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A Summary of Autophagy Mechanisms in Cancer Cells

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ABSTRACT

Autophagy is a well-known vital process in cells and plays a significant role in biological evolution, the immune system, and cell death. It can be effective in fatal disorders, such as nervous system degeneration, autoimmune diseases, and cancer. Autophagy has a dual role; on the one hand, it increases cell survival, and on the other hand, it causes cell death in advanced stages although no agreement has yet been accomplished on the role of autophagy in cellular processes. There is evidence that autophagic signaling regulation is inversely related to oncogenic signaling. Numerous commonly activated oncogenes (class I PtdIns3K, Akt, TOR, Bcl-2) inhibit autophagy, while commonly mutated or epigenetically silenced tumor suppressor genes (p53, PTEN, TSC1/TSC2) promote autophagy. Autophagy promotes cancer progression by supplying sufficient nutrients that enable cancer cell growth. FIP200, a related- autophagy protein, interacts with ATG 13 and induces autophagy. Increased autophagy causes the interaction of Becklin 118 with HER2, resulting in an increase in tumorigenesis. In order to make complete use of the autophagic properties in cancer treatment, further studies on its role in disease in the different biologics fields are essential. Cancer stem cells (CSCs) can regenerate, cause cancer, and enhance resistance to treatment, metastasis, and recurrence. Autophagy moderates stressful conditions and promotes resistance to anticancer therapy. In addition, autophagy regulates the ability of radiation in CSCs and leads to failure in anticancer therapies. Hence, autophagy is a potential therapeutic target for metastasis resistance and anticancer therapy recurrence. Regulation of autophagy using autophagy modulators alone does not improve the therapeutic effects of anticancer reagents. In contrast, it has supplied nutrients for cancer cells. Consequently, clinical trials aiming for autophagy through a combination of autophagy modulations and anticancer reagents are crucial to consider autophagy as a potentially effective therapeutic strategy in anticancer therapy.

1. Introduction

Autophagy as an intracellular process enhances important catabolic and cellular degradation in eukaryotes, which plays a vital role in preserving cellular homeostasis, providing nutritional requirements of cells, and eliminating old and damaged organelle, protein, and other macromolecules[1]. In fact, autophagy is an induced response in starvation conditions, protecting the amino acid pool against gluconeogenesis and synthesizing essential proteins for survival[2]. Autophagy consists of several sequential steps. These steps include inducing paths leading to autophagy, selection of organs and proteins that require destruction, nucleation and formation of membranes (phagocytosis), expansion and evolution of autophagy, reconstruction of used components, fusion of lysosomes with autophagic membranes and formation of phagocytosis, and finally, decompositions of cellular components, in which, proteins, such as Atg10 and Beclin1 play an important role (Figure 1)[3].

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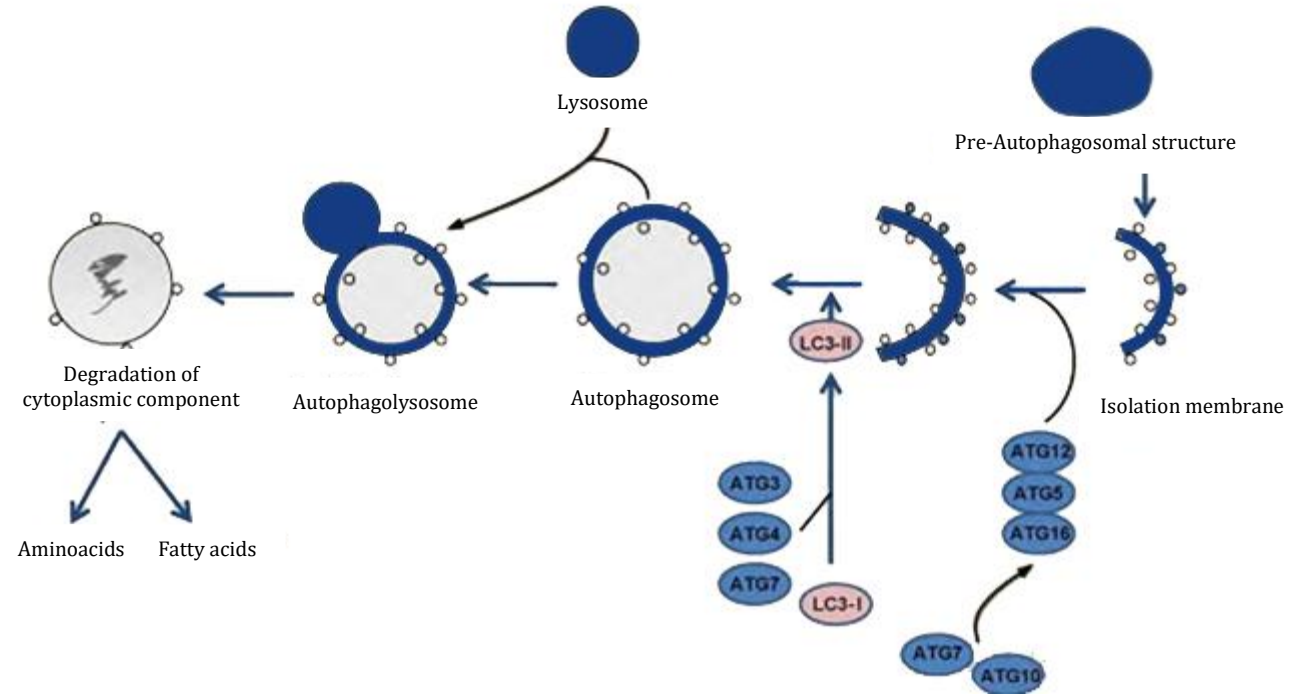

