Autophagy is a double-edged sword in the therapy of colorectal cancer (Review)

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Received July 21, 2020; Accepted January 14, 2021

DOI: 10.3892/ol.2021.12639

Abstract. Colorectal cancer is one of the leading causes of cancer-associated mortality worldwide. The limitations of colorectal cancer treatment include various types of multidrug resistance and the contingent damage to neighboring normal cells caused by chemotherapy. Macroautophagy/autophagy and apoptosis are essential mechanisms involved in cancer cell regulation of chemotherapy. Autophagy can either cause cancer cell death or promote tumor survival during colorectal cancer. Given that autophagy is involved in chemotherapy of colorectal cancer, an improved insight into the potential interactions between apoptosis and autophagy is crucial. The present review aimed to summarize the involvement of autophagy in the regulation of colorectal cancer and its association with chemotherapy. Furthermore, the role of natural product extraction, novel chemicals and small molecules, as well as radiation, which induce autophagy in colorectal cancer cells, were reviewed. Finally, the present review aimed to provide an outlook for the regulation of autophagy as a novel approach to the treatment of cancer, particularly chemotherapy-resistant colorectal cancer.

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Abbreviations: AMPK, AMP-activated protein kinase; ATG, autophagy-related gene; ULK1, unc-51-like autophagy activating kinase 1; ER, endoplasmic reticulum; ATG16L1, autophagy related 16 like 1; EMT, epithelial-to-mesenchymal transition; PLC, phosphoinositide-specific phospholipase C; 5-FU, 5-fluorouracil; CACC, colon carcinogenesis; Nrf2, nuclear factor erythroid 2-related factor 2; PDT, photodynamic therapy; TAM, tumor-associated macrophage

Key words: autophagy, Beclin 1, chemotherapy, colorectal cancer, apoptosis

Contents

1. Introduction

Colorectal cancer is one of the most widespread malignancies in humans, which is the second most common cause of cancer-associated mortality worldwide (1). In 2020, ~147,950 people will be diagnosed with colorectal cancer and ~53,200 will succumb to the disease, including 17,930 cases and 3,640 mortalities among patients younger than 50 years (2). The major treatments for colorectal cancer include surgery, radiotherapy and chemotherapy. However, these treatments are associated with severe side effects and high relapse rates. In addition, chemoresistance is a major obstacle to overcome in patients with colon cancer (3). A recent study demonstrated that reductive stress may be a potential weapon against cancer, acting by priming tumor cells to apoptosis (4).

Autophagy is an evolutionarily conserved mechanism that maintains cellular homeostasis by degrading unnecessary or dysfunctional organelles and proteins (5). Several events, such as shortage of nutrients or energy availability, reactive oxygen species and hypoxia promote autophagy, which is accompanied by the recycling of cellular components under normal conditions in eukaryotic cells (6). In addition, autophagy is considered to serve as a cell survival mechanism implicated in drug resistance, and may be triggered by radiotherapy, chemotherapy and targeted therapy, or other factors, such as oxidative stress, causing cell injury (7). Highly autophagy-dependent cancer cells circumvent the loss of autophagy via upregulation of nuclear factor erythroid 2-related factor 2 (Nrf2) expression (8). Activation of endogenous antioxidants by Nrf2 can decrease oxidative stress, which promotes early lung tumor progression (9). In addition, Nrf2 activation promotes lung cancer metastasis by controlling oxidative homeostasis and targeted therapy, which mediates damage (10). A previous study reported that inhibition of

autophagy can alleviate alcoholic fatty liver injury in alcoholic liver fibrosis model mice and Nrf2 signaling is involved in autophagy (11). Thus, novel therapeutic approaches targeting autophagy are being investigated to improve treatment options for patients with colorectal cancer.

