Effects of autophagy-related gene 5 on tumor development and treatment (Review)

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Abstract. Autophagy is a fundamental cellular metabolic process, whose main role is to remove excess or damaged organelles and maintain the normal structural state of cells. Autophagy-related gene 5 (ATG5) is one of the important genes involved in cellular autophagy, which is widely expressed in tissues and cells and connected to various signaling pathways. It is involved in the regulation of cell proliferation, invasion and migration as well as the tumor immune microenvironment, which affects the resistance to radiotherapy and chemotherapy, as well as the overall survival of tumor patients. Recently, many studies have confirmed that ATG5 plays a double-edged sword role on tumors, as it can play not only pro-tumor but also tumor-suppressive roles. However, its role in tumor treatment has not been systematically summarized. Therefore, this paper provides a systematic summary of the basic functions of ATG5, its role in the development and treatment of tumors and potentially give some ideas for clinical treatment of tumors.

Contents

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1. Introduction

As is well-established, tumors constantly affect human health (1). Numerous studies have demonstrated that tumor development and resistance to radiotherapy and chemotherapy are closely related to abnormal autophagic activities, and a comprehensive understanding of the molecular mechanisms of autophagy on tumors, can help develop targeted therapeutic strategies and provide novel insights into tumor treatment (2-5).

Autophagy is a highly conserved metabolic pathway by which cells regulate autophagy-related genes to remove abnormal proteins, damaged organelles and pathogenic microorganisms, in order to maintain cellular homeostasis (6-8). Under normal physiological conditions, autophagy allows cells to degrade damaged intracellular proteins, circulate nutrients, and generate energy in a timely manner to maintain cell viability in most tissues and under unfavorable conditions such as hypoxia or ischemia, as a cellular protective mechanism (9). However, persistent abnormalities in cellular autophagic activity can lead to various diseases (10-12), such as cardiovascular (13), neurodegenerative (14) and infectious diseases (15), as well as malignant tumors (16).

During the onset of autophagy, there are various autophagy-associated proteins (ATGs) that regulate and control the different stages of autophagosome formation and are key regulators of autophagosome formation (17,18). To date, scientists have identified >40 genes encoding ATG proteins in yeast, and most of them are highly conserved in yeast and mammals (19-21). In mammalian cells, starvation-induced autophagy is regulated by ~20 core ATG genes, and the more studied ATGs include ATG5, ATG6 (Beclin1), ATG7, and ATG8 (LC3-PE), among which ATG5 and ATG7 are decisive regulators of the pre-autophagic ubiquitination (22-24). ATG5 is dysregulated in numerous tumors and its role varies greatly among tumors, making it a double-edged sword with both promoting and inhibiting effects on tumors. This property also provides two concepts for tumor therapy: Inhibition of ATG5 to improve the effect of anticancer therapy or activation of ATG5 to induce autophagic death of tumor cells. The aim of the present study was to provide an overview of the basic functions of ATG5 and its mechanism of action in tumor development and treatment.

2. Methods

A biomedical literature retrieval website (http://www.ncbi.nlm.nih.gov/pubmed) was used to search for topic keywords related to this review. Subsequently, 'advanced' was selected on the PubMed homepage to enter the advanced search page, the corresponding search term was placed in the search box, and 'search' was selected to enter the search results interface.

In terms of 'Introduction', the keyword was 'ATG5', and initially 4,627 articles were gathered. Further screening was conducted, and 24 articles were ultimately selected.

In terms of 'Structure of ATG5', the key word was 'ATG5, structure', and initially 390 articles were collected. Further screening was conducted, and three articles were finally cited.

In terms of 'Biological functions of ATG5', this was divided it into the following aspects: In terms of 'DNA level regulation', the key words were 'ATG5, gene', and 2,262 articles were initially obtained, which were further analyzed and finally three articles were cited; in terms of 'Post-transcriptional level regulation', the key words were 'ATG5, mRNA', and 548 articles were initially selected, which were further screened and two articles were ultimately mentioned; in terms of 'Post-translational modifications', the key words were '(ATG5) AND (Phosphorylation) OR (Ubiquitination) OR (acetylation)'. Initially, 1,179 articles were amassed and further screening was performed, and finally seven articles were cited.

In terms of 'ATG5 is involved in tumorigenesis development', the key words were '(ATG5) AND (cancer)'. Initially, 1,648 articles were obtained and after further assessment, these were divided into the following aspects: In terms of 'ATG5 is involved in the autophagic process of tumors', after further analysis, nine articles were selected; in terms of 'ATG5 promotes tumor cell apoptosis', after further study, five articles were cited; in terms of 'ATG5 is involved in tumorigenesis development in other ways', after further screening, ultimately four articles were selected.

In terms of 'Dual effects of ATG5 on tumors', the key words were '(ATG5) AND (cancer)'. Initially 1,648 articles were obtained and further investigated, and divided into the following aspects: In terms of 'Upregulation of ATG5 expression', after further assessment, four articles were selected; in terms of 'Downregulation of ATG5 expression', after further screening, ultimately 30 articles were cited.

In terms of 'Role of ATG5 in tumor treatment', the key words were '(ATG5) AND (cancer)'. Initially 1,648 articles were obtained and further examined, and divided into the following aspects: In terms of 'Therapeutic strategies for downregulation of ATG5', after further screening, 13 articles were cited; in terms of 'Therapeutic strategies for upregulation of ATG5', following further assessment, five articles were selected.

3. Structure of ATG5

The ATG5 protein consists of three main structural domains (Fig. 1): Two ubiquitin-like structural domains at the N-terminal and C-terminal ends are connected by two junctional regions (L1 and L2) on either side of the multi-helix structural domain, respectively. Thr-193, located in the L2 junctional area, is the site where calpains cleave full-length 33 kDa ATG5 into 24 kDa truncated-ATG5 (tATG5), that promotes apoptosis by targeting mitochondria (25). Both ubiquitin-like structures consist of five-stranded β-pleated sheets and two α-helices. The multi-helix structure consists of one short α-helix and two long α-helices, and the conjugation site Lys-149 of ATG5 and ATG12 is located in this structural domain. The ATG5-ATG12 complex binds ATG16 to generate the autophagy elongation complex to promote autophagy. There is also an α-helix structural domain in addition to the N-terminal ubiquitin-like structural domain (26,27).

4. Biological functions of ATG5

DNA level regulation. The c allele of the rs2245214 ATG5 gene polymorphism is associated with increased susceptibility to non-small cell lung cancer (NSCLC), while the (guanine/cytosine) GC genotype of this polymorphism is associated with reduced risk and therefore may have a protective role in the development of NSCLC (28). SMARCB1 is a tumor suppressor gene that inhibits the malignant proliferation of chordoma cells both *in vitro* and *in vivo*. The molecular mechanism of tumor suppression directly binds to the ATG5 promoter (+8 to +263 bp) and epigenetically suppresses its transcription, which decreases ATG5 expression and downregulates autophagy (29). Nuclear respiratory factor 1 (NRF1) can act as a transcription factor that binds to the ATG5 promoter, promoting ATG5 transcription and subsequently upregulating autophagy levels, while reduced autophagic activity contributes to the development of melanoma (30).

Post-transcriptional level regulation. MicroRNAs (miRNAs/miRs) can negatively regulate ATG5 at the post-transcriptional level by binding to the 3'UTR of ATG5 mRNA (31). LncRNA IDH1-AS1 regulates the stability of ATG5 mRNA by interacting with the selective splicing regulatory protein PTBP3 to upregulate expression, which in turn promotes autophagy and prostate cancer cell proliferation (32).

Post-translational modifications

Phosphorylation. In hypoxia-induced glioblastoma (GBM) cells, hypoxia-induced ELP3-mediated acetylation of PAK1 inhibits PAK1 dimerization and enhances its activity, thus leading to PAK1-mediated phosphorylation of ATG5 at residue T101, which protects ATG5 from ubiquitin-dependent degradation and increases the affinity between the ATG12-ATG5 complex and ATG16L1, that promotes the formation of autophagosomes (33).

