Autophagy regulation and its dual role in blood cancers: A novel target for therapeutic development (Review)

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Abstract. Autophagy, a physiological process in which cellular components are degraded by the lysosome for cell homeostasis, plays an important role in cell metabolism, including cell proliferation, differentiation, survival and apoptosis. Recent studies indicate that autophagy serves as a survival mechanism by eliminating misfolded proteins and attenuating DNA damage. Autophagy can also suppress tumor growth, depending upon the cell context and functional status. Dysfunction of autophagy may be closely linked to the initiation and development of various diseases, including hematological malignancies. Mounting evidence highlights the dual role of autophagy in blood cancers through multifarious signal pathways. Therefore, strategies targeting autophagy will develop innovative therapeutic approaches for blood cancers, improve the efficacy of chemotherapy, and bring significant benefits for patients.

Contents

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Abbreviations: ATG, autophagy-related genes; AMPK, AMP-activated protein kinase; ATRA, all-trans retinoic acid; As_2O_3, arsenic trioxide; ACD, autophagic cell death; ALL, acute lymphocytic leukemia; APL, acute promyelocytic leukemia; CQ, chloroquine; CML, chronic myeloid leukemia; CLL, chronic lymphocytic leukemia; CMA, chaperone-mediated autophagy; DAPK, death-associated protein kinase; DRAM-1, damage-regulated autophagy modulator 1; Dex; dexamethasone; DNR, daunorubicin; ER, endoplasmic reticulum; Fd, fludarabine; GABARAP, γ-aminobutyric acid receptor-associated proteins; HCQ, hydroxychloroquine; HSC, hematopoietic stem cell; HSP, heat shock protein; IM, imatinib; LC3, microtubule-associated protein 1 light-chain 3; 3-MA, 3-methyladenine; MM, multiple myeloma; MDS, myelodysplastic syndrome; mTOR, mammalian target of rapamycin; PI3P, phosphatidylinositol 3-phosphate; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; PE, phosphatidylethanolamine; PI3K, phosphatidylinositol 3-kinase; PML, primary effusion lymphoma; ROS, reactive oxygen species; TKI, tyrosine kinase inhibitor; ULK, unc-51-like kinase

Key words: autophagy, blood cancer, treatment

Introduction

Autophagy is an evolutionarily conserved degradation process that plays an important role in maintaining cellular homoeostasis and metabolism. Unlike the proteasome system, autophagy mainly disintegrates long-lived proteins and impaired organelles, which are engulfed by autophagosomes and transported to lysosomes for the digestion when it is induced under stress conditions such as mitochondrial depolarization, nutrient starvation, aggregation of toxic proteins, and pathogen infection (1,2). It is well known that there are three main types of autophagy: Macroautophagy (hereafter referred to as autophagy), microautophagy and chaperone-mediated autophagy (CMA). Microautophagy directly degrades cellular bulks via endocytic membrane emboly, whereas CMA only delivers specifically marked proteins to the lysosome. Macroautophagy involves the sequestration of cytosol or cytoplasmic organelles by the formation of autophagosomes that subsequently fuse with endosomes and eventually with lysosomes, thereby creating autophagolysosomes or autolysosomes, in which the cell contents are degraded (3,4).

Autophagy is a multi-step process involving at least four distinct phases: i) Initiation and nucleation: the activation of autophagy is associated with the unc-51-like kinase (ULK) complex and phosphatidylinositol 3-kinase (PI3K) complex. Under stressful conditions such as hypoxia and starvation, mTOR complex 1 (mTORC1) is separated from the ULK complex, subsequently activating ULK1/2 and phosphorylating ATG13, ATG101 and FIP200 to induce phagophore formation.

Simultaneously, the excitation of Beclin-1-VPS34-ATG14L generates phosphatidylinositol 3-phosphate (PI3P), motivating membrane proteins and phospholipids for phagophore nucleation (5-7). ii) Membrane elongation and completion: this process is mainly regulated via two ubiquitin-like conjugation complexes. On the one hand, combining with ATG4, LC3 (microtubule associated protein 1 light-chain 3) proteins split into LC3-I, which are incorporated with phosphatidylethanolamine (PE) with the help of ATG3 and ATG17, for the transformation of LC3-II, which surrounds both the internal and external membranes of the phagosome. In addition, the ATG12-ATG5 dipolymer conjugates with ATG16L to form the ATG12-ATG5-ATG16L complex, which can promote LC3 transformation and accelerate transformation from phagophore to autophagosome (8-12). iii) Maturation: the upregulation of γ-aminobutyric acid receptor-associated proteins (GABARAP) contributes to phagophore closure and the formation of airtight double-membrane autophagosomes (13). Rab7, LAMP1/2 proteins, ESCRT, UVRAG and SNAREs also participate in this procedure (1,14,15). iv) Degradation: the outer membrane of the autophagosome fuses with the lysosome to create an autolysosome, whereas the inner membrane and engulfed components are degraded into small molecular nutrients (Fig. 1).