Autophagy is a catabolic process that segregates specific intracellular cargo through engulfment into double-membrane vesicles in the cytosol, referred to as autophagosomes. Recognition of cargo chemical or extracellular stimuli induces autophagosome formation (12). The formation of autophagosomes can be activated by class III phosphoinositide 3-kinase and Beclin 1 (13). During autophagy, LC3 is transformed from its cytosolic form (LC3-I) to the LC3-II form, which is the autophagic membrane-bound form (14). The relative expression of LC3-I and II are considered to be an autophagy index (15).

Autophagy serves a controversial role in cancer, both in protecting against tumor development through isolation of injured organelles, and potentially by contributing to cancer progression (16). Autophagy may serve a pro-survival or pro-death role, depending on the type of cell and particular stimuli, the phase of progression and the intensity of Beclin 1 stimulation (17). In addition, autophagy serves an important role in colon cancer stem cell-related cancer progression (18). Use of the autophagy inhibitors, 3-methyladenine or chloroquine, has been demonstrated to increase sensitivity to chemotherapy in hepatocellular carcinoma (19). Thus, autophagy is a vital cellular mechanism underlying chemoresistance (20).

Apoptosis and autophagy are highly dynamic processes that regulate the final fate of cells (21). A previous study reported the association between autophagy and apoptosis, and related factors in colorectal cancer (22). The equilibrium between autophagy and apoptosis is shifted towards apoptosis via downregulation of JNK1 expression in HT29 colorectal cancer cells (23). Furthermore, there are several signaling pathways that are implicated in the regulation of autophagy, including the ERK (24), AMP-activated protein kinase (AMPK) (25), mTOR, silent information regulator-1, JNK and p38 signaling pathways (26).

Recently, autophagy has become one of the most extensively investigated fields in colorectal cancer research. This may be partially attributed to the development of autophagy that contributes to chemotherapy resistance. Overall, unique investigational therapies that apply natural and modified biological agents stimulated by derivatives from plants, small molecules and newly developed chemicals are an important source of potential anticancer treatments (Fig. 1). The present study aimed to discuss autophagy as a novel target for colorectal cancer therapy.

2. Autophagy genes

Beclin 1 was the first recognized mammalian autophagy gene, and it stimulates the nucleation of the autophagic vesicle (27). Beclin 1 is expressed at high levels in colorectal cancer tissues compared with normal tissues (28). Beclin 1 expression *in vivo* markedly suppresses the proliferation of colon cancer cells in xenograft models by inducing apoptosis, and overexpression may reverse aggressive phenotypes and suppress colon cancer tumor growth (29).

Autophagy-related gene (ATG)5 is a central autophagy protein that is involved in autophagosome formation. Furthermore, it is required for the ubiquitin-like conjugation systems implicated in LC3 lipidation (30). A previous study reported that ATG5 is permanently conjugated to ATG12 by E1-like ATG7 and E2-like ATG10 (31).

The phosphoinositide 3-kinase regulatory subunit 4 (PIK3R4; also named VPS15) is the regulatory subunit that regulates the production of phosphatidylinositol-3-phosphate (32). VPS15, PIK3R4 and Beclin 1 form three distinctive PI3K complexes (33). These central components, along with ATG14L, form the PI3KC3 complex 1, which is crucial for the stimulation of canonical autophagy (34).

Sequestosome 1 (p62) is a multifunctional receptor that is involved in autophagy-related signaling pathways (35,36). p62 is another important protein that targets other proteins for proteasome degradation and autophagic digestion (37). In particular, LC3-II binds to p62 to control protein packaging and to deliver it to the autophagosome (30).

A class III PI3K is required for autophagosomes, and is further associated with the conversion of LC3-I to its membrane-bound LC3-II form (38). LC3-BI is converted to LC3-BII through lipidation by a ubiquitin-like system involving ATG7 and ATG3 that allows LC3 to become associated with autophagic vesicles (39).

Autophagy-related 16 like 1 (ATG16L1) is an autophagy gene that is also involved in the immune response. Autophagy gene polymorphisms are associated with the progression of human colon cancer (18). A non-synonymous single-nucleotide polymorphism in ATG16L1 (Thr300Ala) is associated with the development of overall persistence in human colon cancer (40).