Ubiquitination. Ubiquitination-proteasome is a major intracellular protein degradation pathway in eukaryotes, and the immunoproteasome subunit β5i in cardiac myocytes promotes ubiquitination and degradation of ATG5 protein, thereby inhibiting autophagy that leads to myocardial hypertrophy (34). Ubiquitin-specific peptidase 22 (USP22) stabilizes ATG5 by reducing the ubiquitination of ATG5 at the K27- and K48-linkages Lys118 site, promoting autophagosome formation, inhibiting NLRP3 inflammatory vesicle activation, and preventing excessive inflammation (35).

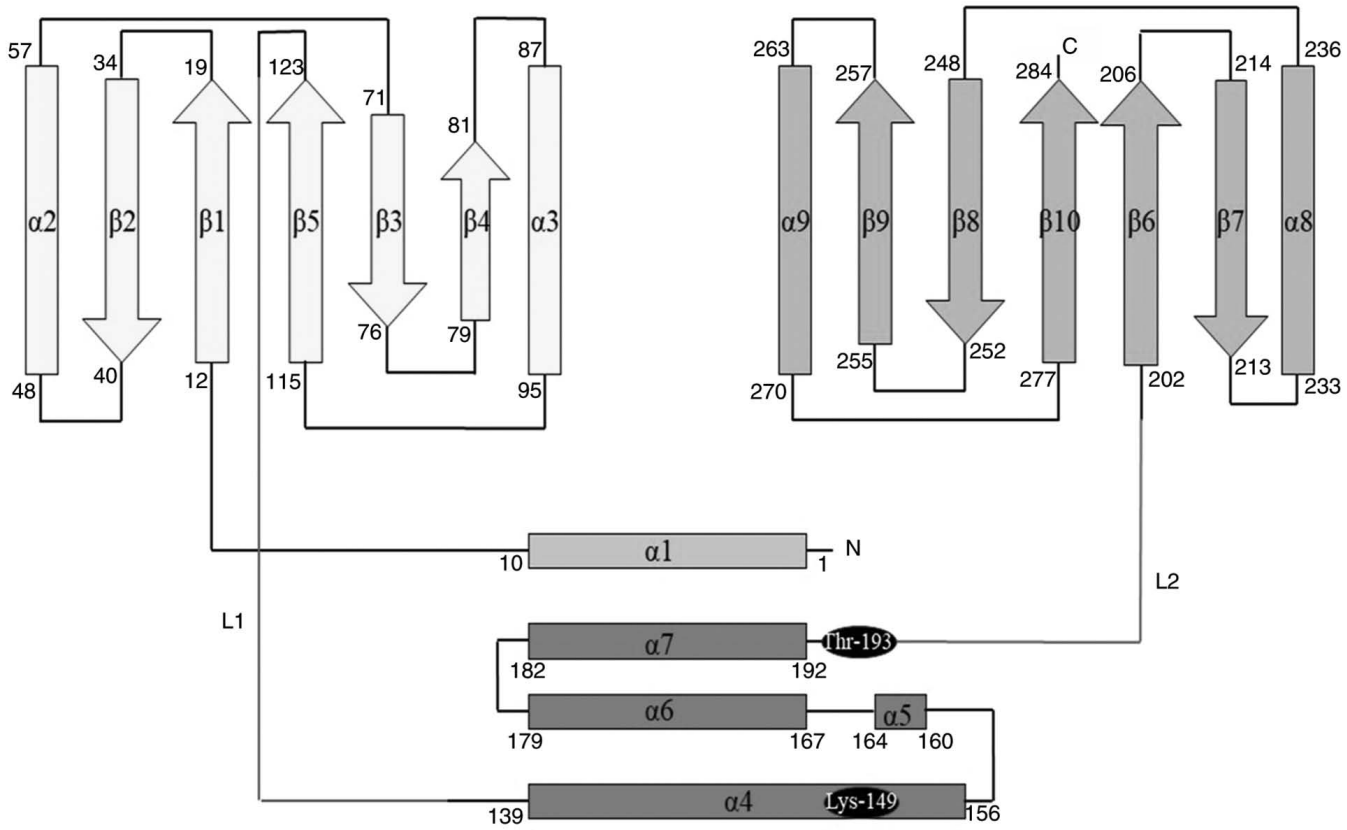

Figure 1. Protein structure diagram of autophagy-related gene 5.

Acetylation. Acetylation which is an important post-translational modification of proteins in mammalian cells, is involved in the regulation of numerous biological processes (36-38). Histone acetyltransferase p300 inhibits autophagy by acetylating other autophagy-related proteins of ATG5, regulating cell growth and proliferation (39).

5. ATG5 is involved in tumorigenesis development

ATG5 is involved in the autophagic process of tumors. Cellular autophagy can be divided into five phases: Autophagy induction phase, nucleation process, extension phase of the autophagosome, maturation phase of the autophagosome, and lysis phase of the autophagosome (40). ATGs are continuously recruited near the vesicles and assembled to form autophagic precursors, whose maturation requires the continuous extension of autophagosomal membranes (41,42). ATG5, as the main regulator of the pre-autophagic ubiquitination process, plays a decisive role in the development of autophagy. ATG12 covalently modifies ATG5 by the E1-like enzyme, ATG7, and the E2-like enzyme, ATG10, and binds to ATG5 to form the ATG12-ATG5 conjugate, which eventually binds to ATG16 to form the ATG12-ATG5-ATG16 ubiquitin-like protein conjugation system that participates in the membrane elongation process in two ways: Directly bound to the membrane or as an E3-like enzyme involved in LC3III-PE splicing for subsequent activation of autophagy (43-45) (Fig. 2).

It has been shown that in HBx-associated hepatocellular carcinoma (HCC) cells, where autophagy levels are upregulated, downregulation of autophagy levels by inhibition of

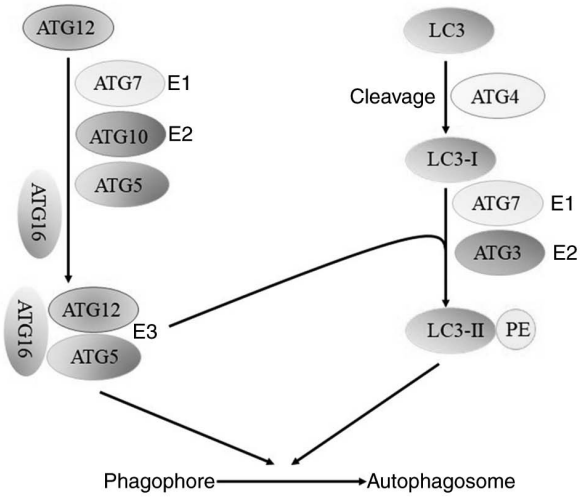

Figure 2. Autophagy-related gene 5 is involved in the formation of autophagosomes.

ATG5 expression attenuates HBx-induced cell cycle acceleration and G1/S block-induced proliferative responses, thereby inhibiting HCC proliferation (46). Wang *et al* (47) revealed that inhibition of ATG5 expression in human colon cancer cells (HCT116) followed by induction of EMT through the SQSTM1-NFKB pathway could promote cell migration and induce invasion. Liang *et al* (48) reported that cadmium, a carcinogenic heavy metal, inhibited cellular autophagy and

