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Original Articles

Unveiling autophagy complexity in leukemia: The molecular landscape and possible interactions with apoptosis and ferroptosis

Young Yun Jung [a], Kwang Seok Ahn [a,*], Mingzhi Shen [b,**]

[a] Department of Science in Korean Medicine, Kyung Hee University, 24 Kyungheedae-ro, Dongdaemun-gu, Seoul, 02447, Republic of Korea
[b] Department of General Medicine, Hainan Hospital of PLA General Hospital, The Second School of Clinical Medicine, Southern Medical University, Guangzhou, Sanya, China

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ABSTRACT

Autophagy is a self-digestion multistep process in which causes the homeostasis through degradation of macromolecules and damaged organelles. The autophagy-mediated tumor progression regulation has been a critical point in recent years, revealing the function of this process in reduction or acceleration of carcinogenesis. Leukemia is a haematological malignancy in which abnormal expansion of hematopoietic cells occurs. The current and conventional therapies from chemotherapy to cell transplantation have failed to appropriately treat the leukemia patients. Among the mechanisms dysregulated in leukemia, autophagy is a prominent one in which can regulate the hallmarks of this tumor. The protective autophagy inhibits apoptosis and ferroptosis in leukemia, while toxic autophagy accelerates cell death. The proliferation and invasion of tumor cells are tightly regulated by the autophagy. The direction of regulation depends on the function of autophagy that is protective or lethal. The protective autophagy accelerates chemoresistance and radio-resistsance. The non-coding RNAs, histone transferases and other pathways such as PI3K/Akt/mTOR are among the regulators of autophagy in leukemia progression. The pharmacological intervention for the inhibition or induction of autophagy by the compounds including sesamine, tanshinone IIA and other synthetic compounds can chance progression of leukemia.

1. Introduction

A malignant pathological event of blood in which oligoclonal expansion of hematopoietic cells is observed is known as leukemia [1]. In this malignancy, the hematopoietic cells show infiltration in the bone marrow and they are capable of blood invasion and also, targeting other extramedullary tissues [2]. The growth of leukemia has been considered as a factor for the expulsion of the normal hematopoietic cells and then, their dysfunction, causing a number of effects such as thrombocytopenia, anemia, and immunodeficiency. According to the epidemiological studies, the haematological tumors are currently considered as 11th common cancer kind and in terms of death, they are at the rank of ten among other malignancies. In 2012, 350,000 new cases of leukemia have been diagnosed in which 265,000 deaths have resulted from these cases, highlighting the high malignancy of these cancers [3]. 4 % of tumor-related deaths in USA are because of the leukemia and they comprise up to 3.5 % of all diagnosed cancer cases. There are geographical changes for the incidence rate of leukemia, but the important thing is that mortality and survival of leukemia rely on the different factors including time of cancer diagnosis and natural history from the malignant transformation of hematopoietic stem cells or progenitor cells in the bone marrow site [4]. There are two ways for the categorization of leukemia that both of them have been already accepted by the researchers and leukemia can be considered acute or chronic, and moreover, another classification is based on lineage that in this case, leukemia can be lymphoid or myeloid. Furthermore, the researchers have considered four main subtypes for the leukemia including acute lymphoblastic leukemia (ALL), chronic lymphoblastic leukemia (CLL), acute myeloid leukemia (AML), and chronic myeloid leukemia (CML). Among these subtypes, the most common one in children is ALL [5], while others commonly occur in adults. As a malignant condition, the lekuemia diagnosis has been of high importance and a number of ways

* Corresponding author.
** Corresponding author. Department of General Medicine, Hainan Hospital of PLA General Hospital, The Second School of Clinical Medicine, Southern Medical University, Guangzhou, Sanya, China.
E-mail addresses: ksahn@khu.ac.kr (K.S. Ahn), shenmz301@163.com (M. Shen).

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including flow cytometry, biopsy and imaging tests are deployed for the diagnosis of leukemia [6]. The progression ranges of leukemia and also, the response of patients to the therapy depend on the leukemia type and rate of its progression. However, it should be kept in mind that in a number of cases, the leukemia cells do not respond to the therapies and this has caused failure of conventional therapies for this tumor. Chemotherapy, radiotherapy and targeted therapies are widely utilized for the treatment of leukemia. Compared to the previously mentioned treatment methods, the new strategies including immunotherapeutic ways and stem cell transplantation have been considered as new ways for leukemia therapy. These methods can be also summarized as cell death stimulation in leukemia by natural killer cells, the treatments based on monoclonal antibodies, chimeric antigen receptor T cell therapy, adoptive cell therapy and vaccination as well as combination mainstays to impair progression of leukemia [7].