Figure 1. Steps of autophagy and cytoplasmic degradation

Set of genes called ATG genes or Autophagy-related ATG genes stimulate the process of autophagy and the formation of autophagic in mammals[4]. These genes encode an intracellular machine that initially controls the autophagic activity, cargo collection, and trafficking to the lysosomal compartment**.** Most of these genes have been conserved between yeast and humans[4]. The accumulation of ubiquitous protein, abnormal organelles, especially mitochondria, and increased Peroxisomes , rough endoplasmic reticulum, lipid particles, and ribosomes have been observed in rat tissues with defective autophagy[5]. Although there is no clear evidence addressing the functional effect of this failure on the quality of protein and organelle control, intracellular proteins have been associated with reactive oxygen species (ROS) production, increased proteotoxicity, and metabolic defects[6]. The analysis of mammalian homolog using yeast of essential proteins for autophagy (Aut and Apg) has indicated that the mentioned proteins directly contribute to the membranes involved in autophagy. The autophagy process begins with forming a double membrane-bound structure called (autophagosome) in response to a ubiquitination-like reaction. Apg12 is covalently bound to Apg5 in which Apg12-Apg5 forms a complex with Apg16L, and through the elongation process, they collect on the separation membrane, and after autophagosome formation, they separate from the membrane[7,8].

LC3 (Aut7/Apg8 Ortholog in yeast), as an important protein, is the only reliable autophagy marker, which localizes on the membrane of complete spherical autophagosomes and on the autolysosome in contrast to Apg12-Apg5. To destroy and recycle the autophagosome metabolic substances, Apg12-Apg5 fuses with lysosomes, and autolysosome is formed[9].

Another protein involved in autophagy is Beclin 1 (yeast homologues of Apg6/Vps30). It plays a significant role in vacuolar transport and forms a complex with phosphatidylinositol (PtdIns) 3-kinase. The mentioned complex is collected in trans- Golgi network (TGN). This complex is proposed to play a crucial role in separating membranes by providing PtdIns^3 P from TGN. It is thought that PtdIns^3 P helps the formation of autophagosomes by mediating other autophagy proteins to make a pre-autophagosomal structure or act as a cargo protein. However, is that TGN itself may be involved in the formation of autophagosomes by providing membranes[10].

Autophagy primarily occurs under the conditions of hypoxia, immune injury, stress, and nutrient deficiency[1,11]. Therefore, it is evident that autophagy mainly happens due to the continuous growth of cancer cells, and consequently, the increasing need for nutrients and oxygen, compared to the non-cancerous ones[12]. In other words, autophagy is a highly regulated process, closely associated with several human diseases, such as cancer[13, 14]. According to the genetic research in *Saccharomyces cerevisiae*, the formation complex ATG1 kinase with ATG17 and ATG13, was introduced as an important factor in autophagy initiation, and in mammals, the ATG1 homologues are Ulk1 and Ulk2. It is also reported that the opposite point of ATG13 and ATG17 is mATG13 and FIP200, respectively. Under glucose starvation, AMPK promotes autophagy by activating Ulk1 through phosphorylation of Ser 317 and Ser 777 under

nutrient sufficiency; high mTOR activity avoids Ulk1 activation by phosphorylating Ulk1 Ser 757 and disrupting the interaction between Ulk1 and AMPK. Phosphorylation Ulk1 through mTORC1 is a response to nutrient signaling in autophagy induction and regulation[15]. Recent studies show that autophagy is connected to both the progression of cancer cells and their cessation[16]. Autophagic signaling pathway regulation in cancer cells induces through oncogenic KRAS. One of the trans-membrane proteins is VMP1 which is essential for autophagosome formation. To induce and maintain the level of autophagy in cancer cells, Oncogenic KRAS requires VMP1. In this process, GLI3, as a transcription factor regulator, binds to the VMP1 promoter. In order to modify this process, histone acetyltransferase p300 complexes are accompanied by GLI3. The PI3K-AKT1 pathway expresses in the GLI3-p300 complex upstream and mediates VMP1 promotional activity[17].

In most cases, autophagy leads to survival in response to growth factors or metabolic stress in cases where apoptosis cannot resume cell growth to normal circumstances, it maintains survival for weeks[18].

Reactive oxygen species is one of the vital molecules in response to oxidative stress, which has been linked to a myriad of pathologies, such as traumatic brain injury, ischemia/reperfusion, and hypoxia in the tumor. Two major resources produce ROS; mitochondria (in the process of Cellular respiration) and NADPH oxidase (NOX) which creates the neutrophil superoxide and membrane phagosomes. The accumulation of high levels of ROS as a result of oxidative stress or mitochondrial dysfunction can disrupt and break cellular homeostasis and, consequently, induce autophagy. In this process, autophagy removes the aggregated proteins and damaged organelles, such as mitochondria, which can decrease the improvement of oxidative stress and reduce ROS levels. The ROS may also trigger the formation of autophagic membranes by modifying and adjusting Atg4 activity as a cellular signaling molecule. Interaction between ROS and autophagy in various pathologies conditions include starvation and tumor. Generally, the autophagic transcription regulatory mechanism by ROS occurs in the cell nucleus. The overproduction of ROS activates transcription factors, such as HIF-1, p53, FOXO3, and NRF2, respectively, and these factors induce BNIP3 and NIX, TIGAR, LC3, and BNIP3, and p62 transcription, correspondingly. Finally, the produced proteins induce autophagy and reduce ROS levels. In addition, ER stress sensor PERK, a downstream inductor, expresses autophagic genes, including LC3. And ATG5 increases autophagic flow[19,20]. ROS can be produced in one of the autophagy mechanisms involved in tumor survival, whose source is chain electron transfer with Ca^{2+} and NADPH oxidases (Nox). ROS production mechanism in starvation-induced autophagy has not been explicitly determined. According to the findings of Sarah et al., ROS produced through Nox in starvation-induced autophagy activates JAK2-STAT3 in the STAT3 pathway. Activation of STAT3, a significant oncogenic protein, triggers cytokine IL6 growth factor and other involved factors signaling, and eventually, it promotes proliferation and survival in cancer cells. Since autophagy was determined as a survival pathway in tumor cells, there has been a tremendous interest in stopping autophagy for cancer treatment[19, 21].