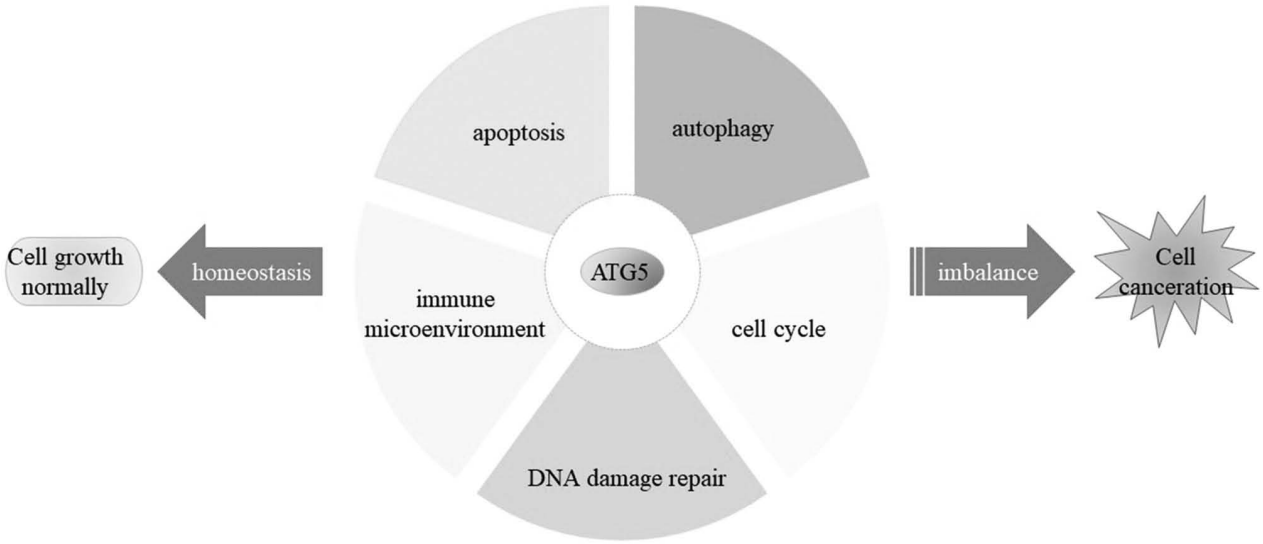

Figure 3. ATG5 is involved in the occurrence and development of tumors. ATG5, autophagy-related gene 5.

promoted the proliferation and migration of breast cancer cells through the downregulation of ATG5 expression, suggesting that ATG5 expression can inhibit the metastasis of certain cancer cells.

ATG5 promotes tumor cell apoptosis. In addition to regulating autophagosome formation of tumor cells, ATG5 also has an important role in tumor cell apoptosis, with direct or indirect pro-apoptotic effects. In breast cancer cells, ATG5 is cleaved by calpain and the cleavage product truncated-ATG5 (1-193) (tATG5), targets mitochondria with pro-apoptotic activity (25). Cyathin Q is a diterpene compound extracted from a fungus that can inhibit the growth and proliferation of HCT116. Upon compound action on cells, mitochondria produce reactive oxygen species (ROS), which on the one hand induces apoptosis by directly downregulating the apoptosis-inhibiting protein Bcl-2 and upregulating the pro-apoptotic protein Bim, and on the other hand, promotes cell death by cleaving the ATG5 protein to convert autophagy into apoptosis (49). Cinobufagin, a butyrolactone steroid with anticancer activity, can reduce the expression of autophagy-related proteins, such as ATG5, to downregulate autophagy levels and enhance apoptosis levels, thus inhibiting gastric cancer cell proliferation (50). In NSCLC, low expression of TECPR1 downregulates ATG5 expression, downregulates Bax and LC3-II/LC3-I, upregulates p62 and Bcl-2, thus inhibiting apoptosis and enhancing cell viability (51). Zheng *et al* (52) reported that in rectal colon cancer cells, high expression of lncRNA HAGLROS targeted upregulation of ATG5 through competitive binding with miR-100, which in turn activated the PI3K/AKT/mTOR pathway and inhibited HCT116 cell apoptosis.

ATG5 is involved in tumorigenesis development in other ways. ATG5 mediates the cell cycle distribution of acute myeloid leukemia mesenchymal stem cells (AML MSC) and silencing of the ATG5 gene increases the proportion of the G0/G1 phase and decreases the proportion of the G2 phase, inhibiting the proliferation of AML MSC (53). ATG5 also has an important role in the tumor immune microenvironment, and it was determined that ATG5 is an essential protein for the presentation of tumor antigens by dendritic cells to activate $CD4^+$ T cells to produce cytokines such as IL-2 and IFN-γ, thus initiating an immune response to inhibit tumor growth and proliferation (54). ATG5 also plays a role in DNA damage repair. Demirbag-Sarikaya *et al* (55) revealed that when 293T and HeLa cells were subjected to genotoxic compounds such as etoposide, cisplatin and adriamycin, ATG5 interacted directly with the non-homologous end joining (NHEJ) repair mechanism protein Ku70 in the nucleus to repair damaged DNA, rendering the cells resistant to the drug, and it was also reported the ATG5-Ku70 interaction was required for DNA damage repair. In addition, nuclear translocation of ATG5 can cause drug resistance in tumor cells. By analyzing clinical rectal colon cancer specimens, Sun *et al* (56) revealed that ATG5 exhibited nuclear translocation in rectal colon cancer cells, nuclear ATG5 bound to Mis18α to form ATG5-Mis18α interaction, and ATG5-Mis18α overexpression induced MLH1 deletion by promoting MLH1 promoter CpG island hypermethylation, thus leading to drug resistance in rectal colon cancer cells. Therefore, ATG5 or ATG5-Mis18α may be used as a therapeutic target for rectal colon cancer cells. The pattern of ATG5 involvement in tumorigenesis development is shown in Fig. 3.

6. Dual effects of ATG5 on tumors

Upregulation of ATG5 expression. Yu *et al* (57) determined that hypoxia-inducible factor HIF1α could directly bind to the ATG5 promoter of human prostate cancer cells (PC-3) to upregulate the expression of ATG5, thereby increasing the level of autophagy and promoting the proliferation and migration of PC-3 cells. Wang *et al* (58) revealed that miR-20a increased the level of autophagy by targeting ATG5 and upregulating its expression to promote the proliferation of osteosarcoma cells. Zhou *et al* (59) through KM analysis demonstrated that among numerous ATGs, ATG5 was the most detrimental

Table I. ceRNA/miRNAs/ATG5 regulatory signaling pathways in various types of tumors.

Types of tumors	Tumor marker	Signaling pathway	ATG5 expression	Autophagy level	Effects on tumors	(Refs.)
Gastric cancer	lncRNA XIST ↑	miR-30c/ATG5	↑	↑	Promotes	(70)
Gastric cancer	lncRNA CCT1 ↑	miR-140-3p/ATG5	↑	↑	Promotes	(71)
Lung cancer	lncRNA PVT1 ↑	miR-140-3p/ATG5	↑	↑	Chemoresistance	(72)
Papillary thyroid Carcinoma	lncRNA GAS8-AS1 ↓	miR-187-3p/ATG5	↓	↓	Promotes	(73)
Non-small cell lung cancer	circ-FOXM1 ↓	miR-149-5p/ATG5	↓	↓	Promotes	(74)
Colorectal cancer	miR-183-3p ↑	miR-183-3p/ATG5	↓	↓	Radioresistance	(75)
Colorectal cancer	miR-20a ↓	miR-20a/ATG5/FI200	↑	↑	Promotes	(76)
Bladder cancer	miR-30a-3p ↓	miR-30a-3p/ATG5	↑	↑	Chemoresistance	(77)
Renal cell carcinoma	miR-30d-5p ↓	miR-30d-5p/ATG5	↑	↑	Promotes	(78)

ATG5, autophagy-related gene 5.

factor affecting the prognosis of patients with cervical cancer, and the survival of patients with cervical cancer with high ATG5 expression was shorter regardless of clinical stage and pathological grading. Analysis also revealed that ATG5 was involved in ERK/NFκBp65/mTOR pathway-induced epithelial-mesenchymal transition (EMT) promoting migration and invasion of cervical cancer cell lines. This suggests that ATG5 may be a potentially powerful therapeutic target for cervical cancer. In prostate cancer cells (PCa) (60), CHRM1 was highly expressed and targeted ATG5 through the AMPK/mTOR signaling pathway to regulate cellular autophagy and promote cancer cell infiltration and metastasis.

Downregulation of ATG5 expression. ATG5 expression was revealed to be significantly reduced in melanoma tissues, and associated with poor patient prognosis, as a consequence of reduced nuclear respiratory factor 1 (NRF1) activity (30). In papillary thyroid carcinoma, RBM47 expression was reduced and decreased ATG5 expression through the SNHG5/FOXO3/ATG5 axis to decrease autophagy levels, thus promoting cancer cell proliferation (61). ANXA1 was demonstrated to promote nasopharyngeal carcinoma cell migration and invasive metastasis by activating the PI3K/AKT signaling pathway, downregulating ATG5 expression, and decreasing autophagy levels (62).