Currently, it has been well-understood that low response of leukemia patients to the therapy is a result of heterogeneous nature of this disease. Hence, the underlying mechanisms and pathways in understanding leukemia pathogenesis has attracted much attention. If such molecular mechanisms are highlighted, the new therapeutics can be developed with high efficiency. The JAK2 suppression in leukemia is used as a promising strategy in tumor suppression, while upregulation of DUSP6 promotes tumor progression and induces resistance to the JAK2 inhibition in leukemia [8]. The modification in the mRNAs can cause changes in the progression of leukemia and m6A is among them. YTHDF1 is considered as an m6A reader protein in which enhances the translation rate of cyclin E2 to accelerate survival of xenograft models [9]. Currently, it has been well-documented that exosomes as minute extracellular vesicles are able to increase survival of leukemia stem cell and promote leukemia progression through providing the crosstalk between stem cells, leukemic blasts and stromal cells in bone marrow niche [10]. In another aspect, the pathogenesis of leukemia can be delayed due to interaction of anti-cancer proteins. The increase in PTEN stabilization through the function of TSPAN32 can suppress PI3K/Akt-induced leukemia progression [11]. The therapeutic targeting of these factors can provide new insights in the treatment of leukemia such as regulation of cytohesin-1 in reversing resistance to ABT-199 [12]. Moreover, application of chenodeoxycholic acid [13] and methionine [14] can suppress progression of leukemia. Table 1 and Fig. 1 summarize the dysregulation of molecular pathways in leukemia.

Table 1
Leukemia and process of tumorigenesis.

Molecular landscape	Highlights	Refs
TET2	Loss of TET2 enhances leukemogenesis through enhancing the homing of leukemia stem cells in the bone marrow niche	[15]
PPARα/HIF1α/PGK1	Chiglitazar avoids the ubiquitination of PPARα to impair glucose metabolism PPARα downregulates HIF1α to suppress PGK1 in impairing cancer stemness	[16]
Hes1	Hes1 downregulates PTEN by binding to its promoter Hes1 stimulates Notch1 axis Increasing proliferation rate of leukemia cells	[17]
STAT3/VISTA	STAT3 increases levels of VISTA to impair function of immune-related cells and reducing the cytotoxicity of T cells	[18]
PLK1/LDHA	PLK1/LDHA undergoes upregulation by USP1 to enhance aerobic glycolysis	[19]
SLED1	SLED1 elevates Bcl-2 expression to prevent apoptosis and increase the proliferation	[20]
Akt, P70S6K and NF-kB	Akt, P70S6K and NF-kB downregulation by curcumin impairs the growth and diminishes the survival rate of tumor cells	[21]
SPRY1	SPRY1 upregulates Hedgehog to impair apoptosis and increase growth rate	[22]
ACSM3	ACSM3 reduces IGF2BP2 level to mediate apoptosis and impair proliferation	[23]
miR-603	miR-603 downregulates TrkB expression to trigger apoptosis and impair proliferation	[24]

Regarding the diversity of the molecular factors in the initiation and malignancy of leukemia, the specific mechanisms with high potential in tumorigenesis should be highlighted. The mission of current review is to provide a state-of-art review of the role of autophagy as a molecular machinery in regulation of leukemia progression. This review emphasizes on the molecular mechanisms regulating autophagy in the leukemia and it is started by providing a summary about autophagy. Then, interaction of autophagy with other cell death mechanisms in leukemia including apoptosis and ferroptosis are provided that can be considered as future perspectives for understanding chemoresistance development. Moreover, proliferation, metastasis, chemoresistance and radioresistance in leukemia may be affected by the autophagy that are aspects of this paper. Finally, the major mechanisms regulating autophagy and finally, therapeutic regulation of autophagy in leukemia are discussed.

2. Autophagy: a summary

The autophagy machinery is a complex mechanism for the researchers, but before highlighting the complexity of this mechanism, its molecular profile and regulation should be revealed. There are three classifications for the autophagy including macroautophagy, microautophagy and chaperone-mediated autophagy [25]. However, macroautophagy, hereafter is simply named autophagy, is the main type. Moreover, the studies have well-documented that macroautophagy is considered as the main mechanism for providing intracellular degradation [26]. The autophagy is a protective mechanism in which engulfed substances are degraded with the purpose of keeping cellular function and homeostasis (Fig. 2) [27]. The damaged, denatured, aged and dysfunctional organelles, denatured proteins and other macromolecules present in the cells can be degraded by autophagy for preserving survival and repair of cells [28]. Autophagy is also known as a catabolic mechanism that stimulates sequestration of misfolded proteins and damaged cytoplasmic organelles. This is pertained to the function of autophagosomes as double-membrane compartments and then, degradation of engulfed materials upon lysosome fusion [29]. Autophagy occurs in several steps that first one is initiation of autophagy regulated by the autophagy-related genes (ATGs) which can interact with other proteins in regulation of autophagy including mTOR, AMPK, ULK1 and PI3K-III complex [30]. To be more specific, upregulation of AMPK or suppression of mTOR can cause initiation of autophagy [31]. AMPK is an energy sensor that causes phosphorylation of mTORC1, ULK1 and Beclin-1 to regulate autophagy [32–35]. When mTORC1 expression is high, the situation is different from the AMPK upregulation and it can impair autophagy mechanism through inducing phosphorylation of ULK1, ULK2 and ATG13 proteins [36]. When ULK1 is overexpressed, it can recruit a complex of Beclin-1-PIK3C3 in the site of autophagosome generation [37]. The expansion and completion of phagophores for the generation of autophagosome is mediated by ATG proteins such as MAP1LC3 [38,39]. The selectivity of autophagy for the cargo and substance degradation can be mediated by autophagy receptors including SQSTM1/p62 that has ability of binding to MAP1LC3 [40].