Mounting evidence has certified that autophagy affects cell metabolism, including cell proliferation, differentiation, survival and apoptosis (16). Autophagy facilitates clearance of damaged cytoplasmic components and maintains cell homeostasis when cells are submitted to hostile environments. Nevertheless, immoderate autophagy can induce autophagic cell death (ACD), also known as type II programmed cell death, leading to tumor self-degradation (17-20). In addition, excessive autophagy can deplete mitochondria and metabolic substances, thereby trapping cells in the state of hunger (21,22). Autophagy can also mobilize cell survival substances to autophagosomes for degradation, incurring the accumulation of reactive oxygen species (ROS), caspases, and concomitant cell death (23,24). This evidence may also explain the antitumor mechanisms of autophagy. Notably, in blood tumors, the role of autophagy remains elusive. In this review, we discuss the autophagy molecular mechanism, its relative signal pathways, and focus on its dual role in hematological malignancies, which may provide some novel strategies for treatment of hematological tumors.

2. Autophagy signal pathways in cancer

The autophagy signal pathways are intricate networks. In this section, we introduce the main molecular regulators of autophagy. A deeper understanding of these regulatory pathways may provide us with potential targets against tumorigenesis (Fig. 2).

Phosphatidylinositol 3-kinase (PI3K) signaling. The phosphatidylinositol 3-kinases are a family of enzymes that can phosphorylate phosphoinositides of cell membranes, and have thus been deemed as the initiators of cellular signal transduction. PI3Ks are divided into three classes. However, only Class I and III PI3Ks have been shown to be associated with autophagy (25). The Class I PI3K promotes the generation of phosphatidylinositol-3,4,5-trisphosphate (PIP3) at the plasma membrane, thereby increasing Akt/PKB recruitment. The activated Akt/PKB hinders its downstream TSC1-TSC2 complex, influences GTP binding, and motivates the mammalian target of rapamycin (mTOR), which acts as a negative regulator of autophagy by sensing variable ATPs, amino acids, and energy metabolism (2,26). In addition, mTOR can be directly inhibited by rapamycin treatment, leading to autophagy induction. Conversely, Class III PI3K activates autophagy. It phosphorylates PI to generate PI3P, which contributes to the movement of lysosomal enzymes for component degradation (27). Previous findings have shown that the Class III PI3K integral protein Beclin-1, which is also known as the mammalian homolog of an essential yeast autophagy gene (*Atg6*), can facilitate phagosome nucleation, maturation and clearance of apoptotic cells (28). Therefore, knockdown or silence of Beclin-1 inhibits autophagy and causes cell death (29).

ER stress response. The endoplasmic reticulum (ER) is in charge of protein folding. Under stressed circumstances, the accumulation of immature proteins provokes ER stress response and boosts autophagy, resulting in autophagic cell death (30). This process is mainly regulated via the IRE1α-JNK and PERK-eIF2α-ATF4 pathways (31,32).

AMP-activated protein kinase (AMPK) pathway. AMP-activated protein kinase is the energy sensor. In energy-defective situations (decreased ATP/AMP ratio and starvation), the AMPK is excited by LKB1 and p53, leading to autophagy activation via the positive regulation of the TSC1-TSC2 complex or negative regulation of mTOR. AMPK can also directly suppress the raptor, which is a subunit of mTORC1 that inhibits autophagy activity (16,33).

RAS system. The relationship between RAS and autophagy is multifaceted. In fact, RAS plays both positive and negative roles in autophagy with different pathways. On the one hand, RAS inhibits autophagy by directly activating Class I PI3K-Akt-mTOR1. By contrast, RAS upregulates Raf-1/MEK/ERK- or Rac1/MKK7/JNK-dependent autophagy activity with the help of ATG5/7 and Beclin-1 (34-36).

