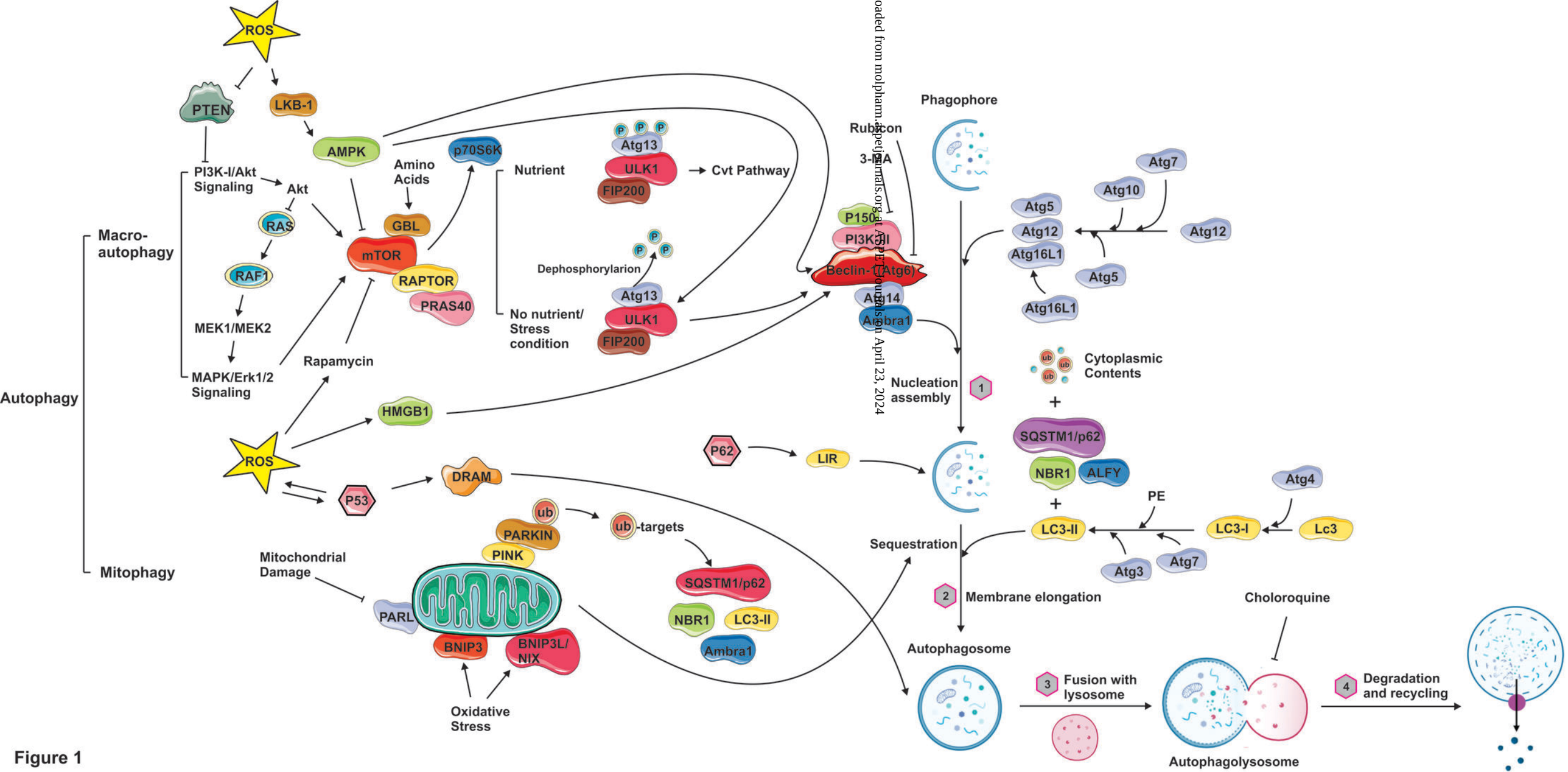

Figure 1

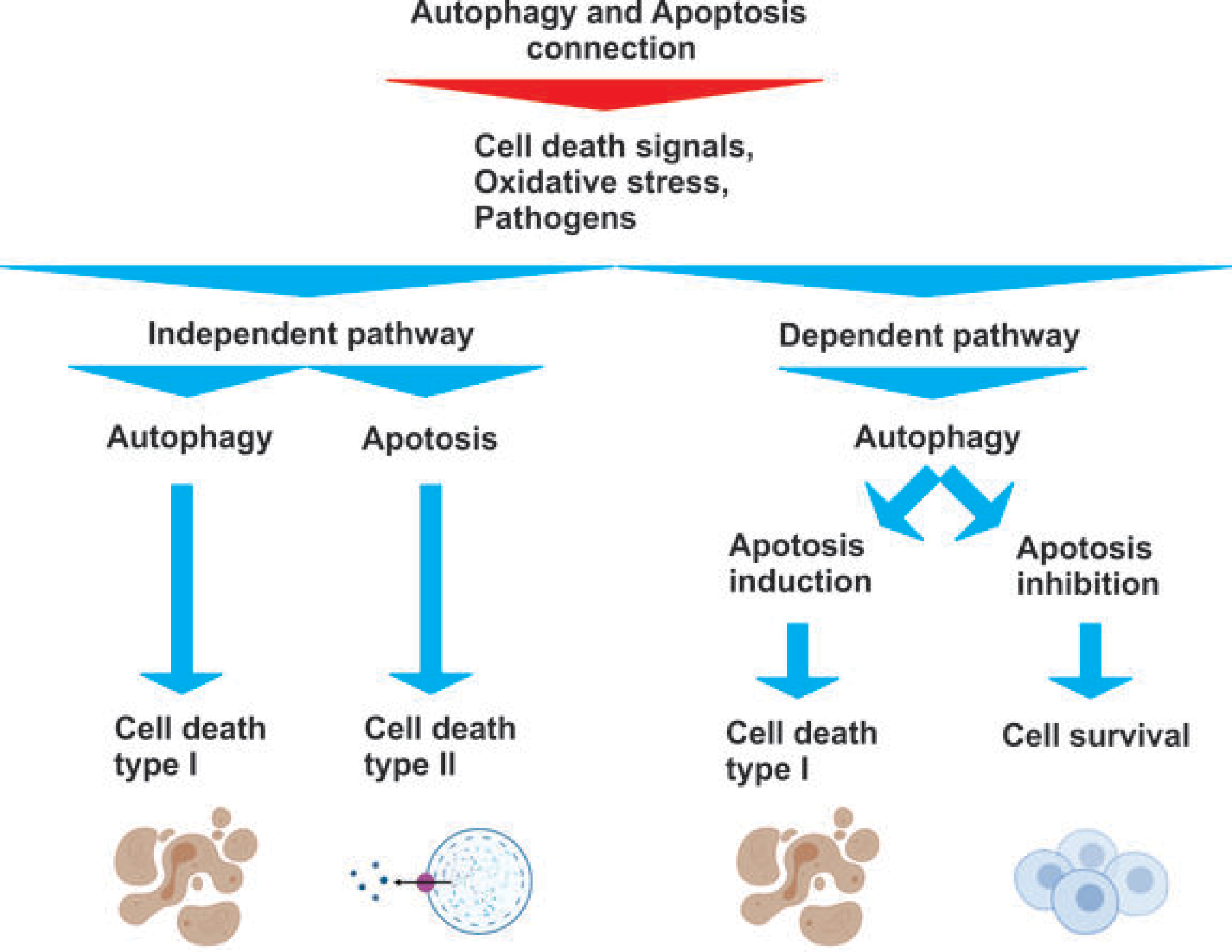
Autophagy and Apoptosis connection
Cell death signals,
Oxidative stress,
Pathogens
Independent pathway
Dependent pathway
Autophagy
Apotosis
Autophagy
Apotosis induction
Apotosis inhibition
Cell death type I
Cell death type II
Cell death type I
Cell survival