The complex part of autophagy is pertained to its dual and intrigue function in human cancers. In spite of the autophagy function in modulating the process of homeostasis and appropriate function of cells, the dysregulation of this mechanism in cancer has caused several types of problems for the treatment of this malignant disease. Currently, there is no solid data showing that function of autophagy in a certain stage of cancer is only protective or cytotoxic, while different studies have mentioned that autophagy can have dual function even in a single type of cancer. Moreover, autophagy is a modulator of growth and metastasis in human cancer and therefore, its dysregulation can affect hallmarks of cancer [41]. The autophagy regulation in cancer can be mediated by non-coding RNAs and also, this molecular mechanism determines chemotherapy response [42]. The biology advances have results in

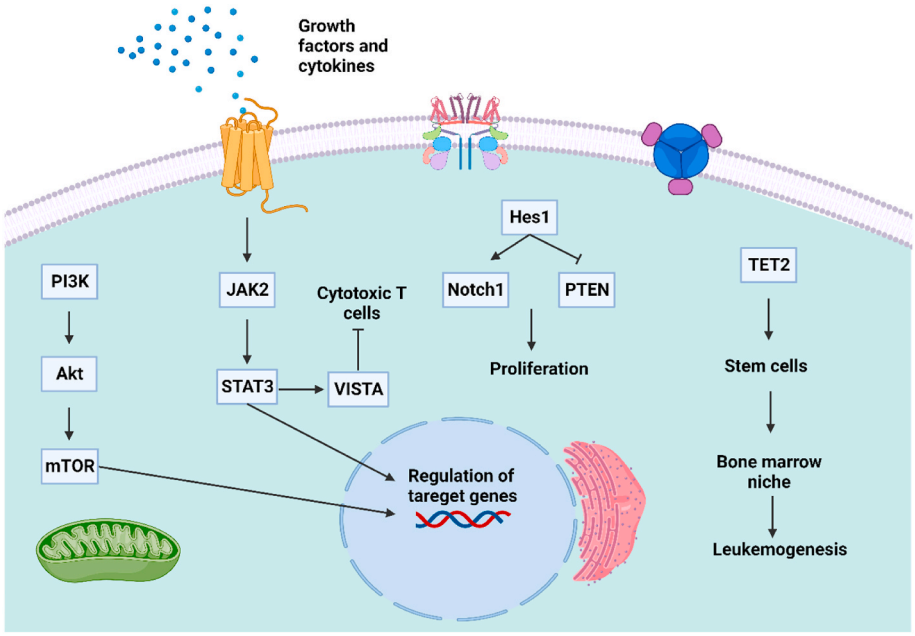

Fig. 1. The dysregulation of pathways in leukemia. The upregulation of PI3K/Akt/mTOR and JAK2/STAT3 can cause progression of leukemia. Moreover, STAT3 increases VISTA expression to impair the function of cytotoxic T cells. The increase in the proliferation of leukemia can be mediated by Hes1. Furthermore, TET2 increases stem cells in the bone marrow niche to accelerate leukemogenesis.

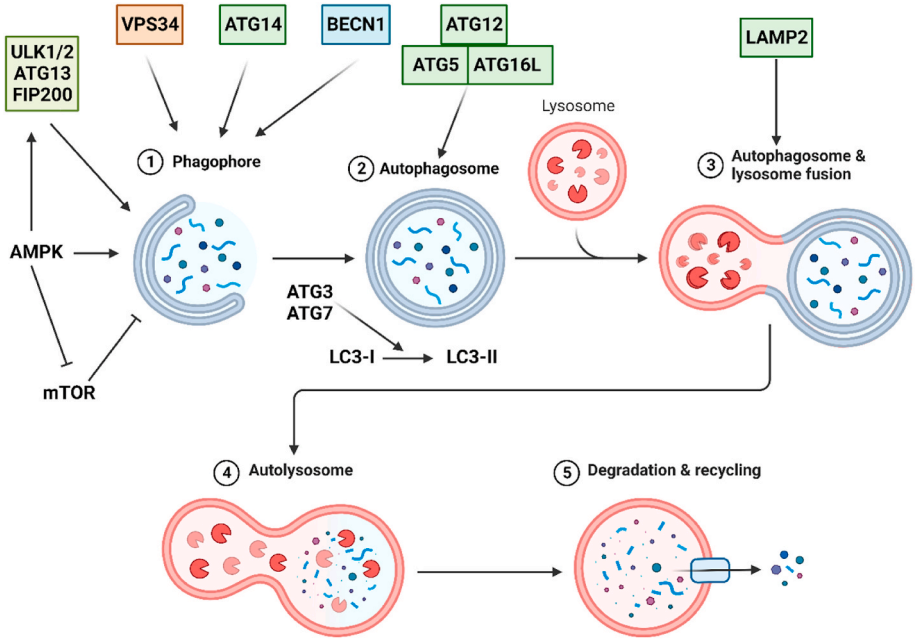

Fig. 2. Autophagy machinery in cell. This regulated machinery is started by the function of AMPK, while it is suppressed by mTOR. The presence of ULK1/2, FIP200 and ATG13 for stimulation of autophagy is necessary. During phagophore formation, ATG14, VPS34 and BECN1 play a significant role. The expansion of autophagosome depends on the LC3-II and function of ATG12, ATG5 and ATG16L complex. Finally, LAMP2 mediates the fusion of lysosomes and autophagosomes.