3. Autophagy pathway and its regulation

The autophagy pathway includes the following stages: i) Nucleation of the autophagic vesicle; ii) elongation and closure of the autophagosome membrane to enclose cytoplasmic constituents; iii) cropping of the autophagosome with lysosome and iv) degradation of the cytoplasmic substance inside the autophagosome (41). Several signaling molecules, including AMPK, mTOR, unc-51-like autophagy activating kinase 1 (ULK1), Beclin 1, Bcl-2, LC3, p62 and ATG contribute to the regulation of individual stages during this process (42).

Previous studies have reported that PI3K/Akt/mTOR inhibitors activate autophagy at the early stage as a survival mechanism that may affect its apoptotic potential (43,44). A novel Akt inhibitor, BI-69A11, induces autophagy at the early stages via inhibition of the Akt/mTOR/p70S6 kinase signaling pathway in colon cancer (45). Furthermore, it has been demonstrated that an increase in phosphorylated-AMPK and stimulation of autophagy in IL-$10^{-/-}$ mice at all stages, as suggested by the accumulation of LC3-II, increases Beclin 1 expression and decreases Bcl-2 expression (46). FOXO has been suggested to be an activator of autophagy via direct transactivation of autophagy genes or via regulation of autophagy activity (5). Endoplasmic reticulum (ER) stress is required for autophagy stimulation during oxaliplatin treatment (47). In addition, a previous study demonstrated that the BRAF oncogene induces key autophagic markers, such as LC3 and Beclin 1, in colorectal tumor cells (44). It has

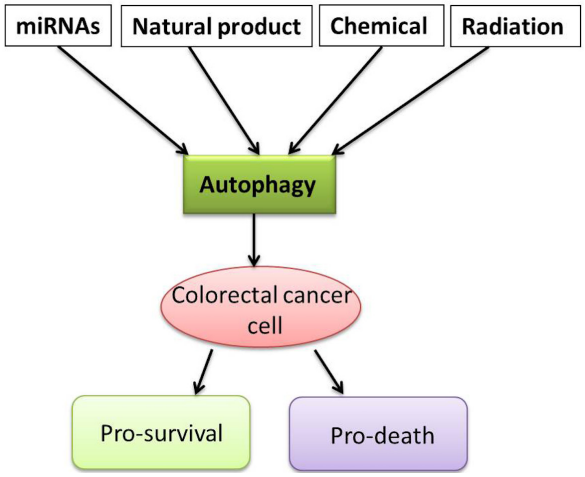

Figure 1. Interaction patterns of autophagy in the regulation of cell death in colorectal cancer. miRNA, microRNA.

also been suggested that BI-69A11 mediates crosstalk among Akt, heat shock protein-90 and Beclin 1, maintaining the fine equilibrium between autophagy and apoptosis (45). Silencing of the colon cancer-associated transcript 2 gene induces apoptosis, as well as autophagy, in BGC-823 gastric cancer cells via inhibition of the PI3K/mTOR signaling pathways (48). Nuclear receptor-binding factor 2 is required for the removal of apoptotic cells and to relieve inflammation during colitis in mice, and modulates autophagy as a regulatory subunit of the ATG14 L-Beclin 1-PIK3C3 complex (49,50). Vitamin D receptor shortage increases the number of apoptotic cells and markedly increases cell death in the small intestine and colon of mice via Beclin 1 and ATG16L1 (51). In addition, treatment with vitamin D3 increases vitamin D receptor and ATG16L1 expression, which are activated by autophagic responses in organoids and colitis IL-$10^{-/-}$ mice (51).