The Bcl-2 family. The Bcl-2 family is divided into three types, based on their BH domains and functions. Bcl-2, Bcl-xL and myeloid cell leukemia sequence-1 (MCL-1) act as anti-apoptosis pathways, while BAX-like proteins (BAX, BAK) and BH3-only proteins (BNIP3) promote apoptosis (2). Similarly, these proteins play a bidirectional role in autophagy. On the one hand, the BNIP3 can integrate with Bcl-2, which correspondingly decreases Bcl-2 binding to Beclin-1, thereby liberating Beclin-1 for autophagy induction (37,38). By contrast, Bcl-2, Bcl-xL and MCL-1 inhibit autophagy.

Other autophagy networks. Death-associated protein kinase (DAPK) is associated with autophagy in cancer. Hyperactive DAPK influences its related protein kinase DRP-1, which increases plasma membrane flexing and blebbing, enabling phagocytosis (39). In addition to the aforementioned p53-AMPK network, DNA damage can trigger autophagy

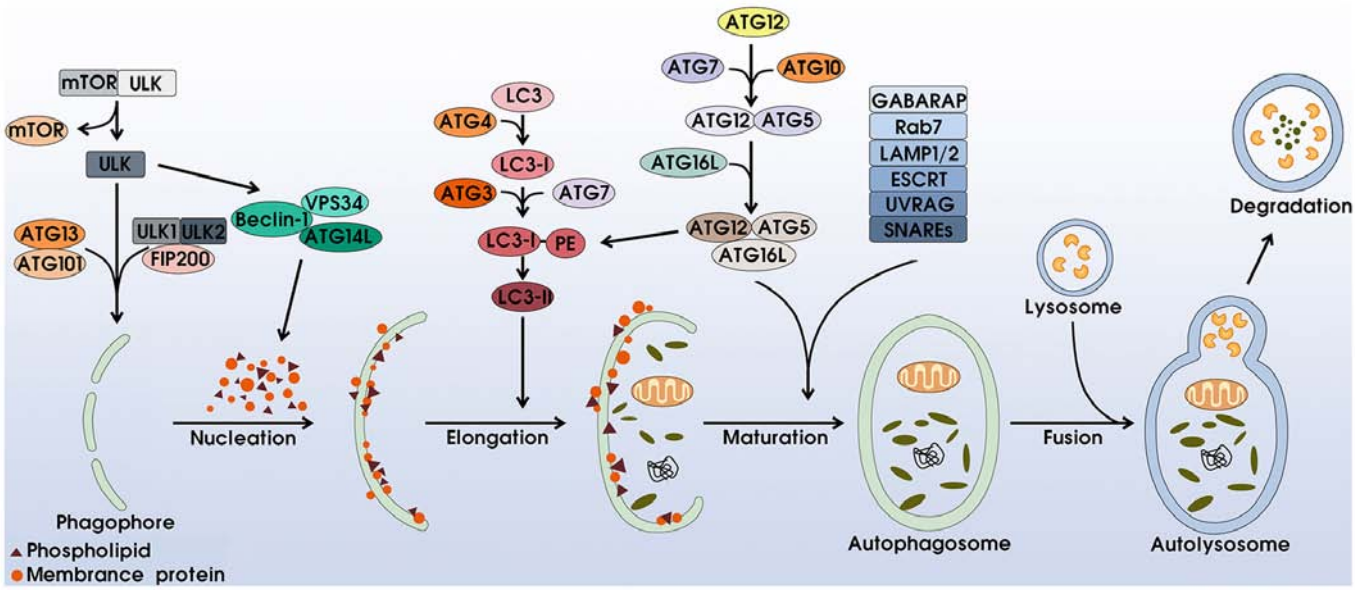

Figure 1. Schematic overview of the autophagy process. Autophagy is initiated from the inhibition of mTOR through starvation or other stressful conditions, followed by phagophore formation and nucleation, membrane elongation and completion, autophagosome maturation, and final degradation of engulfed components with the assistance of over 30 autophagy-related gene (ATG) proteins and two ubiquitin-like conjugation complexes, the ATG12-ATG5-ATG16 and the LC3-PE conjugation complexes.