understanding more factors regulating autophagy in cancer and circular RNAs modulate tumorigenesis through autophagy control [43]. The molecular profile of autophagy has been more highlighted by the recent experiments showing that even the activation of tumor microenvironment compoentns such as cancer-associated fibroblasts is dependent on the autophagy [44]. Due to function of autophagy in regulation of metabolic pathways, it can exert toxic impact. SIRT4-mediated autophagy can suppress glutamine metabolism to increase p53 levels in cancer therapy [45]. The multi-omics analysis has also shown that autophagy stimulation can downregulate DDIT4 expression, as a response for increasing etoposide sensitivity in cancer [46]. The inhibition of toxic autophagy by PSMD14 can accelerate progression of ovarian cancer through increasing LRPPRC stability [47]. However, the suppression of protective autophagy along with MEK downregulation can cause ferroptosis in lung cancer [48]. As a conclusion, autophagy function in cancer is essential and it has been understood in different studies (Table 2) [49,50]. The mission of this paper and following section is to highlight autophagy function in leukemia with focus on molecular profile.

Table 2
A summary of autophagy dysregulation in tumors and related molecular landscape.

Cancer	Molecular landscape	Highlights	Refs
Cervical cancer	AMPK	Maackiain induces autophagy through AMPK upregulation and mTOR downregulation to impair tumorigenesis	[51]
Cervical cancer	–	Autophagy stimulation elevates cell death in tumors exposed to irradiation	[52]
Glioblastoma	O-GlcNAcylation	O-GlcNAcylation suppression diminishes survival rate of cancer and autophagy and promotes temozolomide sensitivity	[53]
Colorectal cancer	CXCL1	The CXCL1 induces immune evasion through autophagy-induced MHC-I degradation	[54]
Lung cancer	CHI3L1	CHI3L1 stimulates autophagy through regulation of JNK	[55]
Endometrial cancer	UBE2C	The suppression of autophagy by UBE2C through SIRT1 ubiquitination increases cancer progression	[56]
Ovarian cancer	P62 Akt/mTOR	Downregulation of p62 and Akt/mTOR by astragaloside II stimulates autophagy and enhances cisplatin sensitivity	[57]
Breast cancer	SCD1	IC2 as a derivative of icaritin downregulates SCD1 to mediate pro-survival autophagy	[58]
Gastric cancer	AAMDC/MYC/ATF4/Sesn2	Solanine modulates AAMDC/MYC/ATF4/Sesn2 axis to induce autophagy in impairing proliferation	[59]
Glioblastoma	MGCG	MGCG increases expression of ATG2A to mediate autophagy	[60]
Gastric cancer	MFAP2	MFAP2 stimulates autophagy to enhance cisplatin resistance	[61]
Bladder cancer	RAB14	RAB12 regulates autophagy/Akt axis to mediate EMT	[62]
Gastric cancer	STAT3/Beclin1	Nintedanib promotes Beclin1 expression through STAT3 suppression to facilitate autophagy-mediated cell death	[63]
Lung cancer	TWF1	TWF1 downregulates cAMP to trigger autophagy and elevate the malignant malignancy of tumor	[64]

3. Autophagy and apoptosis in leukemia

The autophagy function in leukemia may result in disruption of apoptosis, and sometimes, the lethal autophagy causes apoptosis. As a regulated cell death mechanism, apoptosis occurs through two pathways that mitochondrial dysfunction is the most prominent one. Autophagy and apoptosis crosstalk in leukemia can affect the progression of tumor cells. The interaction of autophagy and apoptosis can be regulated by ATM/IKKα [65]. The lethal autophagy induction promotes apoptosis in leukemia cells. Gambogic acid reduces beta-catenin expression and promotes autophagy to facilitate apoptosis in tumor cells [66]. TG101209 as JAK2 suppressor increases LC3 and Beclin-1 expression to induce autophagy and apoptosis in leukemia cells [67]. The protective autophagy can be accelerated through downregulation of Akt/mTOR axis to impair apoptosis. However, suppression of autophagy can elevate apoptosis in leukemia cells [68]. The increase in levels of LC3-II and ATG5 can mediate autophagy by the function of perifosine. The pharmacological suppression of autophagy by chloroquine improves apoptosis in leukemia [69]. The regulation of autophagy by compounds can also affect the apoptosis. Puerarin is able to induce autophagy in mediating apoptosis, while autophagy suppression can reduce apoptosis in leukemia cells [70]. The autophagy and apoptosis regulation and interaction can affect the chemotherapy response in leukemia cells. Celecoxib is able to disrupt autophagy in increasing apoptosis and necroptosis in leukemia [71]. However, downregulation of mTOR by clioquinol can mediate autophagy with toxic function in impairing leukemia progression [72]. Another compound regulating autophagy and mTOR is tanshinone IIa. The inhibition of PI3K/Akt/mTOR axis by tanshinone IIa can accelerate apoptosis and autophagy. The induction of apoptosis in leukemia cells is based on autophagy stimulation [73]. However, autophagy induction by mTOR suppression does not always render the toxic function. The downregulation of EGFR and PI3K/Akt/mTOR by ganoderma tsugae can accelerate apoptosis and induce protective autophagy [74]. Maybe for a synergistic process, it is better to regulate autophagy and other mechanisms. Suppression of CDK4/6 and autophagy can accelerate apoptosis in leukemia [75]. In HL-60 leukemia cells, the blockage of autophagy and impairment of lysosomal function can accelerate apoptosis [76]. A new regulator of autophagy in leukemia is MAP30 that promotes p300 levels to suppress autophagy in facilitating apoptosis in leukemia [77]. Therefore, autophagy can affect apoptosis in leukemia [78]. However, a significant gap of current studies is that how autophagy can regulate the extrinsic pathway of apoptosis through interacting with DR proteins and regulating TRAIL mechanism. Moreover, the interaction of mitochondria and endoplasmic reticulum and their role in regulation of autophagy and apoptosis in leukemia requires significant attention.