Conversely, studies indicate an inverse relationship between autophagy activity and the potential for malignancy[22], especially in malignant cells or cell transfusion with a low basal autophagic activity, compared to their normal reciprocal cells. An increase in the destruction rate of autophagic proteins does not show serum deprivation conditions and high levels of cell density. The rat liver carcinogenesis model has revealed that autophagy activity has briefly decreased in stage preneoplastic and is mostly reduced in primary hepatocellular tumor cells. However, it has not yet been known whether the observed reduction in malignant cells is important in mechanistic tumorigenesis or whether secondary symptoms are associated with malignant cell transformation[1, 22, 23].

Alternatively, reduced autophagy may increase the ability of cell proliferation. It is considered one of the mechanisms of death[23].

P62 is an adapter protein. In cells with a normal autophagy pathway that is not stressed, the p62 protein level is low. P62 is a fundamental nuclear factor erythroid 2-related factor 2 (NRF2). Cells get rid of oxidative stress by removing and relieving mitochondrial ROS sources and protect themselves by activating antioxidant-defense genes. In the mentioned process, NRF2, as a transcription factor, activates this response. Under normal conditions, NRF2 transcription activity by connecting to kelch-like ECH-associated protein 1 (KEAP1) is off or stopped. Oxidative stress causes KEAP1 modification, which leads to the release of NRF2 or, in other words, p62 gene upregulation. Competitive binding between p62 and KEAP1 leads to transfer NRF2, or NRF2 displaces[24].

Defect in autophagy, which prevents p62 degradation, accumulates at a high level, promotes its activity, and establishes the antioxidant defense by connecting to KEAP1 and releasing NRF2. Also, the elimination of the essential gene for autophagy Atg7 in liver cells causes p62 accumulation, upregulation of NRF2-target genes, and tumorigenesis. Therefore, it is clear that degrading p62 by autophagy and termination of NRF2 activity is essential for the mechanism of tumor suppression[24, 25].

Besides their known function, a number of oncogenes and tumor-suppressor genes intervene in the autophagy pathway. Oncogenes that inhibit autophagy include phosphatidylinositol 3-kinase, PI3K, Myc, Ras, Akt1, and Anti-apoptotic proteins from the Bcl-2 family[26, 27].

Autophagy defects due to allelic loss of beclin1 or the activity of the PI-3 kinase / mTOR autophagy pathway are most common in human tumors[28].

It has been shown that beclin1, as an autophagy gene, is monoallelically deleted in 40-75% of patients suffering from sporadic breast, ovarian, and prostate cancer[29].

It is thought that Beclin 1 is vital for the localization of autophagic proteins to a pre-autophagosomal structure. In order to prove this, Qu et al. measured autophagy by obtaining tissues from mice - / + beclin 1 and / ++ beclin 1,

which express GFP-LC3 autophagy marker transgenically. GFP-LC3–positive (dots) level was significantly reduced in the muscle of beclin mice- / + 1, compared to mice / ++ beclin 1 under starvation conditions. It is noted that the elimination of heterozygous beclin 1 reduces autophagy in muscle under starvation conditions. They also observed papillary lung carcinomas in mice - / + beclin 1 that strongly suggested its bronchial cells origin. After two months, by taking the amount of autophagy in the bronchial epithelial cells exposed to starvation conditions, bronchial epithelial cells were significantly reduced, compared to muscle cells. These findings reveal that in mentioned condition, beclin 1 heterozygous deletion lessens autophagic and tumor activity[30].

2. Consequences of autophagic disorder

Autophagic ATG genes encode the intracellular machine, which forms autophagic, collecting (cargo vesicles, and they control the transfer (movement) to the lysosomal compartment, and most of these genes are common between yeast and humans. The accumulation of ubiquitous protein, abnormal organs, especially mitochondria, as well as, additional proxies, endoplasmic reticulum (ER), Ribosomes, and lipid droplets were observed in mutated mice with autophagy defects[31].

Autophagy plays a vital role in removing clumps of protein in stressful situations or in situations where mutant protein expression is associated with increased protein misfolding (without shape and fold) and greater aggregation. Lack of elimination clumps of protein through autophagy leads to the accumulation of them in the form of Mallory-Dunk bodies in the liver, ubiquitous and mutant protein clumps in the brain in the form of masses of 1-antitrypsin in the lungs, liver, and other tissues[32]. Although the proteasome pathway can destroy soluble proteins separately, autophagy is needed to destroy protein aggregation. It may complete the destruction through proteases during stress. Autophagy is stimulated by blocking the path of protease and is very sensitive to defective cells, and there is evidence of a partial interaction and dependence between the two main mechanisms of protein degradation[1, 32, 33].