Long non-coding RNAs (lncRNAs) are a group of non-coding RNAs that are >200 nucleotides in length, typically accounting for >80% of a whole-genome transcript (63-65). Circular RNAs (circRNAs) are a class of non-coding RNAs that do not have a 5' end cap and a 3' end poly(A) tail and are covalently bonded to form a circular structure (66). LncRNAs and circRNAs can both compete as endogenous competing RNAs (ceRNAs) to bind miRNAs (67-69). MiRNAs are a group of small non-coding RNAs of ~22-24 nucleotides in length that negatively regulate target genes at the post-transcriptional level by binding to the 3'UTR of target mRNAs, and the competitive binding of ceRNAs to miRNAs can reverse this negative regulation. An increasing number of studies (70-78) have shown that the regulatory pattern of ceRNA/miRNAs/ATG5 plays an important role in tumorigenesis development. The ceRNA/miRNAs/ATG5 regulatory patterns in different types of tumors are listed in Table I.

Therefore, ATG5 has a dual role in tumors through the activation of autophagic activity. This dual role is reflected in different stages of tumor development. On the one hand, usually, autophagy plays an oncogenic role in the initiation stage of tumorigenesis, and in the early stage of tumorigenesis, autophagy can reduce tumorigenesis by inhibiting the continuous growth of precancerous cells. Tumor cells can survive by using the autophagy mechanism to fight against nutrient deficiency and hypoxia in the intermediate and advanced stages of tumor development (43,79,80), which indicates that autophagy inhibition may be an effective anticancer therapy for intermediate and advanced cancers. On the other hand, cellular autophagy also plays a dual role in tumor migration, infiltration, and differentiation of tumor stem cells, being involved in both inhibition of tumor growth to promote cancer cell death (cytotoxic/non-protective autophagy) and possibly providing nutrients to tumor cells to promote cancer cell survival (protective autophagy) (81-83). Moreover, ATG5 has different dual roles for various types of cancer cells, with high ATG5 expression associated with poor prognosis in CESC (59), early esophageal squamous cell carcinoma (84), and neuroblastoma (85). By contrast, high ATG5 expression predicts a favorable prognosis for patients with breast cancer (86) and osteosarcoma (87). This property also provides two concepts for tumor treatment: Inhibition of ATG5 to improve anticancer therapy or activation of ATG5 to induce autophagic death of tumor cells.

7. Role of ATG5 in tumor treatment

Studies have revealed that inhibition of non-protective autophagy in tumor cells has little effect on the sensitivity of cancer cells to chemotherapy and radiotherapy (88), but

inhibition of protective autophagy can increase chemotherapeutic drug-induced apoptosis in cancer cells (89), and inhibition of protective autophagy in tumor cells can suppress STAT3 signaling pathway-mediated DNA damage repair (90), thus increasing the sensitivity of tumor cells to radiotherapy. Therefore, protective autophagy inhibitors combined with conventional treatment of tumors provide novel therapeutic strategies for cancer treatment (91-95). ATG5 plays a pivotal role in regulating cancer resistance to radiation and drug resistance through the activation of autophagy, and blocking or activating autophagy through ATG5 may be used to develop a promising tumor treatment strategy.

Therapeutic strategies for downregulation of ATG5. Chen *et al* (96) revealed that the cisplatin-induced apoptosis of A549 lung cancer cells could be promoted by inhibiting the expression of ATG5, suggesting that ATG5 can be used as a drug target for tumor treatment, thus providing theoretical support for the precise treatment of tumors. SMARCB1, an oncogene, is a core component of the SWI/SNF complex that binds directly to the promoter region of ATG5 in the nucleus to epigenetically repress ATG5 transcription, thereby downregulating autophagy and inhibiting cell carcinogenesis (29). Mo *et al* (97) revealed that inhibition of the expression of the autophagy-related gene ATG5, decreased Rad51 mRNA expression and increased DNA damage levels and induced apoptosis in tumor cells, enhancing the radiosensitivity of nasopharyngeal carcinoma cells. It was reported that the radiosensitivity of head and neck squamous cell carcinoma (HNSCC) could be activated by inhibiting ATG5 expression, and ATG5 inhibitor combined with solute carrier family 3 member 2 targeting (SLC3A2) may be an effective strategy for radiosensitization of HNSCC (98). Bellare *et al* (99) revealed that autophagy in breast cancer cells could cause the development of PARP inhibitor (PARPi) talazoparib resistance, and that drug-induced DNA damage repair could be converted to NHEJ by inhibiting ATG5 expression, ultimately leading to genomic instability and cell death. Han *et al* (100) reported that MCF10A cells secreting exosomes delivering miR-567 could be taken up by trastuzumab-resistant cells, thus reversing trastuzumab resistance in breast cancer cells by targeting the downregulation of ATG5. Decreased miR-137 expression in adriamycin-activated pancreatic cancer cells, rendered pancreatic cancer cells resistant to chemotherapy. In this study, miR-137 could also enhance cellular chemosensitivity by directly inhibiting ATG5 and downregulating autophagy levels (101). In ADR-resistant liver carcinoma (HepG2/ADR) cells, the downregulation of miR-155-5p expression and the upregulation of ATG5 expression rendered HCC cells resistant to the drug (102). In NSCLC, miRNA-153-3p suppressed autophagy by directly binding to the ATG5 gene to downregulate ATG5 expression. However, in gefitinib-resistant NSCLC, miRNA-153-3p expression was reduced, leading to the upregulation of autophagy levels, thus rendering the cells resistant to the drug (103). Polypyrimidine tract-binding protein 1 (PTBP1) is a common RNA-binding protein whose main function is to selectively splice exons or introns to produce different mRNA isoforms by binding to specific sequences of target gene precursor mRNAs as a splicing factor. Compared to sensitive cells, IncRNA ZNF649-AS1 was revealed to be more highly

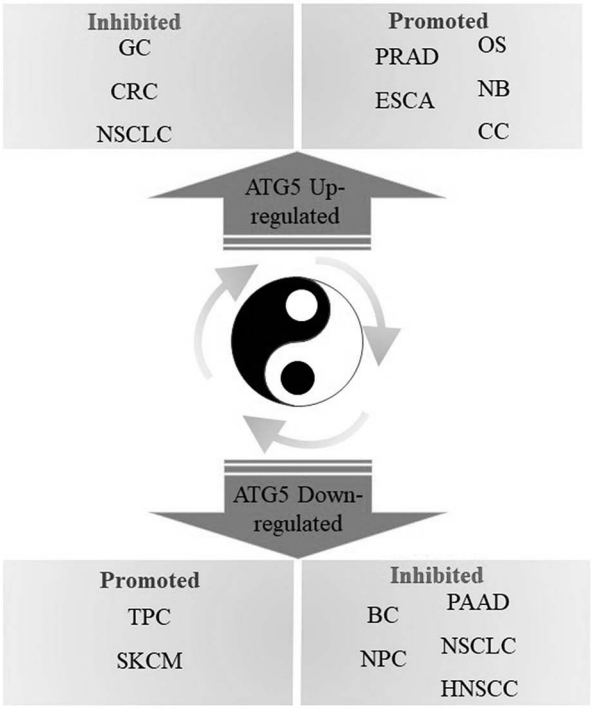

Figure 4. Double-edged sword role of ATG5 in tumor treatment. ATG5, autophagy-related gene 5; GC, gastric cancer; NSCLC, non-small cell lung cancer; BC, breast cancer; CRC, colorectal cancer; NB, neuroblastoma; OS, osteosarcoma; PRAD, prostate cancer; CC, cervical cancer; ESCA, esophageal squamous cell carcinoma; PAAD, pancreatic adenocarcinoma; NPC, nasopharyngeal carcinoma; HNSCC, head and neck squamous cell carcinoma; SKCM, skin cutaneous melanoma; TPC, thyroid papillary carcinoma.