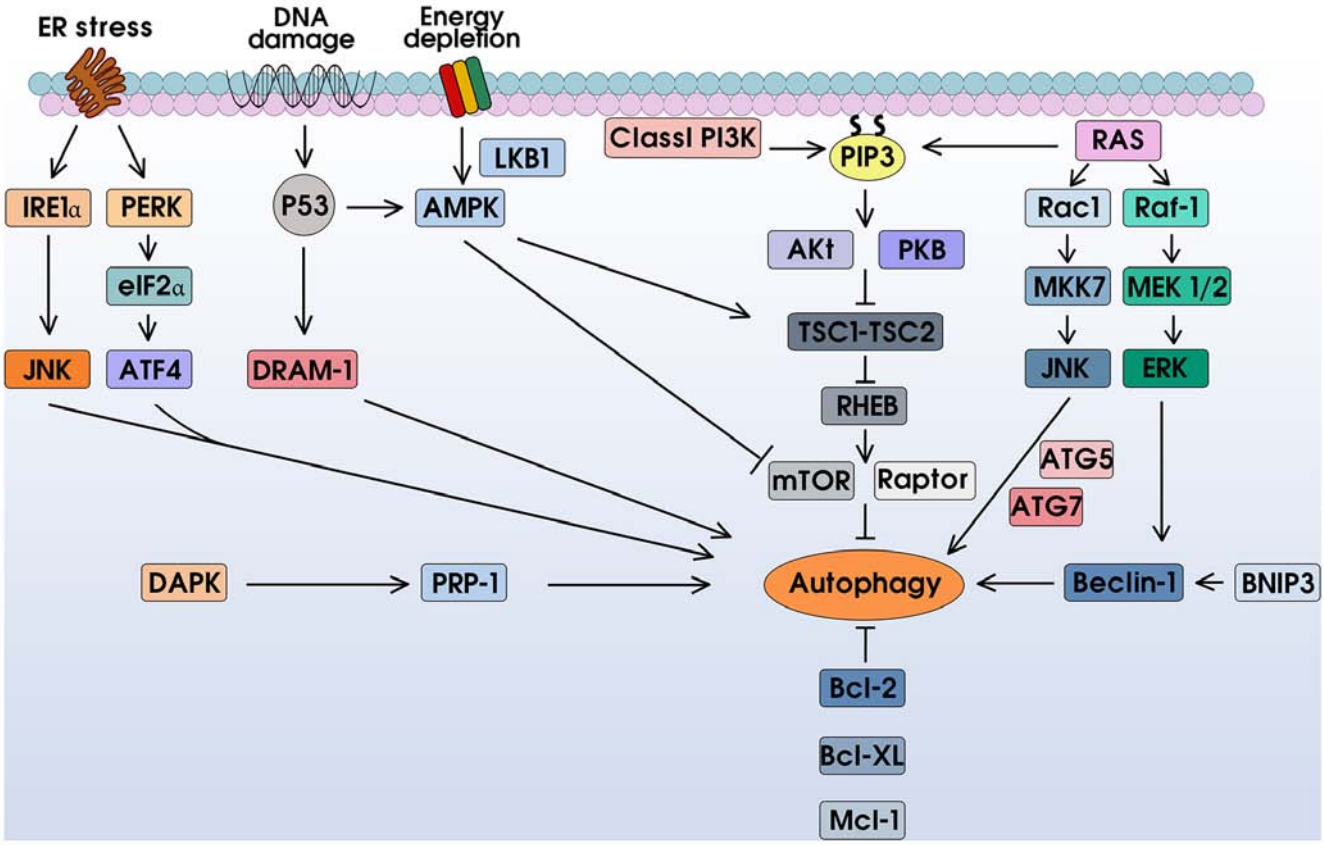

Figure 2. Schematic overview of signal regulations of autophagy in cancer. Autophagy is tightly controlled by several signaling pathways. The PI3K-AKT-mTOR pathway plays the central role. The ER stress response regulates autophagy through the IRE1α-JNK and PERK-eIF2α-ATF4 pathways. The DNA damage and energy depletion can trigger autophagy by AMPK and p53 pathways. The RAS system inhibits or induces autophagy via the PI3K-AKT-mTOR or the Raf-1/MEK/ERK and Rac1/MKK7/JNK pathways, respectively. The Bcl-2 family also plays both positive and negative roles in autophagy regulation. Other pathways such as the DAPK-DRP1 signaling pathway are also important in regulating autophagy.

through p53-dependent damage-regulated autophagy modulator-1 (DRAM-1) activation (40).