3. Autophagy dysfunctions associated with cancer

Over the past decade, it has been shown that oncology is genetically linked to an imbalance in autophagy mechanisms, and cancer progression has a dual role. In the early stages of cancer, autophagy suppresses the development of tumors by clearing damaged proteins and organs and induces cell death. In contrast, in advanced cancers under stress conditions, autophagy by tumor cells is used to meet metabolic needs for survival and rapid tumor replication. Therefore, autophagy as a tumor promoter has been reported in advanced cancers. For example, negative tumor suppressor genes through various signaling mechanisms (such as AMPK and mTOR) can cause autophagy and suppress cancer onset; however, oncogenes' activation can lead to autoimmune inhibition and the spread of cancer cells. Autophagy modulates the growth and development of cancer cells depending on the type of tumor and its developmental stage, and genetic tissue. Autophagy is considered a mechanism of cancer suppressor in normal cells. However, in stressful situations (such as hypoxia and ROS), abnormal autophagy leads to the breakdown inhibition of damaged organs and proteins and cancer progression. However, mutations in autophagy proteins lead to tumor suppression/progression in a variety of cancers. For example, in gastric and colorectal cancer, there are no related proteins BECN1 (such as BIF-1)[34, 35]. BECN1 often was monoallelically deleted in ovarian, breast, and testicular cancer. In addition, in mice with partially deficient autophagy due to the removal of BECN1, it is susceptible to liver cancer and lung tumors at older ages[36]. Also, the activation of oncogenes, such as (PI3KCA) and the inactivation of tumor suppressors (e.g., PTEN and LKB1) are associated with autophagy inhibition and tumor formation[37]. On the other hand, the disorder in autophagy due to the deletion of ATG5 mosaic leads to benign liver tumors, which shows that different tissues have different responses to autophagy disorder. In addition, mutations in UVRAG protein are related to autophagy reduction and subsequent growth of colorectal cancer[38]. On the other hand, high levels of autophagy in several types of activated cancer with RAS (for example, pancreatic cancer) have been reported, and inhibition of autophagy in these cancers prevents the formation of tumors[39].

Cellular transformation and disruption in many signaling pathways are directly or indirectly related to autophagy modulation, and depend on biological factors, such as oncogenesis, tumor suppression, and tumor type. So, autophagy is considered a double-edged sword. It has also been observed that increased autophagy in hypoxic regions of solid tumors has been attributed to cell survival and inhibition of autophagy leads to a strong induction of cell death in these areas[1, 4, 35].

4. Autophagy and cancer prevention

Since autophagy plays a role in tumor suppression, induction of autophagy may be a significant way to prevent cancer. In human tumors, PI3K-AKT-mTOR signaling is often impaired, and by inhibiting mTOR signaling autophagic activity can be induced. The use of metformin in order to inhibit mTOR signaling can weaken tumor formation[40]. Additionally, it was seen that the inhibition of intestinal neoplasia is enhanced by continuous treatment and low-dose rapamycin in $APC^{Min/+}$ mice with AKT-mTOR signaling[41]. Abnormal activation of Wnt signaling by autophagy leads to the formation of colorectal tumors[42]. Other autophagy activator drugs may also be useful in preventing cancer, and further research is needed. Thus, autophagy can be constructive in cancer prevention by limiting inflammation, tissue damage, and genome instability[40,43].

Deficiency in P62 can result in tumorigenesis, indicating

that inhibition of P62 may be valuable for cancer prevention and treatment[24,44]. Anti-inflammatory and autophagy stimulants can be helpful in cancer prevention, especially in cancers in which autophagy is suppressed and accompanied by increased inflammation[45]. There is also evidence that cancer suppression due to caloric restriction and the health benefits of exercise may be related to autophagy. In other words, caloric restriction increases the level of autophagy[46].

Consequently, Autophagy may help suppress tumor in some areas by cleaning waste cell, particularly the mutant proteins (aggregated), damaged mitochondria, and P62. So it can be predicted[44].

5. Autophagy in the treatment of cancer

Autophagy in cancer treatment can be understandable when it becomes a tumor-cell survival pathway, so there is a great interest in inhibiting autophagy in cancer treatment. Although autophagy inhibitors are small molecules developing, lysosomotropic agents and hydroxychloroquine anti-material, which by inhibiting lysosomal function, block destroys autophagy products, are actively evaluated in a clinical trial[23,47].

It is unknown at this time whether HCQ is an effective autophagy inhibitor in human tumors or not, how patients who benefit from it are identified and their tumors evaluated and how to find out the most excellent drugs to combine with HCQ. Furthermore, the potential anticancer activity of HCQ can be associated with autophagy or may be triggered by other mechanisms[48].

The induction of autophagy when it is cytotoxic may be by induction of cell death by itself or by activating another cell death mechanism (apoptosis), which can help recover the efficiency of anticancer therapies. Some drugs/natural extracts, some of which have previously been used clinically, have been described to cause cell death by inducing autophagy in different cancer cells. For example, combining vitamin D with radiation increases cytotoxic autophagy in breast tumor cells. Resveratrol and curcumin lead to cell death in human tumor cells via apoptotic and autophagy. Naphthazarin, a naphthoquinone derivative, as a microtubule depolymerizing agent induces apoptosis and autophagy in lung cancer cells, and finally, it leads to cell death in tumor cells. In addition, the Small STF-62247 molecule induces autophagic cell death in renal cell carcinoma with a deficiency in von Hippel-Lindau (VHL) and TXA1 (small thioxanotic molecule) that decreases the viability of cells in melanoma and breast cancer by induction of autophagy[47, 49].