Knockdown of Beclin 1 using small interfering RNA markedly inhibits the stimulation of autophagy caused by rapamycin, resulting in suppression of epithelial-to-mesenchymal transition (EMT), and a decrease in invasiveness of colon cancer cells, which suggests an association between EMT and activation of autophagy (52). Enhanced unfolded protein response in differentiated colon epithelial cells is accompanied by the induction of autophagy (53). Phosphoinositide-specific phospholipase C (PLC) γ1 suppression induces autophagy, and the protein tyrosine kinase 2/PLCγ1 axis is a potential downstream effector of the AMPK activation-dependent autophagy signaling cascade in HCT-116 cells (54). Cationic amphipathic KT2 induces nuclear condensation and apoptotic cell death, and this inhibits autophagy via the suppression of autophagy-related proteins in HCT-116 cells (55).

Recently, the role of microRNAs (miRNAs/miRs) as modulators in autophagy has improved our understanding of the role of autophagy in cancer (56). However, overexpression of miR-409-3p inhibits chemotherapy-induced autophagy in a Beclin 1-dependent manner (57). Overexpression of miR-30d suppresses cell viability, and this may be due to the inhibition of autophagy and promotion of apoptosis (58). Furthermore, miR-30d decreases cell autophagy by directly targeting the mRNA of ATG5 Beclin 1, which promotes the apoptosis of colon cancer cells (58). A recent study revealed that stimulation of autophagy decreases miR-183 expression in colorectal cancer cells (59). Furthermore, high miR-183 expression attenuates rapamycin- or starvation-induced autophagy in human cancer cells (59).

Overall, the autophagy pathway is both positively and negatively regulated by various environmental and immunological signals, as well as miRNAs.

4. Natural products induce autophagy in colon cancer

In addition to traditional surgery, chemotherapy and radiotherapy, western medicine and natural products offer potential methods for the treatment of colon cancer (60,61). Currently, natural medicine has become an area of clinical anticancer drug research due to its multi-link, multi-target and multi-channel antitumor effects (62). A previous study reported that autophagy is involved in resistance to radiotherapy or chemotherapy (63).

A dibenzylbutyrolactone type lignin, which was isolated from *Combretum fruticosum*, continually induces autophagic cell death with cytoplasmic vacuolization and development of autophagosomes regulated by increasing LC3 activation and altering Beclin 1 expression in HCT-116 cells (64). Luteolin treatment upregulates the expression levels of Beclin 1, ATG-5 and LC3B-I/II in human colon cancer SW620 cells (65).

Extracts obtained from different parts of the *Grias neuberthii* plant may affect autophagy in colon RKO (normal p53) and SW613-B3 (mutated p53) cell lines (66). As botanical drugs, ginkgolic acids, which are extracted from the seed coat of *Ginkgo biloba* L., induce intrinsic apoptosis rather than autophagy, which is regulated by reactive oxygen species generation, and contributes to human colon cancer cell death (67). Another study demonstrated that salidroside, which is a phenylpropanoid glycoside extracted from *Rhodiola rosea*, induces autophagy accompanied by cell apoptosis by suppressing the PI3K/Akt/mTOR signaling pathway in colorectal cancer cells (68). Pancratistatin, which is extracted from the spider lily or amaryllidaceae family of angiosperms, is associated with increased autophagy and apoptosis through G_2/M cell cycle arrest in HCT-15 cells (69). *Rhus coriaria* extract induces Beclin 1-independent autophagy and caspase-7-dependent apoptosis in human colorectal cancer Caco-2 and HT-29 cells via inactivation of the AKT/mTOR signaling pathway (70). Berbamine is a plant-derived alkaloid that may trigger the progress of autophagic vesicles in HT-29 cells, along with an increase in the expression levels of LC3B-I, ATG-12, ATG-5 and Beclin 1 (71). Dentatin is an important coumarin derivative, mainly isolated from *Murraya koenigii*, which induces autophagy by inhibiting the JAK/STAT signaling pathway in colon cancer HT-29 cells (72).