In summary, autophagy networks are sophisticated. Dysfunctions of these signal pathways are involved in

tumorigenesis, and targeting signal transduction proteins may provide potential therapeutic schemes for cancer.

3. Autophagy in hematological malignancies

Several studies have demonstrated the important role of autophagy in blood tumors. Autophagy participates in the regulation of hematopoietic stem cell (HSC) differentiation, and the downregulation of autophagy would facilitate leukemic transformation from normal HSC (41). Recently, the potential anti-leukemic effect of tetrandrine was proven through the promotion of the autophagy-dependent megakaryocytic differentiation of leukemia cells (42). In addition, Schläfli *et al* revealed that autophagy scaffold protein ALFY was, not only involved in APL cell differentiation induced by ATRA, but also contributed to degradation of oncoprotein PML-RARα (43). However, autophagy also played a cytoprotective role and led to chemoresistance in leukemia. In lymphoma, on the one hand, autophagy was capable of suppressing lymphomagenesis through the modulation of autophagy proteins and signal pathways. On the other hand, activated autophagy acted as the mechanism of lymphoma cell survival, and additional autophagy inhibitors enhanced antitumor activity (44). The survival of myeloma cells was also dependent on autophagy for protein degradation and energy recycling, which potentially results in drug resistance. For example, Zhang *et al* reported that bortezomib induced pro-survival autophagy, which reduced the chemosensitivity of bortezomib in myeloma cells (45), whereas excessive autophagy may lead to autophagic cell death, providing an available approach for myeloma treatment (46). Therefore, we discussed the dual role of autophagy mediated by conventional chemotherapeutics and summarized promising strategies associated with autophagy modulation in Table I.

Autophagy as a pro-death mechanism. The pro-death role of autophagy is vital for suppressing tumor progression and enhancing antitumor response. Fludarabine (Fd), a nucleoside analog that inhibits DNA/RNA synthesis and DNA repair, is widely used for chronic lymphocytic leukemia (CLL). Mahoney *et al* observed fludarabine-triggered autophagy activity in CLL cells. However, the inhibition of autophagy did not enhance or diminish cell death induced by fludarabine (47). Recently, a study by Sharma *et al* reported that fludarabine induced BECN-dependent autophagy by decreasing Mcl-1 expression, resulting in autophagic cell death in Fd-sensitive leukemic B cells (48). However, in Fd-resistant leukemic cells, Mcl-1 expression was increased, which inhibited BECN-dependent autophagic cell death. The Bcl-2 family also contributed to promoting cell survival via sequestering BECN. Moreover, activated AMPK-dependent autophagy assisted Fd-resistant cells escape cell death. Of note, adding the BCL-2 inhibitor obatoclax can induce cell death in both Fd-sensitive and Fd-resistant leukemic cells. The findings suggest that combining autophagy repressors such as Mcl-1, Bcl-2 and AMPK inhibitors, with fludarabine may improve the curative effect for CLL patients, especially those who acquire Fd-resistance after several cycles of fludarabine chemotherapy.

Metformin, an anti-diabetic agent, has already been proven to play a positive role in cancer control, including acute leukemia (47-50). Wang *et al* reported that metformin enhanced the anti-leukemic effect of sorafenib by triggering mTOR-dependent autophagy in FLT3-ITD-positive AML, which suggested the combination strategy of the two drugs in AML treatment (51). Metformin also induced a dose-dependent inhibition of lymphoma cell proliferation *in vitro* and *in vivo* via the negative control of the mTOR signal pathway (52). Metformin-induced autophagy enhanced the anti-lymphoma effect of doxorubicin and temsirolimus (mTOR inhibitor), offering a novel therapeutic strategy.

Sertraline, a widely used antidepressant drug, was found to induce leukemia cell death mediated by autophagy and apoptosis. It also enhanced the sensitivity of chemotherapy drugs, thereby providing potential alternative strategies for leukemia treatment (53).

Trocoli *et al* observed that all-trans retinoic acid (ATRA) can promote autophagy by reducing the activity of Bcl-2 and mTOR in acute promyelocytic leukemia (APL). In addition, the upregulation of Beclin-1 contributed to the stability of mature APL cells in a non-autophagic manner, although autophagy-related cell differentiation was not explored (54). Notably, by combining ATRA with RAD001 (mTOR1C inhibitor), Nishioka *et al* observed step-down cell growth and enhanced cell differentiation of AML cells (55). Similarly, Isakson *et al* reported that ATRA-dependent autophagy induced the degradation of PML-RARα, which is known to create abnormal granulocytic differentiation, via inhibition of the mTOR pathway as well (56). Thus, the simultaneous use of ATRA and mTOR suppressant may be a valid protocol for APL patients.