Based on the findings reported by the vast majority of studies in this field, it seems that autophagy induction rather than autophagy inhibition could be utilized to improve the outcome of cancer treatment, at least in immune-competent hosts. Hence, nutraceuticals, exercise, and calorie restriction (such as metformin), which can induce autophagy, are considered possible alternatives to treat cancer in combination with chemotherapies. In addition, it gives the impression that inhibiting autophagy, specifically in cancer cells, may enhance the abscopal response to radiation therapy, that is, the ability of localized radiation to trigger systemic antitumor effects. Thus, it is shown that selective autophagy inhibition in cancer cells and systemic induction of autophagy could be combined to improve the outcome of anticancer therapy. Considering the role of autophagy in regulating the expression of oncogenes and modulating the function of the cells of the tumor environment, such as fibroblasts and immune cells, more questions than answers have been raised by this review. As a result, more investigations are needed to further clarify the possible consequences of autophagy manipulation in cancer therapy[47, 50].

6. Autophagy and cancer stem cells

Cancer stem cells (CSCs) are a small subpopulation of cells that can self-renewal and differentiation and have a role in the onset of the tumor, chemotherapy, and metastasis[51]. Numerous studies have examined the fundamental mechanism of maintaining this stem cell resistance, and autophagy may play an important role in this process. A previous study has shown autophagy regulates CSC homeostasis[52,53]. In glioma stem cells, inhibition of autophagy suppresses differentiation, while consist increase in autophagy leads to differentiation[54]. One study has shown that a decrease in LC3B-II and Beclin-1 is associated with the progression of astrocytic tumors[55]. However, autophagy cell death is detectable in glioma stem cells. The suppression of autophagy by cilengitide, an integrin antagonist, reduces cell cytotoxicity[54].

Therefore, it is not clear whether autophagy diminishes the amount of glioma stem cells. According to a study, On breast cancer stem cells, CSCs have a vital role in cancer recurrence and metastasis[56]. Silencing of two autophagy-related proteins, LC3B and ATG12, or treatment with autophagy inhibitors directly decreases cancer stem-cell-like phenotypes. Autophagy is linked to protective effects against various cellular stresses in breast CSCs. Necrosis also occurs in carcinoma under hypoxia and metabolic stress and as a result, causes induction of inflammation and progression of metastasis. One of the important factors in cancer metastasis is EMT which some EMT-regulators can boost EMT by eliminating cell adhesion and autophagy. It is found that autophagy deficiency, with stabilization of TWIST1, can enhance EMT[57].

7. The goal of autophagy in cancer treatment

Numerous studies show that autophagy can reinforce the tumor as well as suppress the tumor. The modulation of autophagy is a promising potential strategy to improve cancer therapy[23, 47]. A study has identified the drugs targeting all steps of the autophagic processes, from the initiation of the autophagosome to the degradation step[41,49]. Additionally, several studies have confirmed that autophagy plays key roles in anticancer therapy, including acquiring resistance to anticancer therapy. Autophagy enhanced by chemotherapy declines cell death, raises

cancer-cell survival, and is linked with drug resistance in cancer. Also, a previous study found that autophagy can facilitate cancer-cell survival and drug resistance to anticancer reagents and maintains stem cell-like properties in hepatocellular carcinoma. Another study illustrates that the suppression of autophagy leads to the promotion of apoptosis and the therapeutic effects of anticancer therapy. Besides, the use of the autophagy inhibitor chloroquine can enhance apoptosis and the therapeutic effects of photososan-II-mediated photodynamic therapy (PS-PDT) in colorectal cancer cells. To a large extent, evidence supports autophagy modulation as a promising and potential therapeutic target[23, 41, 47, 49].

Some autophagy regulators, such as rapamycin, rapamycin water-soluble derivatives (temsirolimus and everolimus), chloroquine (CQ: antimalarial agent), and hydroxychloroquine (HCQ: CQ derivative), are used in cancer therapy. Temsirolimus and everolimus, which inhibit mTORC1 and induce autophagy, are approved by the Food and Drug Administration (FDA) for cancer therapy. Everolimus treats progressive neuroendocrine tumors of pancreatic origin and breast cancer combined with exemestane. Additionally, temsirolimus is used to treat relapsed or refractory mantle-cell lymphoma in the European Union, while rapamycin is for coronary stents (a stent is a wire mesh stainless steel tube that holds an artery open and remains in the artery permanently) and rare pulmonary diseases[23, 57].

The CQ and HCQ, which have previously been used to prevent and treat malaria, are lysosomal inhibitors and directly inhibit autophagy through modification of lysosomal pH, inhibition of autophagic degradation, and accumulation of autophagosomes. The same approach, CQ or HCQ, can suppress cancer-cell growth in bladder cancer and pancreatic adenocarcinoma. In addition, some studies have shown that these reagents enhance the therapeutic effects of chemotherapy through the inhibition of autophagy-mediated resistance to cancer therapy[58]. Furthermore, Lys05 is a water-soluble analog of HCQ and was developed as a new lysosomotropic agent. It functions at a low dose and increases the pH of the lysosome, leading to autophagy inhibition. Notably, Lys05 indicates higher anticancer special effects than HCQ *in vitro* and *in vivo* in melanoma and colon cancer xenograft models.