expressed in trastuzumab-resistant breast cancer cells, where it increased ATG5 transcription by binding to PTBP1 in the cytoplasm, thereby increasing the level of ATG5 expression, which in turn upregulated the level of autophagy and rendered the cells resistant to the drug (104). Curcumin was demonstrated to upregulate miR-181a expression in triple-negative breast cancer cells (TNBC). miR-181a downregulated ATG5 levels by binding directly to ATG5, thus downregulating autophagy levels in TNBC cells, maintaining cell stemness, and inhibiting tumor cell growth (31). Lomeguatrib inhibited the proliferation, invasion, migration, and autophagy of PanC-1/GEM cells by inhibiting MGMT, downregulating the expression of the apoptosis inhibitory proteins Bcl-2, Beclin1, and autophagy-related protein ATG5. Upregulation of the expression of pro-apoptotic proteins caspase-3 and Bax could promote apoptosis in PanC-1/GEM cells (105). Icariin could significantly downregulate the expression of autophagy-related proteins such as ATG5, inhibit cellular autophagy, and induce G0/G1 phase cell cycle arrest and apoptosis, thereby inhibiting MCF-7/TAM cell proliferation (106). Therefore, combining ATG5 inhibitors with traditional antitumor treatment modalities can provide novel insights into tumor treatment.

Therapeutic strategies for upregulation of ATG5. Quinoline derivatives are a new class of antitumor drugs with the potential for development. A series of 4,7-disubstituted quinoline derivatives were designed, synthesized, and evaluated for their anti-proliferative activity. The results revealed that compounds

10c, 10g, 10i, 10j, and 10k had strong anti-proliferative activity against human tumor cells, with compound 10k being the most active, and could inhibit colorectal cancer cell growth by targeting and stabilizing ATG5 to induce autophagy (107).

It has also been recently revealed that ATG5 is required for the presentation of tumor antigens by dendritic cells to initiate an anti-tumor $CD4^+$ T cell immune response, acting as an antitumor agent. Therefore, upregulation of ATG5 expression in certain tumors can exploit the immune response of the tumor tissue to act as an antitumor agent (54). Procyanidin B2 (PB2) is a natural flavonoid compound with antitumor effects that can inhibit gastric cancer cell proliferation by inhibiting the PI3K/Akt/mTOR pathway, promoting the protein expression of ATG5 and Beclin-1, and upregulating autophagy levels (108). Muyin extract (MSE), a 1:1 mixture of Muyin seed and *Epimedium* extract, has been revealed to regulate apoptosis-related protein expression by blocking the Akt/mTOR pathway, regulate apoptosis-related proteins to promote apoptosis, upregulate the expression levels of autophagy-related genes ATG5 and Beclin-1, induce autophagy, and exhibits favorable antitumor activity in NSCLC (109). Cinnamaldehyde (CA) is the active component in cinnamon with inhibitory effects on tumor growth, migration, and invasion, which can induce the expressions of Beclin-1, ATG5, and LC3B and inhibit the expression of p62 through the PERK/ATF4/CHOP pathway to lead to autophagic cell death (110).

ATG5 is a double-edged sword in cancer progression, as autophagy induced by ATG5 provides essential nutrients to cancer cells, maintains their metabolism, and allow cells to survive after increased stress. However, after excessive induction of autophagy degradation, cancer cell death may also be induced. During tumor progression, ATG5 expression is also regulated by other pathways, not by the autophagy pathway. Therefore, the tumor suppressive function of ATG5 in cancer may exist independently of autophagy. In addition, ATG5 expression levels may vary in different types of tumor cells and at different stages of tumor development. These observations suggest that inhibiting or activating ATG5 may be a favorable strategy to inhibit cancer progression. On the one hand, in some cancers, such as colorectal (107), gastric (108,110) and non-small cell lung cancer (109), autophagy can be induced by ATG5 activator to promote the apoptosis of tumor cells, thus aiding tumor treatment. On the other hand, in some cancers, such as nasopharyngeal (97), breast (100) and pancreatic cancer (101), autophagy can be inhibited by ATG5 inhibitors to achieve successful tumor treatment (Fig. 4).

8. Conclusion

ATG5 is an important member of numerous autophagy-related genes. In addition to participating in the classical autophagy pathway, ATG5 also plays an important role in the occurrence and development of tumors, such as apoptosis (51), cell cycle regulation (53), maintaining genomic stability (55) and immune inflammatory signaling pathways (54).

In conclusion, the study of the molecular mechanism of the effect of ATG5 on tumors can help develop targeted therapeutic strategies and provide novel insights into tumor treatment (4). In the future, activators or inhibitors of ATG5 could be used as drug candidates for cancer treatment. ATG5 may also be used as a tumor marker for diagnosis (59), and has a reference value for predicting patient prognosis. Although the interplay between its involvement in the autophagy activation mechanism and apoptosis, as well as the association between autophagy and clinical drug resistance still requires further investigation, it is considered that more drugs selectively targeting ATG5 will be used in the future, which may aid in overcoming cancer.

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Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Xue C, Chu Q, Zheng Q, Jiang S, Bao Z, Su Y, Lu J and Li L: Role of main RNA modifications in cancer: N^6-methyladenosine, 5-methylcytosine, and pseudouridine. Signal Transduct Target Ther 7: 142, 2022.
2. Kocaturk NM, Akkoc Y, Kig C, Bayraktar O, Gozuacik D and Kutlu O: Autophagy as a molecular target for cancer treatment. Eur J Pharm Sci 134: 116-137, 2019.
3. Onorati AV, Dyczynski M, Ojha R and Amaravadi RK: Targeting autophagy in cancer. Cancer 124: 3307-3318, 2018.
4. Ferro F, Servais S, Besson P, Roger S, Dumas JF and Brisson L: Autophagy and mitophagy in cancer metabolic remodelling. Semin Cell Dev Biol 98: 129-138, 2020.
5. Amaravadi RK, Kimmelman AC and Debnath J: Targeting autophagy in cancer: Recent advances and future directions. Cancer Discov 9: 1167-1181, 2019.
6. Lin PW, Chu ML and Liu HS: Autophagy and metabolism. Kaohsiung J Med Sci 37: 12-19, 2021.
7. Gómez-Virgilio L, Silva-Lucero MD, Flores-Morelos DS, Gallardo-Nieto J, Lopez-Toledo G, Abarca-Fernandez AM, Zacapala-Gómez AE, Luna-Muñoz J, Montiel-Sosa F, Soto-Rojas LO, *et al*: Autophagy: A key regulator of homeostasis and disease: An overview of molecular mechanisms and modulators. Cells 11: 2262, 2022.
8. Wen X, Yang Y and Klionsky DJ: Moments in autophagy and disease: Past and present. Mol Aspects Med 82: 100966, 2021.