Arsenic trioxide (As_2O_3), another metalloid poison that has conventionally been used in APL patients, also induced cell death. We previously reported that As_2O_3 led to cell growth arrest by means of both apoptosis and Beclin-1-dependent autophagy (58). Goussetis *et al* also documented a MEK-ERK-mediated autophagic cell death in leukemia cells (59). The studies demonstrated As_2O_3-induced autophagy as the mechanism of cell death.

Autophagy in response to idarubicin served as a pro-death mechanism in leukemic cells as well. Idarubicin restrained mTOR either by upregulation of its upstream inhibitor AMPK, or downregulation of its activator Akt, thus leading to autophagic cell death. Pharmacological impairment (bafilomycin A1 or chloroquine) of autophagy partially reduced the cytotoxicity of idarubicin towards REH cells, which highlighted its cell-killing function (60).

Dexamethasone (Dex) also contributed to cell death in lymphoid leukemia and multiple myeloma. Several experiments observed Dex-induced autophagic cell death through the marked upregulation of promyelocytic leukemia protein (PML) and PML-dependent Akt dephosphorylation (61,62). In depth studies on PML and Akt-dependent intracellular pathways may provide optimized use of Dex in the treatment of lymphoid malignancies.

Autophagy as a pro-survival mechanism. Besides its potential to induce cell death, autophagy is appropriated to serve as a cell survival mechanism as well.

For example, the tyrosine kinase inhibitor AG490 was found to induce both apoptosis and autophagy by inhibiting STAT3, reducing the expression of HSF1/HSP70, and

Table I. Therapeutic compounds-induced autophagy and its outcomes in hematological malignancies.

Compounds	Signal pathways	Types of tumor	Outcome	Additional treatment	Refs.
Fludarabine	Mcl-1-BECN1, Bcl-2, AMPK	Leukemia	Cell death/ survival	Obatoclax	48
Metformin	AMPK-mTOR	B/T-lymphoma, AML	Cell death	Doxorubicin, temsirolimus, sorafenib	52-53
Sertraline	Not mentioned	AML	Cell death	Not mentioned	54
ATRA	Bcl-2, mTOR	APL	Cell death	Everolimus, rapamycin	55-58
As_2O_3	MEK-ERK, Beclin-1	Leukemia	Cell death	Not mentioned	59-60
Idarubicin	AMPK-mTOR, Akt-mTOR	Leukemia	Cell death	Not mentioned	61
Dexamethasone	PML-Akt	Leukemia, multiple myeloma	Cell death	Rapalogues	62-63
2-Deoxy-5-azacytidine	Intrinsic pathway	CML	Cell death	Not mentioned	83
AG490 (TKI)	STAT3-Mcl-1	PEL	Cell survival	Bafilomycin, 2-phenylethynesulfonamide	64,66
Imatinib	PI3K-AKT-mTOR, Beclin-1	CML	Cell survival/ death	3-MA, CQ, NVP-BEZ235	67-72
Interferon	JAK1-STAT1, NF-κB, BECN1	CML	Cell survival	CQ	73
Cytarabine	Akt-mTOR, AMPK, ERK	Leukemia	Cell survival	Bafilomycin, CQ	74
Doxorubicin, Melphalan	Bcl-2-Beclin-1, Beclin-1-PI3KC3	MM	Cell survival	HCQ, 3-MA	75
Bortezomib	JNK-Bcl2, Bcl-2-Beclin-1, Beclin-1-PI3KC3	B-ALL, B-lymphoma	Cell survival	CQ, 3-MA, SP600125	76-77
Daunorubicin	MEK-ERK	Myeloid leukemia	Cell survival	U0126	78
Dasatinib	AMPK	CLL, Ph^+ leukemia	Cell survival/ death	Not mentioned	79-80
Sorafenib	mTOR	MM	Cell survival	3-MA, CQ, ABT737	81
L-asparaginase	ROS-p53	ALL	Cell survival	CQ	82
5-Azacitidine	Beclin-1	MDS	Cell survival	CQ, leupeptin	84