Additionally, Lys05 combined with a BRAF inhibitor efficiently inhibited cancer *in vivo*. Thus, the development of autophagy-specific inhibitors is a novel therapeutic strategy for anticancer therapy. Other autophagy-related drugs have been developed for anticancer therapy. Spautin-1 inhibits autophagy and leads to the induction of proteasomal elimination of class III PI3K kinase complexes. The pro-apoptotic effect of Spautin-1 is related to GSK3β and affects a fundamental downstream effector of PI3K/Akt. Hence, Spautin-1 is a potential therapeutic agent for anticancer therapy. Moreover, SAR405 is a kinase inhibitor of Vps18 and Vps34 and spoils lysosomal function as well as influences the interaction between the late endosome and lysosome. SAR405 combined with everolimus enhances the inhibition of cancer proliferation in renal cancer cell lines. These results indicate that SAR405 has anticancer therapeutic effects as a Vps34 inhibitor[59].

8. Conclusion

Given the role of autophagy in tumor suppression, activation of autophagy may be an important strategy for cancer chemoprevention. To identify new strategies that selectively target autophagy in cancer cells without harming normal tissue, we must continue to define the cellular and metabolic functions of autophagy in both normal and tumor cells.

Declarations

Competing interests

The authors declare that they have no conflict of interest.

Authors' contribution

All authors were involved in interpretation and data collection, design of the article, review, and manuscript preparation.

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Ethical considerations

The authors checked for plagiarism and consented to the publishing of the article. The authors have also checked the article for data fabrication, double publication, and redundancy.

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References

1. Parzych KR and Klionsky DJ. An overview of autophagy: Morphology, mechanism, and regulation. Antioxid Redox Signal. 2014; 20(3): 460-73. DOI: 10.1089/ars.2013.5371
2. Yang Z and Klionsky DJ. Mammalian autophagy: Core molecular machinery and signaling regulation. Curr Opin Cell Biol. 2010; 22: 124-131. DOI: 10.1016/j.ceb.2009.11.014
3. Teng S, Li MY, Li PF, and Cao JM. Micro RNAs in cardiac autophagy: Small molecules and big role. Cells. 2018; 7(8): 104. DOI: 10.3390/cells7080104
4. Li X, He S, and Ma B. Autophagy and autophagy-related proteins in cancer. Mol Cancer. 2020; 19(1): 12. DOI: 10.1186/s12943-020-1138-4
5. Rajawat YS, Hilioti Z, and Bossis I. Aging: Central role for autophagy and the lysosomal degradative system. Ageing Res Rev. 2009; 8(3): 199-213. DOI: 10.1016/j.arr.2009.05.001
6. White E (2012). Deconvoluting the context-dependent role for autophagy in cancer. Nat Rev Cancer. 12(6): 401-410. DOI: 10.1038/nrc3262
7. Gozuacik D and Kimchi A. Autophagy as a cell death and tumor