9. Cao W, Li J, Yang K and Cao D: An overview of autophagy: Mechanism, regulation and research progress. Bull Cancer 108: 304-322, 2021.
10. Saha S, Panigrahi DP, Patil S and Bhutia SK: Autophagy in health and disease: A comprehensive review. Biomed Pharmacother 104: 485-495, 2018.
11. Klionsky DJ, Petroni G, Amaravadi RK, Baehrecke EH, Ballabio A, Boya P, Bravo-San Pedro JM, Cadwell K, Cecconi F, Choi AMK, *et al*: Autophagy in major human diseases. EMBO J 40: e108863, 2021.
12. Behera J, Ison J, Tyagi A, Mbalaviele G and Tyagi N: Mechanisms of autophagy and mitophagy in skeletal development, diseases and therapeutics. Life Sci 301: 120595, 2022.
13. Mameli E, Martello A and Caporali A: Autophagy at the interface of endothelial cell homeostasis and vascular disease. FEBS J 289: 2976-2991, 2022.
14. Yu QY, Ye LQ and Li HL: Molecular interaction of stress granules with Tau and autophagy in Alzheimer's disease. Neurochem Int 157: 105342, 2022.
15. Carinci M, Palumbo L, Pellielo G, Agyapong ED, Morciano G, Patergnani S, Giorgi C, Pinton P and Rimessi A: The multifaceted roles of autophagy in infectious, obstructive, and malignant airway diseases. Biomedicines 10: 1944, 2022.
16. Hernandez GA and Perera RM: Autophagy in cancer cell remodeling and quality control. Mol Cell 82: 1514-1527, 2022.
17. Li X, He S and Ma B: Autophagy and autophagy-related proteins in cancer. Mol Cancer 19: 12, 2020.
18. Levine B and Kroemer G: Biological functions of autophagy genes: A disease perspective. Cell 176: 11-42, 2019.
19. Song Q, Liu H, Zhen H and Zhao B: Autophagy and its role in regeneration and remodeling within invertebrate. Cell Biosci 10: 111, 2020.
20. Pradel B, Robert-Hebmann V and Espert L: Regulation of Innate Immune Responses by Autophagy: A Goldmine for Viruses. Front Immunol 11: 578038, 2020.
21. Cao Y, Luo Y, Zou J, Ouyang J, Cai Z, Zeng X, Ling H and Zeng T: Autophagy and its role in gastric cancer. Clin Chim Acta 489: 10-20, 2019.
22. Shu F, Xiao H, Li QN, Ren XS, Liu ZG, Hu BW, Wang HS, Wang H and Jiang GM: Epigenetic and post-translational modifications in autophagy: Biological functions and therapeutic targets. Signal Transduct Target Ther 8: 32, 2023.
23. Zheng W, Xie W, Yin D, Luo R, Liu M and Guo F: ATG5 and ATG7 induced autophagy interplays with UPR via PERK signaling. Cell Commun Signal 17: 42, 2019.
24. He M, Li M, Guan Y, Wan Z, Tian J, Xu F, Zhou H, Gao M, Bi H and Chong T: A New prognostic risk score: Based on the analysis of autophagy-related genes and renal cell carcinoma. Front Genet 12: 820154, 2021.
25. Yousefi S, Perozzo R, Schmid I, Ziemiecki A, Schaffner T, Scapozza L, Brunner T and Simon HU: Calpain-mediated cleavage of Atg5 switches autophagy to apoptosis. Nat Cell Biol 8: 1124-1132, 2006.
26. Matsushita M, Suzuki NN, Obara K, Fujioka Y, Ohsumi Y and Inagaki F: Structure of Atg5.Atg16, a complex essential for autophagy. J Biol Chem 282: 6763-6772, 2007.
27. Noda NN, Fujioka Y, Hanada T, Ohsumi Y and Inagaki F: Structure of the Atg12-Atg5 conjugate reveals a platform for stimulating Atg8-PE conjugation. EMBO Rep 14: 206-211, 2013.
28. Nikseresht M, Shahverdi M, Dehghani M, Abidi H, Mahmoudi R, Ghalamfarsa G, Manzouri L and Ghavami S: Association of single nucleotide autophagy-related protein 5 gene polymorphism rs2245214 with susceptibility to non-small cell lung cancer. J Cell Biochem 120: 1924-1931, 2019.
29. Li M, Shen Y, Xiong Y, Wang S, Li C, Bai J and Zhang Y: Loss of SMARCB1 promotes autophagy and facilitates tumour progression in chordoma by transcriptionally activating ATG5. Cell Prolif 54: e13136, 2021.
30. Frangež Ž, Gérard D, He Z, Gavriil M, Fernández-Marrero Y, Seyed Jafari SM, Hunger RE, Lucarelli P, Yousefi S, Sauter T, *et al*: ATG5 and ATG7 expression levels are reduced in cutaneous melanoma and regulated by NRF1. Front Oncol 11: 721624, 2021.
31. Park JW, Kim Y, Lee SB, Oh CW, Lee EJ, Ko JY and Park JH: Autophagy inhibits cancer stemness in triple-negative breast cancer via miR-181a-mediated regulation of ATG5 and/or ATG2B. Mol Oncol 16: 1857-1875, 2022.
32. Zhang N, Li Z, Bai F and Zhang S: PAX5-induced upregulation of IDH1-AS1 promotes tumor growth in prostate cancer by regulating ATG5-mediated autophagy. Cell Death Dis 10: 734, 2019.
33. Feng X, Zhang H, Meng L, Song H, Zhou Q, Qu C, Zhao P, Li Q, Zou C, Liu X and Zhang Z: Hypoxia-induced acetylation of PAK1 enhances autophagy and promotes brain tumorigenesis via phosphorylating ATG5. Autophagy 17: 723-742, 2021.
34. Xie X, Bi HL, Lai S, Zhang YL, Li N, Cao HJ, Han L, Wang HX and Li HH: The immunoproteasome catalytic β5i subunit regulates cardiac hypertrophy by targeting the autophagy protein ATG5 for degradation. Sci Adv 5: eaau0495, 2019.
35. Di Q, Zhao X, Tang H, Li X, Xiao Y, Wu H, Wu Z, Quan J and Chen W: USP22 suppresses the NLRP3 inflammasome by degrading NLRP3 via ATG5-dependent autophagy. Autophagy 19: 873-885, 2023.
36. Chen L, Liu S and Tao Y: Regulating tumor suppressor genes: Post-translational modifications. Signal Transduct Target Ther 5: 90, 2020.
37. Zhou L, Ng DS, Yam JC, Tham CC, Pang CP and Chu WK: Post-translational modifications on the retinoblastoma protein. J Biomed Sci 29: 33, 2022.
38. Yang J, Song C and Zhan X: The role of protein acetylation in carcinogenesis and targeted drug discovery. Front Endocrinol (Lausanne) 13: 972312, 2022.
39. Wan W, You Z, Xu Y, Zhou L, Guan Z, Peng C, Wong CCL, Su H, Zhou T, Xia H and Liu W: mTORC1 Phosphorylates Acetyltransferase p300 to Regulate Autophagy and Lipogenesis. Mol Cell 68: 323-335.e6, 2017.
40. Levy JMM, Towers CG and Thorburn A: Targeting autophagy in cancer. Nat Rev Cancer 17: 528-542, 2017.
41. Lin TY, Chan HH, Chen SH, Sarvagalla S, Chen PS, Coumar MS, Cheng SM, Chang YC, Lin CH, Leung E and Cheung CHA: BIRC5/Survivin is a novel ATG12-ATG5 conjugate interactor and an autophagy-induced DNA damage suppressor in human cancer and mouse embryonic fibroblast cells. Autophagy 16: 1296-1313, 2020.
42. Otto FB and Thumm M: Mechanistic dissection of macro- and micronucleophagy. Autophagy 17: 626-639, 2021.
43. Cicchini M, Karantza V and Xia B: Molecular pathways: Autophagy in cancer-a matter of timing and context. Clin Cancer Res 21: 498-504, 2015.
44. Don Wai Luu L, Kaakoush NO and Castaño-Rodríguez N: The role of ATG16L2 in autophagy and disease. Autophagy 18: 2537-2546, 2022.
45. Changotra H, Kaur S, Yadav SS, Gupta GL, Parkash J and Duseja A: ATG5: A central autophagy regulator implicated in various human diseases. Cell Biochem Funct 40: 650-667. 2022.
46. Lei Y, Xu X, Liu H, Chen L, Zhou H, Jiang J, Yang Y and Wu B: HBx induces hepatocellular carcinogenesis through ARRB1-mediated autophagy to drive the G_1/S cycle. Autophagy 17: 4423-4441, 2021.
47. Wang Y, Xiong H, Liu D, Hill C, Ertay A, Li J, Zou Y, Miller P, White E, Downward J, *et al*: Autophagy inhibition specifically promotes epithelial-mesenchymal transition and invasion in RAS-mutated cancer cells. Autophagy 15: 886-899, 2019.
48. Liang Y, Pi H, Liao L, Tan M, Deng P, Yue Y, Xi Y, Tian L, Xie J, Chen M, *et al*: Cadmium promotes breast cancer cell proliferation, migration and invasion by inhibiting ACSS2/ATG5-mediated autophagy. Environ Pollut 273: 116504, 2021.
49. He L, Han J, Li B, Huang L, Ma K, Chen Q, Liu X, Bao L and Liu H: Identification of a new cyathane diterpene that induces mitochondrial and autophagy-dependent apoptosis and shows a potent in vivo anti-colorectal cancer activity. Eur J Med Chem 111: 183-192, 2016.
50. Xiong X, Lu B, Tian Q, Zhang H, Wu M, Guo H, Zhang Q, Li X, Zhou T and Wang Y: Inhibition of autophagy enhances cinobufagin-induced apoptosis in gastric cancer. Oncol Rep 41: 492-500, 2019.
51. Cao L and Lin F: TECPR1 Induces apoptosis in non-small cell lung carcinoma via ATG5 Upregulation-Induced autophagy promotion. Ann Clin Lab Sci 52: 580-592, 2022.
52. Zheng Y, Tan K and Huang H: Long noncoding RNA HAGLROS regulates apoptosis and autophagy in colorectal cancer cells via sponging miR-100 to target ATG5 expression. J Cell Biochem 120: 3922-3933, 2019.
53. Li Y, Jiang Y, Cheng J, Ma J, Li Q and Pang T: ATG5 regulates mesenchymal stem cells differentiation and mediates chemosensitivity in acute myeloid leukemia. Biochem Biophys Res Commun 525: 398-405, 2020.
54. Oh DS and Lee HK: Autophagy protein ATG5 regulates CD36 expression and anti-tumor MHC class II antigen presentation in dendritic cells. Autophagy 15: 2091-2106, 2019.