APL, acute promyelocytic leukemia; ATRA, all-trans retinoic acid; As_2O_3, arsenic trioxide; B-ALL, B acute lymphocytic leukemia; CML, chronic myeloid leukemia; CLL, chronic lymphocytic leukemia; CQ, chloroquine; HCQ, hydroxychloroquine; MM, multiple myeloma; MDS, myelodysplastic syndrome; 3-MA, 3-methyladenine; PML, primary effusion lymphoma; TKI, tyrosine kinase inhibitor.

downregulating Mcl-1 in primary effusion lymphoma (PEL) cells. A combination of AG490 with autophagy inhibitor bafilomycin is believed to enhance the cytotoxic effect (63,64). The HSP70 and its main transcription factor HSF1 have been reported as essential for PEL survival by affecting protein folding and cell stability, and HSP70 inhibition via 2-phenylethynesulfonamide could block the autophagic process and induce immunogenic cell death (65). Therefore, a combination of AG490 and HSP inhibitors may provide a potential treatment strategy. Another TKI, imatinib (IM), was also reported to activate a cytoprotective autophagy in chronic myeloid leukemia (CML) (66). Rothe *et al* identified that CML stem/progenitor cells obtained imatinib resistance due to its intensive pro-survival activities associated with elevated autophagy gene transcripts and proteins, especially ATG4B (67). Mancini *et al* describe a survival role of autophagy in imatinib-treated Bcr-Abl-positive cells, possibly connected with ER stress and following responses (68). The group of Howard Hughes Medical Institute suggested that imatinib-induced autophagy was associated with the Bcr-Abl/PI3K/Akt/FOXO4/ATF5/mTOR pathways (69). Recently, the combination of NVP-BEZ235 (dual PI3K/mTOR inhibitor) and imatinib was reported to significantly inhibit CML cell growth and proliferation, as well as enhance sensitivity to imatinib

in imatinib-resistant CML cells (70). Inversely, imatinib-induced autophagy also isolated the mosaic gene *Bcr-Abl* in autophagosomes through the regulation of Beclin-1, which prevented disease progression (71). Therefore, autophagy inhibition of the aforementioned specific autophagic pathways would enhance the treatment effect of imatinib in CML.

Zhu *et al* also reported a pro-survival role of autophagy in CML treated with interferon. Interferon-1 activated both JAK1-STAT1 and NF-κB pathways, leading to increasing BECN1-ATG5-ATG7, one of the major regulators of the classical autophagy pathway. Inhibiting autophagy by using chloroquine enhanced the cytotoxic effect of interferon-1 (72).

Cytarabine was reported to increase the phosphorylation of AMPK/ERK, inhibit Akt and attenuate mTOR activity, thereby inducing cytoprotective autophagy in leukemic cells. Pharmacological (bafilomycin A1 and chloroquine treatment) or genetic (siRNA downregulation of either LC3b or autophagic cargo receptor p62) impairment of autophagy markedly increased cell death by accumulating DNA fragmentation and mitochondrial damage as well as activating oxidative stress, thus providing the combination strategy of cytarabine and autophagy inhibitor in leukemia treatment (73).

Notably, doxorubicin and melphalan were shown to motivate autophagy in multiple myeloma (MM) cells, which provided an adaptive condition for evading DNA-damaging stimulus. The increasing Beclin-1-PI3KC3 complex and Bcl-2 disintegrated from Beclin-1, functioned as a cell survival mechanism in this process. Thus, the inhibition of autophagy with DNA-damaging agents likely augmented anti-myeloma activities without additional side effects (74). In cases of acute lymphocytic leukemia (ALL) treated with bortezomib, cytoprotective autophagy was also associated with the balance between the Bcl-2-Beclin-1 complex and the Beclin-1-PI3KC3 complex, as its downregulation by chloroquine potentiated anti-ALL activity (75). The aforementioned results indicated a pivotal role of Bcl-2-Beclin-1-PI3KC3 complexes in autophagy and provided a novel target to improve clinical efficacy. Another experiment provided evidence of autophagic cell proliferation in aggressive B-cell lymphoma managed with bortezomib. In that study, ER stress-associated IRE1-JNK was stimulated, followed by phosphorylated Bcl-2 and elevated LC3-II, which was widely used for autophagic flex surveillance. Certainly, the addition of JNK inhibitor SP600125 enhanced the anti-lymphoma effects of bortezomib (76).