4. Autophagy and ferroptosis in leukemia

Ferroptosis discover was made in 2012 as an iron-dependent cell death [79] in which cells undergoing ferroptosis have necrotic chances including swelling and plasma membrane rupture and they can be distinguished from the apoptotic cells [80]. The morphological alterations during ferroptosis are unique including decrease in the volume of mitochondria, emergence of fractures in the outer membrane of mitochondria, reduction in mitochondria crest, nucleus with normal size and no concentration that make ferroptosis a distinct type of cell death and recognizable to other types of cell death mechanisms [81]. The lipooxygenases normally oxidize PUFAs, but GPX4 and GSH as cofactor reduce the levels of PUFAs oxidized by lipooxygenases [82]. The inhibition of cysteine-glutamate antiporter can decrease the biosynthesis of GSH and then, downregulation of GPX4 to induce ferroptosis [83]. Then, increase in lipid peroxidation is observed to cause cell death [84,85]. Currently, a number of drugs such as sorafenib and sulfasalazine are considered as inducers of ferroptosis in cancer [86]. The interaction of autophagy and ferroptosis has been well-evidenced in different kinds of human cancers [87,88]. In leukemia, autophagy and ferroptosis demonstrate close interaction. In this case, also the function of autophagy determines that whether ferroptosis can occur or no. The AMPK/mTOR/p70S6k is regulated by DHA in leukemia that AMPK expression increases, while mTOR is suppressed to mediate autophagy for increasing degradation of ferritin to induce ferroptosis [89]. Another experiment also highlights the fact that upregulation of AMPK can cause autophagy to increase degradation of ferritin for increasing ferroptosis [90]. The regulation of FBXW7 by autophagy can also determine the occurrence of ferroptosis in leukemia. Autophagy downregulates FBXW7 expression to increase VDAC3 stability in leukemia for accelerating ferroptosis [91]. Noteworthy, the regulation of ferroptosis by autophagy can determine apoptosis in leukemia cells. Neratinib promotes LC3-II, ATG5 and Beclin-1 expression to induce autophagy-mediated ferroptosis in facilitating apoptosis in leukemia [92]. This evidence is also more confirmed by study of Lou and colleagues that found the idea that ATG5/7 downregulation inhibits autophagy-mediated ferroptosis and reduces apoptosis in leukemia [93]. As a conclusion, autophagy is a regulator of ferroptosis in leukemia, but the idea that ferroptosis has ability of influencing autophagy and tumorigenesis in leukemia requires investigation (Fig. 3).

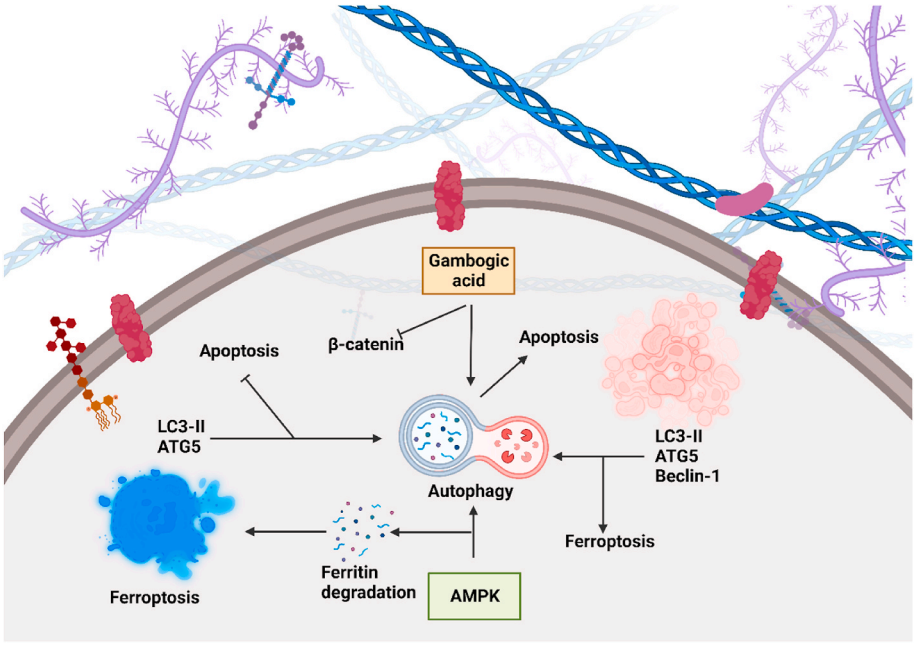

Fig. 3. The regulation of apoptosis and ferroptosis by autophagy in leukemia. The induction of autophagy through the function of AMPK can accelerate ferroptosis by ferritin degradation. Moreover, tanshinone IIA can stimulate autophagy through Akt/mTOR downregulation to cause apoptosis.