suppressor mechanism. Oncogene. 2004; 23(16): 2891-2906. DOI: 10.1038/sj.onc.1207521
8. Bampton ETW, Goemans CG, Niranjan D, Mizushima N, and Tolkovsky AM. The dynamics of autophagy visualised in live cells: From autophagosome formation to fusion with endo/lysosomes. Autophagy. 2005; 1(1): 23-36. DOI: 10.4161/auto.1.1.1495
9. Tanida I, Ueno T, and Kominami E. LC3 conjugation system in mammalian autophagy. Int J Biochem Cell Biol. 2004; 36(12): 2503-2518. DOI: 10.1016/j.biocel.2004.05.009
10. Xu HD and Qin ZH. Beclin 1, Bcl-2 and autophagy. Adv Exp Med Biol. 2019; 1206: 109-126. DOI: 10.1007/978-981-15-0602-4_5
11. Chavez-Dominguez R, Perez-Medina M, Lopez-Gonzalez JS, Galicia-Velasco M, and Aguilar-Cazares D. The double-edge sword of autophagy in cancer: from tumor suppression to pro-tumor activity. Front Oncol. 2020; 10: 578418. DOI: 10.3389/fonc.2020.578418
12. Chang YT, Tseng HC, Huang CC, Chen YP, Chiang HC, and Chou FP. Relative down-regulation of apoptosis and autophagy genes in colorectal cancer. Eur J Clin Invest. 2011; 41(1): 84-92. DOI: 10.1111/j.1365-2362.2010.02383.x
13. Kenific CM and Debnath J. Cellular and metabolic functions for autophagy in cancer cells. Trends Cell Biol. 2015; 25(1): 37-45. DOI: 10.1016/j.tcb.2014.09.001
14. Choi KS. Autophagy and cancer. Exp Mol Med. 2012; 44(2): 109-120. Available at: https://www.nature.com/articles/emm201215
15. Kabeya Y, Kamada Y, Baba M, Takikawa H, Sasaki M, and Ohsumi Y. Atg17 functions in cooperation with Atg1 and Atg13 in yeast autophagy. Mol Biol Cell. 2005; 16(5): 2544-2553. DOI: 10.1091/mbc.e04-08-0669
16. Lorin S, Hamaï A, Mehrpour M, and Codogno P. Autophagy regulation and its role in cancer. Semin Cancer Biol. 2013; 23(5): 361-379. DOI: 10.1016/j.semcancer.2013.06.007
17. Ré AE, Fernández-Barrena MG, Almada LL, Mills LD, Elsawa SF, Lund G, et al. Novel AKT1-GLI3-VMP1 pathway mediates KRAS oncogene-induced autophagy in cancer cells. J Biol Chem. 2012; 287(30): 25325-25334. DOI: 10.1074/jbc.m112.370809
18. Nitsche BM, Burggraaf-van Welzen AM, Lamers G, Meyer V, and Ram AF. Autophagy promotes survival in aging submerged cultures of the filamentous fungus Aspergillus niger. Appl Microbiol Biotechnol. 2013; 97(18): 8205-8218. DOI: 10.1007/s00253-013-4971-1
19. Wen X, Wu J, Wang F, Liu B, Huang C, and Wei Y. Deconvoluting the role of reactive oxygen species and autophagy in human diseases. Free Radic Biol Med. 2013; 65: 402-410. DOI: 10.1016/j.freeradbiomed.2013.07.013
20. Redza-Dutordoir M and Averill-Bates DA. Interactions between reactive oxygen species and autophagy: Special issue: Death mechanisms in cellular homeostasis. Biochim Biophys Acta Mol Cell Res. 2021; 1868(8): 119041. DOI: 10.1016/j.bbamcr.2021.119041
21. Mannan A, Germon ZP, Chamberlain J, Sillar JR, Nixon B, and Dun MD. Reactive oxygen species in acute lymphoblastic leukaemia: Reducing radicals to refine responses. Antioxidants. 2021; 10(10): 1616. DOI: 10.3390/antiox10101616
22. Haruki K, Kosumi K, Hamada T, Twombly TS, Väyrynen JP, Kim SA, et al. Association of autophagy status with amount of Fusobacterium nucleatum in colorectal cancer. J Pathol. 2020; 250(4): 397-408. DOI: 10.1002/path.5381
23. Yun CW and Lee SH. The roles of autophagy in cancer. Int J Mol Sci. 2018; 19(11): 3466. DOI: 10.3390/ijms19113466
24. Eskelinen EL, Kageyama S, and Komatsu M. p62/SQSTM1 droplets initiate autophagosome biogenesis and oxidative stress control. Mol Cell Oncol. 2021; 8(2): 1890990. DOI: 10.1080/23723556.2021.1890990
25. Tian Y, Song W, Li D, Cai L, and Zhao Y. Resveratrol as a natural regulator of autophagy for prevention and treatment of cancer. Onco Targets Ther. 2019; 12: 8601-8609. DOI: 10.2147/ott.s213043
26. Revathidevi S and Munirajan AK. Akt in cancer: Mediator and more. Semin Cancer Biol. 2019; 59: 80-91. DOI: 10.1016/j.semcancer.2019.06.002
27. Zhang J, Zhang S, Shi Q, Allen TD, You F, and Yang D. The anti-apoptotic proteins Bcl-2 and Bcl-xL suppress Beclin 1/Atg6-mediated lethal autophagy in polyploid cells. Exp Cell Res. 2020; 394(1): 112112. DOI: 10.1016/j.yexcr.2020.112112
28. Usman RM, Razzaq F, Akbar A, Farooqui AA, Iftikhar A, Latif A, et al. Role and mechanism of autophagy-regulating factors in tumorigenesis and drug resistance. Asia Pac J Clin Oncol. 2021; 17(3): 193-208. DOI: 10.1111/ajco.13449
29. Kaur S and Changotra H. The beclin 1 interactome: Modification and roles in the pathology of autophagy-related disorders. Biochimie. 2020; 175: 34-49. DOI: 10.1016/j.biochi.2020.04.025
30. Qu X, Yu J, Bhagat G, Furuya N, Hibshoosh H, Troxel A, et al. Promotion of tumorigenesis by heterozygous disruption of the beclin 1 autophagy gene. J Clin Invest. 2003; 112(12): 1809-1820. DOI: 10.1172/JCI20039
31. Nasb M, Kirberger M, and Chen N. Molecular processes and regulation of autophagy. In: Chen N, editor. Exercise, autophagy and chronic diseases. Springer, Singapore; 2021; p. 1-27. DOI: 10.1007/978-981-16-4525-9_1
32. Yerbury JJ, Ooi L, Dillin A, Saunders DN, Hatters DM, Beart PM, et al. Walking the tightrope: Proteostasis and neurodegenerative disease. J Neurochem. 2016; 137(4): 489-505. DOI: 10.1111/jnc.13575
33. Reggiori F, Komatsu M, Finley K, and Simonsen A. Autophagy: More than a nonselective pathway. Int J Cell Biol. 2012; 2012: 219625. DOI: 10.1155/2012/219625
34. Udristioiu A and Nica-Badea D. Autophagy dysfunctions associated with cancer cells and their therapeutic implications. Biomed Pharmacother. 2019; 115: 108892. DOI: 10.1016/j.biopha.2019.108892
35. White E. The role for autophagy in cancer. J Clin Investig. 2015; 125(1): 42-46. DOI: 10.1172/JCI73941
36. Antunes F, Erustes AG, Costa AJ, Nascimento AC, Bincoletto C, Ureshino RP, et al. Autophagy and intermittent fasting: The connection for cancer therapy?. Clinics. 2018; 73(Suppl 1): e814s. DOI: 10.6061/clinics/2018/e814s
37. Maiuri MC, Tasdemir E, Criollo A, Morselli E, Vicencio JM, Carnuccio R, et al. Control of autophagy by oncogenes and tumor suppressor genes. Cell Death Differ. 2009; 16(1): 87-93. DOI: 10.1038/cdd.2008.131
38. Ariosa AR, Lahiri V, Lei Y, Yang Y, Yin Z, Zhang Z, et al. A perspective on the role of autophagy in cancer. Biochim Biophys Acta Mol Basis Dis. 2021; 1867(12): 166262. DOI: 10.1016/j.bbadis.2021.166262
39. Levy JM, Towers CG, and Thorburn A. Targeting autophagy in cancer. Nat Rev Cancer. 2017; 17(9): 528-542. Available at: https://www.nature.com/articles/nrc.2017.53
40. Chen HY and White E. Role of autophagy in cancer prevention. Cancer Prev Res. 2011; 4(7): 973-983. DOI: 10.1158/1940-6207.capr-10-0387
41. Yang ZJ, Chee CE, Huang S, and Sinicrope FA. The role of autophagy in cancer: Therapeutic implications. Mol Cancer Ther. 2011; 10(9): 1533-1541. DOI: 10.1158/1535-7163.mct-11-0047
42. Zhao H, Ming T, Tang S, Ren S, Yang H, Liu M, et al. Wnt signaling in colorectal cancer: Pathogenic role and therapeutic target. Mol Cancer. 2022; 21(1): 144. DOI: 10.1186/s12943-022-01616-7
43. Chen N and Karantza-Wadsworth V. Role and regulation of autophagy in cancer. Biochim Biophys Acta. 2009; 1793(9): 1516-1523. DOI: 10.1016/j.bbamcr.2008.12.013
44. Moscat J and Diaz-Meco MT. p62 at the crossroads of autophagy, apoptosis, and cancer. Cell. 2009; 137(6): 1001-1004. DOI: 10.1016/j.cell.2009.05.023
45. Zhong Z, Sanchez-Lopez E, and Karin M. Autophagy, inflammation, and immunity: A troika governing cancer and its treatment. Cell. 2016; 166(2): 288-298. DOI: 10.1016/j.cell.2016.05.051
46. Yessenkyzy A, Saliev T, Zhanaliyeva M, Masoud AR, Umbayev B, Sergazy S, et al. Polyphenols as caloric-restriction mimetics and autophagy inducers in aging research. Nutrients. 2020; 12(5): 1344. DOI: 10.3390/nu12051344
47. Pietrocola F, Pol J, Vacchelli E, Baracco EE, Levesque S, Castoldi F, et al. Autophagy induction for the treatment of cancer. Autophagy. 2016; 12(10): 1962-1964.
48. Shi TT, Yu XX, Yan LJ, and Xiao HT. Research progress of hydroxychloroquine and autophagy inhibitors on cancer. Cancer Chemother Pharmacol. 2017; 79(2): 287-924. DOI: 10.1007/s00280-016-3197-1
49. Udristioiu A and Nica-Badea D. Autophagy dysfunctions associated with cancer cells and their therapeutic implications. Biomed Pharmacot. 2019; 115: 108892. DOI: 10.1016/j.biopha.2019.108892
50. Vidoni C, Ferraresi A, Esposito A, Maheshwari C, Dhanasekaran DN, Mollace V, et al. Calorie restriction for cancer prevention and therapy: mechanisms, expectations, and efficacy. J Cancer Prev. 2021; 26(4): 224-236. DOI: 10.15430/jcp.2021.26.4.224
51. Desai A, Yan Y, and Gerson SL. Concise reviews: Cancer stem cell targeted therapies: Toward clinical success. Stem Cells Transl Med. 2019; 8(1): 75-81. DOI: 10.1002/sctm.18-0123
52. Nazio F, Bordi M, Cianfanelli V, Locatelli F, and Cecconi F. Autophagy