55. Demirbag-Sarikaya S, Akkoc Y, Turgut S, Erbil-Bilir S, Kocaturk NM, Dengjel J and Gozuacik D: A novel ATG5 interaction with Ku70 potentiates DNA repair upon genotoxic stress. Sci Rep 12: 8134, 2022.
56. Sun SY, Hu XT, Yu XF, Zhang YY, Liu XH, Liu YH, Wu SH, Li YY, Cui SX and Qu XJ: Nuclear translocation of ATG5 induces DNA mismatch repair deficiency (MMR-D)/microsatellite instability (MSI) via interacting with Mis18α in colorectal cancer. Br J Pharmacol 178: 2351-2369, 2021.
57. Yu K, Xiang L, Li S, Wang S, Chen C and Mu H: HIF1α promotes prostate cancer progression by increasing ATG5 expression. Anim Cells Syst (Seoul) 23: 326-334, 2019.
58. Wang H, Yin J, Huang J, Liu Z and Pei S: miR-20a-enhanced cell migration and invasion via ATg5 in osteosarcoma. Minerva Endocrinol 44: 415-417, 2019.
59. Zhou S, Wang X, Ding J, Yang H and Xie Y: Increased ATG5 expression predicts poor prognosis and promotes EMT in cervical carcinoma. Front Cell Dev Biol 9: 757184, 2021.
60. Wang Q, Chen J, Zhang M, Wang H, Zeng Y, Huang Y and Xu C: Autophagy induced by muscarinic acetylcholine receptor 1 mediates migration and invasion targeting Atg5 via AMPK/mTOR pathway in prostate cancer. J Oncol 2022: 6523195, 2022.
61. Qin Y, Sun W, Wang Z, Dong W, He L, Zhang T, Lv C and Zhang H: RBM47/SNHG5/FOXO3 axis activates autophagy and inhibits cell proliferation in papillary thyroid carcinoma. Cell Death Dis 13: 270, 2022.
62. Zhu JF, Huang W, Yi HM, Xiao T, Li JY, Feng J, Yi H, Lu SS, Li XH, Lu RH, *et al*: Annexin A1-suppressed autophagy promotes nasopharyngeal carcinoma cell invasion and metastasis by PI3K/AKT signaling activation. Cell Death Dis 9: 1154, 2018.
63. He J, Huang B, Zhang K, Liu M and Xu T: Long non-coding RNA in cervical cancer: From biology to therapeutic opportunity. Biomed Pharmacother 127: 110209, 2020.
64. Yan H and Bu P: Non-coding RNA in cancer. Essays Biochem 65: 625-639, 2021.
65. Wang L, Cho KB, Li Y, Tao G, Xie Z and Guo B: Long Noncoding RNA (lncRNA)-mediated competing endogenous RNA networks provide novel potential biomarkers and therapeutic targets for colorectal cancer. Int J Mol Sci 20: 5758, 2019.
66. Yang Q, Li F, He AT and Yang BB: Circular RNAs: Expression, localization, and therapeutic potentials. Mol Ther 29: 1683-1702, 2021.
67. Volovat SR, Volovat C, Hordila I, Hordila DA, Mirestean CC, Miron OT, Lungulescu C, Scripcariu DV, Stolniceanu CR, Konsoulova-Kirova AA, *et al*: MiRNA and LncRNA as potential biomarkers in Triple-negative breast cancer: A review. Front Oncol 10: 526850, 2020.
68. Zhang H and Lu B: The roles of ceRNAs-mediated autophagy in cancer chemoresistance and metastasis. Cancers (Basel) 12: 2926, 2020.
69. Huang J, Huang B, Kong Y, Yang Y, Tian C, Chen L, Liao Y and Ma L: Polycystic ovary syndrome: Identification of novel and hub biomarkers in the autophagy-associated mRNA-miRNA-lncRNA network. Front Endocrinol (Lausanne) 13: 1032064, 2022.
70. Fisher L: Retraction: Long non-coding RNA XIST promotes proliferation, autophagy and inhibits apoptosis by regulating microRNA-30c/ATG5 axis in gastric cancer. RSC Adv 11: 4233, 2021.
71. Yang F, Peng ZX, Ji WD, Yu JD, Qian C, Liu JD and Fang GE: LncRNA CCAT1 upregulates ATG5 to enhance autophagy and promote gastric cancer development by absorbing miR-140-3p. Dig Dis Sci 67: 3725-3741, 2022.
72. Wang J, Dong Z, Sheng Z and Cai Y: Hypoxia-induced PVT1 promotes lung cancer chemoresistance to cisplatin by autophagy via PVT1/miR-140-3p/ATG5 axis. Cell Death Discov 8: 104, 2022.
73. Qin Y, Sun W, Wang Z, Dong W, He L, Zhang T, Shao L and Zhang H: ATF2-Induced lncRNA GAS8-AS1 promotes autophagy of thyroid cancer cells by targeting the miR-187-3p/ATG5 and miR-1343-3p/ATG7 Axes. Mol Ther Nucleic Acids 22: 584-600, 2020.
74. Wei H, Li L, Zhang H, Xu F, Chen L, Che G and Wang Y: Circ-FOXM1 knockdown suppresses non-small cell lung cancer development by regulating the miR-149-5p/ATG5 axis. Cell Cycle 20: 166-178, 2021.
75. Zheng S, Zhong YF, Tan DM, Xu Y, Chen HX and Wang D: miR-183-5p enhances the radioresistance of colorectal cancer by directly targeting ATG5. J Biosci 44: 92, 2019.
76. Che J, Wang W, Huang Y, Zhang L, Zhao J, Zhang P and Yuan X: miR-20a inhibits hypoxia-induced autophagy by targeting ATG5/FIP200 in colorectal cancer. Mol Carcinog 58: 1234-1247, 2019.
77. Hwang TI, Chen PC, Tsai TF, Lin JF, Chou KY, Ho CY, Chen HE and Chang AC: Hsa-miR-30a-3p overcomes the acquired protective autophagy of bladder cancer in chemotherapy and suppresses tumor growth and muscle invasion. Cell Death Dis 13: 390, 2022.
78. Liang L, Yang Z, Deng Q, Jiang Y, Cheng Y, Sun Y and Li LL: miR-30d-5p suppresses proliferation and autophagy by targeting ATG5 in renal cell carcinoma. FEBS Open Bio 11: 529-540, 2021.
79. White E: The role for autophagy in cancer. J Clin Invest 125: 42-46, 2015.
80. Das S, Shukla N, Singh SS, Kushwaha S and Shrivastava R: Mechanism of interaction between autophagy and apoptosis in cancer. Apoptosis 26: 512-533, 2021.
81. Russo M and Russo GL: Autophagy inducers in cancer. Biochem Pharmacol 153: 51-61, 2018.
82. Seo W, Silwal P, Song IC and Jo EK: The dual role of autophagy in acute myeloid leukemia. J Hematol Oncol 15: 51, 2022.
83. Babaei G, Aziz SG and Jaghi NZZ: EMT, cancer stem cells and autophagy; The three main axes of metastasis. Biomed Pharmacother 133: 110909, 2021.
84. Yang PW, Hsieh MS, Chang YH, Huang PM and Lee JM: Genetic polymorphisms of ATG5 predict survival and recurrence in patients with early-stage esophageal squamous cell carcinoma. Oncotarget 8: 91494-91504, 2017.
85. Cheng X, Xu Q, Zhang Y, Shen M, Zhang S, Mao F, Li B, Yan X, Shi Z, Wang L, *et al*: miR-34a inhibits progression of neuroblastoma by targeting autophagy-related gene 5. Eur J Pharmacol 850: 53-63, 2019.
86. Wang L, Yao L, Zheng YZ, Xu Q, Liu XP, Hu X, Wang P and Shao ZM: Expression of autophagy-related proteins ATG5 and FIP200 predicts favorable disease-free survival in patients with breast cancer. Biochem Biophys Res Commun 458: 816-822, 2015.
87. Zhao GS, Gao ZR, Zhang Q, Tang XF, Lv YF, Zhang ZS, Zhang Y, Tan QL, Peng DB, Jiang DM and Guo QN: TSSC3 promotes autophagy via inactivating the Src-mediated PI3K/Akt/mTOR pathway to suppress tumorigenesis and metastasis in osteosarcoma, and predicts a favorable prognosis. J Exp Clin Cancer Res 37: 188, 2018.
88. Dong M, Ye T, Bi Y, Wang Q, Kuerban K, Li J, Feng M, Wang K, Chen Y and Ye L: A novel hybrid of 3-benzyl coumarin seco-B-ring derivative and phenylsulfonylfuroxan induces apoptosis and autophagy in non-small-cell lung cancer. Phytomedicine 52: 79-88, 2019.
89. Rong L, Li Z, Leng X, Li H, Ma Y, Chen Y and Song F: Salidroside induces apoptosis and protective autophagy in human gastric cancer AGS cells through the PI3K/Akt/mTOR pathway. Biomed Pharmacother 122: 109726, 2020.
90. Xu Q, Zhang H, Liu H, Han Y, Qiu W and Li Z: Inhibiting autophagy flux and DNA repair of tumor cells to boost radiotherapy of orthotopic glioblastoma. Biomaterials 280: 121287, 2022.
91. Yang X, Zhao M, Wu Z, Chen C, Zhang Y, Wang L, Guo Q, Wang Q, Liang S, Hu S, *et al*: Nano-ultrasonic contrast agent for chemoimmunotherapy of breast cancer by immune metabolism reprogramming and tumor autophagy. ACS Nano 16: 3417-3431, 2022.
92. Mi W, Wang C, Luo G, Li J, Zhang Y, Jiang M, Zhang C, Liu N, Jiang X, Yang G, *et al*: Targeting ERK induced cell death and p53/ROS-dependent protective autophagy in colorectal cancer. Cell Death Discov 7: 375, 2021.
93. Kinsey CG, Camolotto SA, Boespflug AM, Guillen KP, Foth M, Truong A, Schuman SS, Shea JE, Seipp MT, Yap JT, *et al*: Protective autophagy elicited by RAF→MEK→ERK inhibition suggests a treatment strategy for RAS-driven cancers. Nat Med 25: 620-627, 2019.
94. Liu J, Liu Y, Li H, Wei C, Mao A, Liu W and Pan G: Polyphyllin D induces apoptosis and protective autophagy in breast cancer cells through JNK1-Bcl-2 pathway. J Ethnopharmacol 282: 114591, 2022.
95. Ho CY, Chang AC, Hsu CH, Tsai TF, Lin YC, Chou KY, Chen HE, Lin JF, Chen PC and Hwang TI: Miconazole induces protective autophagy in bladder cancer cells. Environ Toxicol 36: 185-193, 2021.
96. Chen J, Zhang L, Zhou H, Wang W, Luo Y, Yang H and Yi H: Inhibition of autophagy promotes cisplatin-induced apoptotic cell death through Atg5 and Beclin 1 in A549 human lung cancer cells. Mol Med Rep 17: 6859-6865, 2018.
97. Mo N, Lu YK, Xie WM, Liu Y, Zhou WX, Wang HX, Nong L, Jia YX, Tan AH, Chen Y, *et al*: Inhibition of autophagy enhances the radiosensitivity of nasopharyngeal carcinoma by reducing Rad51 expression. Oncol Rep 32: 1905-1912, 2014.