5. Autophagy in regulation of cancer drug resistance

The most prominent function of autophagy can be followed in regulation of cancer drug resistance in leukemia. Currently, the problem for autophagy mechanism is not only related to leukemia and it can be observed in both solid and haematological tumors that exact function of autophagy is not certain. Different kinds of studies in animal models, in vitro and even other species such as zebrafish have been performed to understand why the autophagy function is protective or lethal in a certain type of cancer. A major limitation of current studies is lack of major focus on the status of autophagy in the different stages of cancer that can also provide more insights and helps in highlighting its function. Regarding the function of autophagy, there is concrete evidences that autophagy modulates chemoresistance in leukemia. The first note related to the chemotherapy is that it can mediate autophagy in leukemia. The SIRT6 promotes PARP-1 expression to upregulate HMGB1. Then, HMGB1 causes dissociation of Beclin-1 and Bcl-2 to mediate complexation of Beclin-1 and PI3KC3 in autophagy induction. Moreover, overexpression of ULK1 complex and its association with other members of this complex including ATG13, FIP200 and ATG101 can cause autophagy in triggering chemoresistance in leukemia [94]. However, ULK1 and Beclin01 are not the only targets of HMGB1 in autophagy modulation in leukemia. The HMGB1 upregulation in leukemia can cause increases in levels of LC3-II and sequestration of p62. Moreover, when the inhibition of PI3K-III and ERK occurs, the potential of HMGB1 in autophagy induction is abrogated to cause drug resistance [95]. On the other hand, it was mentioned that HMGB1 increases ULK1 expression in autophagy induction. Moreover, it is worth mentioning that ULK1 expression can be elevated by AMPK to cause resistance of leukemia cells to BET inhibitor JQ1 [96]. These studies highlight that the initial step of autophagy that is regulated by AMPK, ULK1 and Beclin-1, can be affected by other molecular mechanisms. However, it should be noted that the other steps of autophagy and the related regulators such as ATGs that modulate expansion of autophagosome, can participate in regulation of chemoresistance. EVI1 is a factor participating in upregulation of ATG7 mRNA along with sitmulation of autophagy and increase in ROS levels to cause drug resistance in leukemia [97]. This highlights that the molecular profile of expansion step of autophagy is also of high importance in regulation of chemoresistance in leukemia. Another regulator of autophagosome expansion is ATG12 with critical function in drug resistance. The competition between OIP5-AS1 and miR-30e-5p in binding to ATG12 can regulate autophagy. miR-30e-5p is suppressed by OIP5-AS1 to increase ATG12 expression in the development of imatinib resistance in leukemia [98].

The proteomics analysis reveals that the presence of a negative feedback loop between autophagy and ROS can cause the development of imatinib resistance in leukemia [99]. The function of autophagy is not certain to a chemotherapy and it can cause multidrug resistance. In fact, dysregulation of autophagy in leukemia causes resistance to different types of tumors that Adriamycin is among them. The circPAN3 increases AMPK expression to downregulate mTOR in autophagy induction and development of chemoresistance [100]. Now, it is obvious that autophagy is a regulator of chemoresistance in leukemia. In the previous sections, it was mentioned that autophagy has interaction with apoptosis in leukemia. Now, the question is that is there any possibility for the function of apoptosis-related proteins in modulation of autophagy? The study of Amrein and colleagues has responded to this question and the fact is that p53 as a regulator of apoptosis able to induce autophagy in the development of chemoresistance in leukemia. When there is lack of p53-mediated autophagy, the sensitivity of leukemia cells to the dasatinib increases. Moreover, they have shown that optimal doses of dasatinib can cause endoplasmic reticulum stress in primary CLL lymphocytes, while it only mediated autophagy in primary CLL lymphocytes with wild-type p53 [101]. In treatment of ALL, the response to the glucocorticoid therapy is vital. It has been well understood that changes in expression level of autophagy-related genes cause resistance to this therapy in ALL [102]. However, case of autophagy can be beneficial in reversing drug resistance in leukemia. The Beclin-1 upregulation and mTOR downregulation can cause autophagy to mediate necroptosis in suppressing glucocorticoid resistance in ALL (Fig. 4) [103]. Table 3 is a summary of autophagy function in drug resistance in leukemia.