and cancer stem cells: Molecular mechanisms and therapeutic applications. Cell Death & Differentiation. 2019; 26(4): 690-702. Available at: https://www.nature.com/articles/s41418-019-0292-y
53. Smith AG and Macleod KF. Autophagy, cancer stem cells and drug resistance. The J Pathol. 2019; 247(5): 708-718. DOI: 10.1002/path.5222
54. Zhao Y, Huang Q, Yang J, Lou M, Wang A, Dong J, et al. Autophagy impairment inhibits differentiation of glioma stem/progenitor cells. Brain Res. 2010; 1313: 250-258. DOI: 10.1016/j.brainres.2009.12.004
55. Huang X, Bai HM, Chen L, Li B, and Lu YC. Reduced expression of LC3B-II and Beclin 1 in glioblastoma multiforme indicates a down-regulated autophagic capacity that relates to the progression of astrocytic tumors. J Clin Neurosci. 2010; 17(12): 1515-1519. DOI: 10.1016/j.jocn.2010.03.051
56. Gangopadhyay S, Nandy A, Hor P, and Mukhopadhyay A. Breast cancer stem cells: A novel therapeutic target. Clin Breast Cancer. 2013; 13(1): 7-15. DOI: 10.1016/j.clbc.2012.09.017
57. Yun CW and Lee SH. The roles of autophagy in cancer. Int J Mol Sci. 2018; 19(11): 3466. DOI: 10.3390/ijms19113466
58. Mauthe M, Orhon I, Rocchi C, Zhou X, Luhr M, Hijlkema KJ, et al. Chloroquine inhibits autophagic flux by decreasing autophagosome-lysosome fusion. Autophagy. 2018; 14(8): 1435-1455. DOI: 10.1080/15548627.2018.1474314
59. Kocak M, Ezazi Erdi S, Jorba G, Maestro I, Farrés J, Kirkin V, et al. Targeting autophagy in disease: Established and new strategies. Autophagy. 2022; 18(3): 473-495. DOI: 10.1080/15548627.2021.1936359