Urolithin A is a major ellagitannin metabolite that has been demonstrated to induce autophagy and inhibit the metastatic potential of SW620 cells (73). Betulinic acid analogue is capable of inducing autophagy by altering the expression levels of several autophagic proteins, such as Beclin-1 and ATG-5, in HT-29 cells (74). 6-C-(E-phenylethenyl) naringenin, which is a small molecule found in naringenin fortified fried beef, can induce autophagy and necrosis in human colon cancer cells (75). Treatment with ophiopogon polysaccharide-B, which

is a saponin compound extracted from Radix *O. japonicus*, induces autophagy by increasing Beclin 1 expression and the conversion of LC3I to LC3II, by upregulating the JNK/c-Jun signaling pathway (76). Physalin B, which can be isolated from *Physalis divericata*, triggers autophagosome formation and accumulates LC3-II and p62 in colon cancer cells (77).

Artesunate is a semi-synthetic derivative of artemisinin, which dose-dependently induces DNA damage and apoptosis in embryonal rhabdomyosarcoma cell lines (78). Artesunate induces autophagy by increasing LC3 and Beclin 1 expression, and the occurrence of autophagosomes in HCT-116 colon cancer cells (79). Pharmacological inhibition of autophagy stimulation using hydroxychloroquine markedly improves artesunate induced apoptosis (80). Brevilin A promotes cell autophagy and apoptosis via the mitochondrial signaling pathway and PI3K/AKT/mTOR inactivation in CT26 cells (81). *Codonopis bulleynana* Forest ex Diels induces cell apoptosis and inhibits autophagy via NF-κB signaling pathway activation in HCT-116 and SW480 colon cancer cells (82). In addition, evodiamine activates autophagy accompanied by apoptosis in SW480 cells by enhancing LC3 II and Beclin 1 expression (83). Vitexin induces apoptosis through suppression of autophagy in multidrug-resistant colorectal cancer cells (84). Litchi exocarp and endocarp activate a premature autophagic response, as well as cell death, via autophagy inhibitor or Beclin 1 silencing, suggesting that autophagy may be originally activated as a pro-survival response (85).

Recently, combining antineoplastic agents with autophagy blockers has been suggested as a therapeutic method for the treatment of patients with cancer (86). Pre-treatment with curcumin followed by 5-fluorouracil (5-FU) treatment promotes autophagy turnover both *in vitro* and *in vivo* through AMPK/ULK1-dependent autophagy suppression and AKT alteration, which provides an explanation for the increased susceptibility of colon cancer cells or cancer xenografts to the cytotoxicity of 5-FU (87). 5-FU-resistant SNUC5 colon cancer cells exhibit lower levels of autophagy compared with parental SNUC5 cells, indicating that reduced autophagy is associated with 5-FU resistance in colon cancer cells (88). Chloroquine in combination treatment with low concentrations of 5-FU can block autophagy in HCT-116 colon cancer cells (89).

5. Chemicals induce autophagy in colon cancer

17-hydroxywortmannin was identified as a drug that re-sensitizes tumor necrosis factor-related apoptosis-inducing ligand-resistant colon cancer cells, along with increased Beclin 1 expression accompanied by a deficiency of caspase-8 protein (90). Furthermore, angustifoline treatment of COLO-205 cells has been observed to markedly upregulate the protein expression levels of Beclin 1 and LC3-II, which leads to the generation of autophagic cell vesicles (91). Autophagic vacuoles are formed in glioblastoma stem cells following treatment with endothelial-monocyte-activating polypeptide-II combined with temozolomide (92).