6. Autophagy in regulation of radioresistance

The increasing evidences have highlighted the function of autophagy in the regulation of radioresistance in cancers. The radiation increases the levels of HIF-1α that interacts with BTN3A1 in the nucleus to

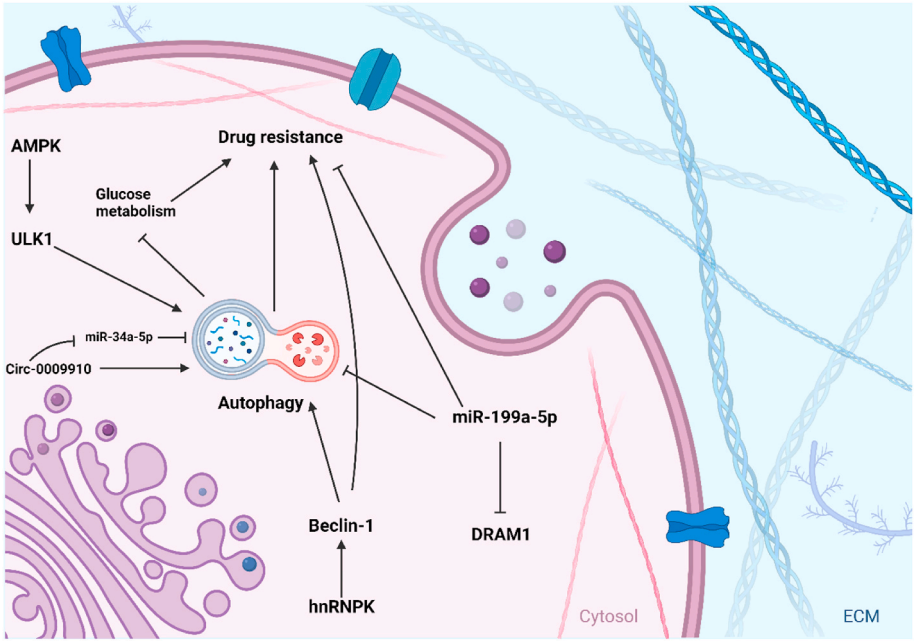

Fig. 4. The regulation of drug resistance by autophagy occurs through different mechanisms that in one of them, autophagy suppresses glucose metabolism to reverse drug resistance. Moreover, AMPK increases ULK1 expression to mediate autophagy-induced drug resistance. DRAM1 downregulation by miR-199a-5p can impair autophagy and chemoresistance in leukemia. The Beclin-1 expression enhances by hnRNPK to mediate autophagy-induced chemoresistance.

enhance its expression and cytoplasmic translocation, overexpressing ULK1, inducing autophagy and mediating radioresistance [131]. The ionizing radiation has been reported to increase levels of NRBF2, ATG14 and VPS34 complex to induce protective autophagy, causing radioresistance in glioblastoma [132]. The genetic mutations in the cancer can also change the biological mechanisms in the tumor cells in the regulation of radioresistance. The mutation of *SMAD4* gene causes overproduction of ROS and stimulation of autophagy to mediate radioresistance [133]. The stimulation of survival autophagy by Wnt3a can also mediate the development of radioresistance [134]. Although there is solid evidence that autophagy is a modulator of radioresistance, only one experiment has evaluated potential of autophagy in radiotherapy response modulation in leukemia. This study provides the fact that autophagy is regulated and stimulated by p53 in leukemia during irradiation and the fact that function of autophagy is protective [135]. More evolution about the regulation of autophagy by molecular interactions during radiotherapy should be provided. The radiation causes DNA damage in the development of cancer cell damage. However, autophagy shows interactions with DNA damage repair mechanisms that in case of protective autophagy, DNA damage repair is accelerated and this can cause radioresistance. Moreover, radiation aims in the stimulation of cell death in the tumor cells including apoptosis [136,137] and ferroptosis [138]. In case of toxic autophagy, it can increase apoptosis and ferroptosis to mediate irradiation sensitivity. However, when pro-survival autophagy occurs, it diminishes apoptosis and ferroptosis to enhance radioresistance. Therefore, the interaction of autophagy with cell death mechanisms in case of radioresistance requires investigation in leukemia.

7. Molecular profile in autophagy regulation in leukemia proliferation and metastasis

Regarding the much importance of autophagy for regulation of cancer hallmarks, this section aims in describing the function of autophagy in regulation of proliferation and metastasis in leukemia and then, related molecular profile is revealed. The epigenetic factors are considered as the main regulators of autophagy in leukemia. The family of epigenetic factors is large, but miRNAs, lncRNAs and circRNAs are the main members of this family. The recent studies have clearly displayed that miRNAs [139], lncRNAs [140] and circRNAs [141] modulate tumorigenesis in leukemia. Therefore, they are promising targets in cancer therapy. The acceleration of autophagy by lncRNA HOTAIRM1 in leukemia causes tumorigenesis. The nuclear interactions can change the expression level of lncRNA HOTAIRM1. The mutant NPM1-mA causes interaction of KLF5 with WWP1 and then, this causes upregulation of HOTAIRM1 in nucleus. Then, HOTARIM1 promotes degradation of EGFR1 and moreover, it sponges miR-152-3p to increase ULK3 expression in autophagy induction [142]. The function of HOTAIRM1 in regulation of autophagy can even affect the differentiation of cells. Silencing lncRNA HOTAIRM1 can reduce the degradation of PLM-RARA and then, it prevents the differentiation of promyelocytic to granulocytic cells and HOTAIRM1 downregulation can suppress autophagy. More investigation revealed that HOTAIRM1 sponges miR-125b and miR-20a/106b to increase ULK1 expression and other targets such as E2F1 and DRAM2 in autophagy induction [143]. Although the main focus of studies has been on the autophagy, the chaperone-mediated autophagy (CMA) can be also regulated in leukemia. The lncRNA OBFC2A promotes apoptosis and autophagy in leukemia through upregulation of LAMP2 as a regulator of CMA [144]. In spite of the distinct function of miRNAs, it appears that miRNA expression can be regulated by lncRNAs. This is caused through miRNA sponging that can affect autophagy mechanism. miR-485-5p impairs autophagy in facilitating apoptosis in leukemia. However, LINC00265 upregulation in leukemia cells causes IRF2 upregulation through miR-485-5p sponging to promote autophagy-suppressed apoptosis in leukemia tumorigenesis [145].