Anthracycline daunorubicin (DNR) revealed potent leukemia killing activity by DNA damage. However, DNR-induced autophagy was inversely cytoprotective, and authors of that study identified the activation of MAPK (MEK-ERK) in DNR-treated myeloid leukemia cells (77). Obviously, adding MEK1/2 inhibitor U0126 to daunorubicin would enhance chemotherapeutic response and reduce drug toxicities.

The example of the autophagic pro-survival role in CLL originated from the observation that dasatinib was capable of sustaining stable cellular metabolism from AMPK activation and consequent autophagy motivation, which was also the mechanism of drug resistance (78). However, Morita *et al* reported that dasatinib induced autophagy-dependent cell death in Bcr-Abl-positive leukemia cells with central nervous system (CNS) infiltration *in vitro* and *in vivo*, confirming the important mechanism of autophagy for CNS leukemia treatment (79).

Of note, sorafenib regulated the mTOR or Mcl-1 pathway in multiple myeloma with different outcomes (80): on the one hand, mTOR inhibition by sorafenib induced cytoprotective autophagy; on the other hand, sorafenib-triggered downregulation of Mcl-1 was essential to cell death, and the addition of ABT737 (Bcl-2 antagonist) improved the efficacy of sorafenib. As a result, a combination of sorafenib with autophagy inhibitor and ABT737 is a potentially new treatment strategy in multiple myeloma.

Recently, Takahashi *et al* demonstrated that L-asparaginase (L-asp)-triggered autophagy contributed to ALL cell survival by eliminating accumulated DNA damage and injured mitochondria with the help of a ROS-p53 loop, indicating that combination treatment with an autophagy inhibitor enhanced anti-leukemic effects of L-asp and overcame drug resistance for ALL patients (81).

Thus, the aforementioned studies fully demonstrated the dual role of autophagy in hematological malignancies, of which induction or inhibition may improve the therapeutic efficacy depending on the types of antitumor agents and pathways of stress responses.

4. Conclusions and perspectives

Autophagy, an evolutionarily conserved degradation process, has recently been proven to play a dual role in cancer, by triggering autophagic cell death or by protecting tumor cells from harsh conditions and DNA damage. From the research discussed above in this review, autophagy can be triggered via various conventional chemotherapeutic agents in blood tumors, which results in different effects. Indeed, the outcome of autophagy can be diametrically opposite. Some agent-induced autophagy promotes tumor cell death and prevents disease progression (47-62), whereas in some circumstances, activated autophagy acts as a protective mechanism, and adding autophagy inhibitors enhances treatment efficacy (72-77,80,81). Furthermore, in a few cases, agent-induced autophagy fills both pro-death and pro-survival roles (66-71,78,79,82,83). Thus, therapeutic development in blood tumors targeting autophagy remains to be elucidated. It is well known that, the autophagy signal transduction pathway is intricate, and upregulation or downregulation of autophagy is hampered through diverse molecular regulators at multiple levels. Therefore, the role of autophagy modulated by these drugs depends on cell types, differentiation status, and signal transformation pathways (84,85).

We present different changes of autophagy signaling pathways induced by conventional chemotherapeutic agents and potential combination treatment strategies in Table I, which may improve the therapeutic effect and provide novel targets for the treatment of hematologic malignancies. However, several basic questions remain to be elucidated.

First, induction or inhibition of autophagy is a complicated process because of its dual role in different types of blood tumors with different chemotherapy regimens. Another significant challenge is to determine concrete molecular mechanisms in the process, and interpret the crosstalk between autophagy pathways and intracellular responses. Fully understanding

these issues may provide more precise treatment involving the addition of autophagy regulators such as mTOR repressor, AMPK agonist, and hydroxychloroquine to increase efficacy and overcome drug resistance. Additionally, some studies did report that autophagy contributed to cell protection and its pharmacological inhibition improved drug sensitivity. Further research is required to determine whether autophagy inhibitors directly affect cell fate or affect it in a more indirect manner.

In the near future, with awareness of the molecular mechanism and accurate targets underlying this complex process, clinicians will identify patients who are likely to benefit from treatment involving autophagy regulation by agonists or blockers.

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Available data and materials

All data generated or analyzed during this study are included in this published article.

Author's contributions

JSH and YLS conceived and designed the study. JSH and WJY researched related literatures and drafted the manuscript. QWB and LH reviewed and revised the manuscript. All authors read and approved the manuscript and agree to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no conflict of interest.

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