Figure 2

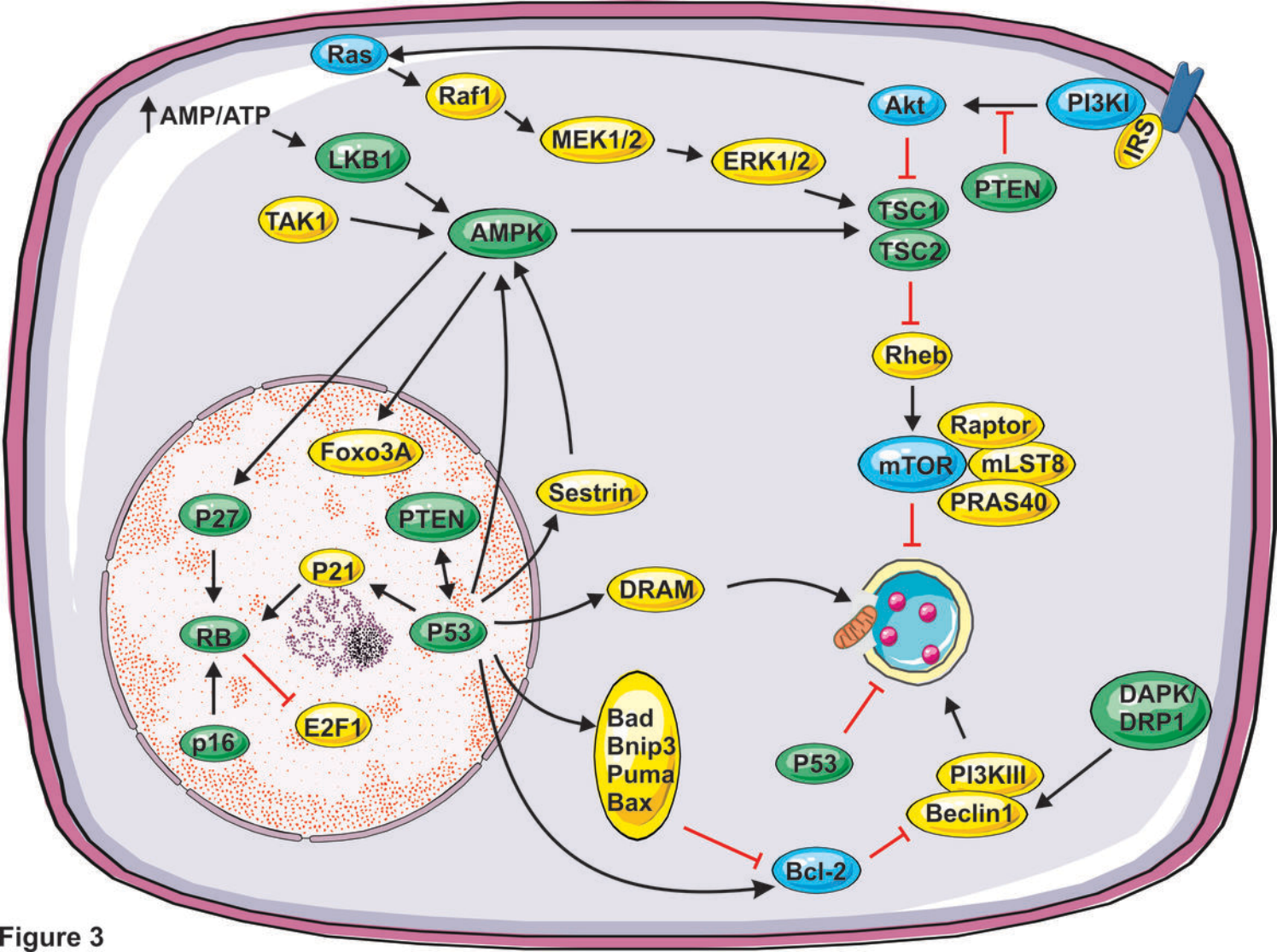
Ras
Raf1
MEK1/2
ERK1/2
AMP/ATP
LKB1
TAK1
AMPK
Akt
PI3KI
IRS
PTEN
TSC1
TSC2
Rheb
Raptor
mTOR
mLST8
PRAS40
Foxo3A
Sestrin
P27
PTEN
P21
DRAM
RB
P53
E2F1
p16
Bad
Bnip3
Puma
Bax
P53
DAPK/
DRP1
PI3KIII
Beclin1
Bcl-2