98. Digomann D, Linge A and Dubrovska A: SLC3A2/CD98hc, autophagy and tumor radioresistance: A link confirmed. Autophagy 15: 1850-1851, 2019.
99. Pai Bellare G, Saha B and Patro BS: Targeting autophagy reverses de novo resistance in homologous recombination repair proficient breast cancers to PARP inhibition. Br J Cancer 124: 1260-1274, 2021.
100. Han M, Hu J, Lu P, Cao H, Yu C, Li X, Qian X, Yang X, Yang Y, Han N, *et al*: Exosome-transmitted miR-567 reverses trastuzumab resistance by inhibiting ATG5 in breast cancer. Cell Death Dis 11: 43, 2020.
101. Wang ZC, Huang FZ, Xu HB, Sun JC and Wang CF: MicroRNA-137 inhibits autophagy and chemosensitizes pancreatic cancer cells by targeting ATG5. Int J Biochem Cell Biol 111: 63-71, 2019.
102. Yu Q, Xu XP, Yin XM and Peng XQ: miR-155-5p increases the sensitivity of liver cancer cells to adriamycin by regulating ATG5-mediated autophagy. Neoplasma 68: 87-95, 2021.
103. Zhang W, Dong YZ, Du X, Peng XN and Shen QM: MiRNA-153-3p promotes gefitinib-sensitivity in non-small cell lung cancer by inhibiting ATG5 expression and autophagy. Eur Rev Med Pharmacol Sci 23: 2444-2452, 2019.
104. Han M, Qian X, Cao H, Wang F, Li X, Han N, Yang X, Yang Y, Dou D, Hu J, *et al*: lncRNA ZNF649-AS1 induces trastuzumab resistance by promoting ATG5 expression and autophagy. Mol Ther 28: 2488-2502, 2020.
105. Shi Y, Wang Y, Qian J, Yan X, Han Y, Yao N and Ma J: MGMT expression affects the gemcitabine resistance of pancreatic cancer cells. Life Sci 259: 118148, 2020.
106. Cheng X, Tan S, Duan F, Yuan Q, Li Q and Deng G: Icariin induces apoptosis by suppressing autophagy in tamoxifen-resistant breast cancer cell line MCF-7/TAM. Breast Cancer 26: 766-775, 2019.
107. Li X, Chen Q, Ao J, Lin W, Qiu L and Cao R: Synthesis of novel 4,7-disubstituted quinoline derivatives as autophagy inducing agents via targeting stabilization of ATG5. Bioorg Chem 127: 105998, 2022.
108. Li Y, Lu X, Tian P, Wang K and Shi J: Procyanidin B2 induces apoptosis and autophagy in gastric cancer cells by inhibiting Akt/mTOR signaling pathway. BMC Complement Med Ther 21: 76, 2021.
109. Kan Y, Song M, Cui X, Yang Q, Zang Y, Li Q, Li Y, Cai W, Chen Y, Weng X, *et al*: Muyin extract inhibits non-small-cell lung cancer growth by inducing autophagy and apoptosis in vitro and in vivo. Phytomedicine 96: 153834, 2022.
110. Kim TW: Cinnamaldehyde induces autophagy-mediated cell death through ER stress and epigenetic modification in gastric cancer cells. Acta Pharmacol Sin 43: 712-723, 2022.