The PI3K-Akt signaling pathway regulates autophagy and apoptosis via different mechanisms; however, mTORC1-mediated autophagy appears to not be involved in cell death initiation by 2,3-dihydro-2-(naphthalene-1-yl) quinazolin-4(1H)-one from the quinazolinone series (93). Incubation of HT-29 colon cancer cells with inositol-6 phosphate induces autophagy via inhibition of the Akt/mTOR signaling pathway (94). BH3 mimetic induces autophagy and disruption of BCL2-Beclin 1 binding in mouse embryonic fibroblasts and in human colon cancer cells, which are apoptosis-lacking cell types with a shortage of BAX and BAK1 (95). MHY218 is a hydroxamic acid derivative that can induce apoptosis and autophagy based on observing the accumulation of acidic vesicular organelles in HCT-116 cells (96). Zoledronic acid, which is a third-generation bisphosphonate molecule, regulates autophagy and promotes apoptosis in colon cancer CT26 cells (97). The recently improved polyamine analogue, N1, N11-diethylnorspermine, induces autophagy which is blocked by 3-methyladenine and Beclin 1 suppression; however, apoptosis is increased in HCT-116, SW480 and HT29 colon cancer cells (98). Upregulation of dimethyl fumarate, a dimethyl ester of fumaric acid (99), is associated with the expression of apoptotic markers in human colon cancer HT-29 and colorectal carcinoma T84 cells (99).

Melatonin treatment decreases the progression of colitis-associated colon carcinogenesis (CACC) by down-regulating the process of autophagy, as demonstrated by the expression pattern of several autophagy markers combined with increased Nrf2 expression in the colon of mice with CACC (100). Autophagosome formation and autophagy are associated with the efficacy of cetuximab treatment in colon cancer CACO-2 cells (101). Purvalanol is a novel cyclin-dependent kinase inhibitor that induces ER stress-mediated apoptosis and triggers autophagy in HCT-116 cells (102).

6. Radiation and autophagy

Radiotherapy is a primary method for cancer treatment. It is particularly crucial to overcome radioresistance and to enhance radiosensitivity in patients with colon cancer. Chloroquine has gained consideration among anticancer treatments due to its potential use as an anticancer agent and as a chemotherapy sensitizer (103). Chloroquine has lysosomotropic effects via the suppression of the fusion of autophagosomes and lysosomes (104). A study revealed that chloroquine can sensitize HCT-116 cells to radiation and can improve the therapeutic outcome of radiation therapy *in vivo* (105). Furthermore, ATG7 knockdown or chloroquine treatment increases apoptotic cell death in HCT-116 cells (106).

Light emitting-diode irradiation induces markedly higher LC-3 and Beclin 1 expression levels and autophagosome formation in irradiated HT-29 or HCT-116 human colon cancer cells via photoreceptor Opsin 3 (107). Photodynamic therapy (PDT) is a simple method for invasive cancer treatment (108). Autophagy has been detected directly after the 5-ALA-mediated PDT process, with the strongest expression of autophagy-related proteins in human colon carcinoma SW620 cells (109). Photosensitive agents, such as protoporphyrin IX, induce double membrane autophagosomes (110). The radiosensitivity of colorectal cancer cells is associated with autophagy of tumor associated macrophages (TAMs), and promoting TAM autophagy may increase the radiosensitivity of colorectal cancer cells (111).

7. Conclusions and future direction

Autophagy can either stimulate tumor survival or induce cancer cell death in colorectal cancer. This ‘double-edged sword’ role

of autophagy in colorectal cancer is dependent on the cancer stage and conditions of the microenvironment. Furthermore, autophagy is promoted in response to high-energy requests in the earlier phase of cell transformation. Autophagy is an adaptive tumor cell response in the later phases in human colorectal cancer cells. Combinatorial therapeutic methods may be of value in colorectal tumor therapy. Thus, an improved understanding of the molecular mechanisms underlying the interaction between autophagy and apoptosis are crucial for identifying the effects of combinatorial treatments on human colorectal cancer cells. In conclusion, autophagy is considered a novel therapeutic target for the treatment of chemoresistant colorectal cancer.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

BZ and LL confirmed the authenticity of all the raw data. BZ and LL performed the literature review. BZ drafted the initial manuscript, while LL revised the manuscript for important intellectual content. Both authors have read and approved the final manuscript.

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.

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