Figure 3

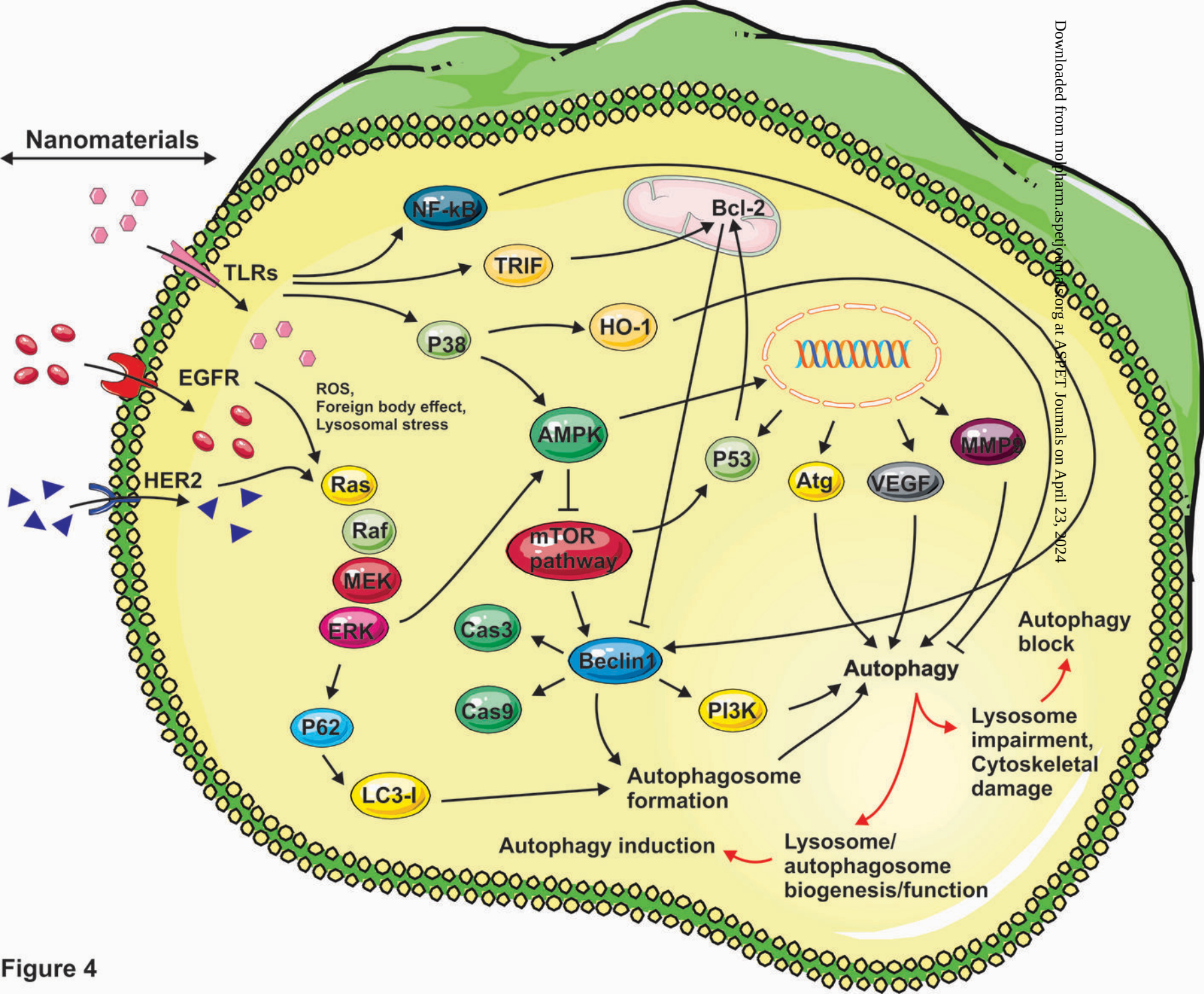

Figure 4