The function of autophagy can be changed during the progression of leukemia. Currently, the limitation is that studies have not evaluated the autophagy status in different stages of leukemia progression. Each cancer has different stages of progression and if autophagy status is evaluated in this progression process, more insights about function of this mechanism can be provided. However, the consensus of current studies is that autophagy function in leukemia is not certain. Upregulation of miR-21 causes tumorigenesis in leukemia, while its suppression can overexpress Beclin-1, Vps34 and LC3-II to induce autophagy and increase response to etoposide or doxorubicin in leukemia [146]. This has been also more confirmed that miRNA-mediated autophagy

Table 3
Understanding autophagy function in cancer drug resistance.

Molecular profile	Outcome	Ref
AMPK/ULK1	Upregulation of AMPK/ULK1 axis can induce autophagy-mediated chemoresistance	[104]
ULK1	Inhibition of ULK1 reduces MCL1 expression as antiapoptotic protein and is vital for reversing chemoresistance	[105]
Circ-0009910	miR-34a-5p inhibition to increase ULK1 expression in autophagy-mediated imatinib resistance	[106]
miR-199a-5p	DRAM1 suppression by miR-199a-5p to impair autophagy and drug resistance	[107]
–	Suppression of autophagy in bone marrow stromal cells can impair vorinostat resistance	[108]
–	Autophagy induction disrupts glucose metabolism to suppress chemoresistance	[109]
hnRNPK/ Beclin1	hnRNPK increases Beclin-1 expression to induce autophagy and imatinib resistance	[110]
hnRNPK	hnRNPK increases LC3C-II expression to induce autophagy-mediated chemoresistance	[111]
MEK	Downregulation of MEK stimulates autophagy and increases sensitivity to dexamethasone	[112]
HO-1	HO-1 reduces mTOR expression to induce autophagy-mediated imatinib resistance	[113]
GCA-TRAF6-ULK1	GCA stimulates TRAF6 to increase stability of ULK1 in autophagy induction and regulating imatinib resistance	[114]
HMGB1	HMGB1-mediated autophagy causes chemoresistance	[115]
HMGB1	HMGB1 suppresses Akt phosphorylation and p70S6K to induce autophagy and imatinib resistance	[116]
–	Autophagy suppression increases sensitivity of tumor cells to glucocorticoid therapy	[117]
–	Downregulation of PP2A or suppression of autophagy increases potential of ruxolitinib in proliferation inhibition	[118]
–	The acceleration of acquired drug resistance by stimulation of autophagy	[119]
ERK1/2	Autophagy induction through upregulation of ERK1/2 can prevent daunorubicin-mediated apoptosis	[120]
–	Silencing autophagy promotes potential of NL-101 in treatment of leukemia	[121]
–	Translatome proteomics reveals potential of autophagy in the development of FLT3 inhibitor resistance	[122]
–	The stimulation of autophagy in leukemia with FLT3-ITD mutation contributes to the FLT3 inhibitor resistance	[123]
PERK/NRF2	PERK/NRF2 has a positive association with autophagy in the development of resistance to therapy	[124]
miR-30a	miR-30a increases Beclin-1 expression to induce autophagy and imatinib resistance	[125]
–	The suppression of autophagy and mTOR can cause reversal in resistance to TKI drugs	[126]
–	The stimulation of mitophagy and autophagy by dexamethasone can cause T-ALL glucocorticoid resistance	[127]
SIRT1	SIRT1 promotes CXCR4 expression to upregulate ATG5 and LC3 in autophagy induction and development of chemoresistance	[128]
TCP1	TCP1 stimulates Akt/mTOR axis to impair autophagy and drug resistance	[129]
–	Concomitant inhibition of autophagy and Hedgehog signalling can reverse chemoresistance	[130]

regulation can influence chemotherapy process. There is no doubt that miRNAs are chemotherapy regulators, but the specific function in autophagy regulation in leukemia is of importance. miR-15a-5p downregulates ATG9A, ATG14, GABARAPL1 and SMPD1 to impair autophagy in daunorubicin resistance development [147]. The protective autophagy suppression by miRNAs can increase apoptosis in leukemia. HMGB1 suppression by miR-451 causes autophagy suppression, while it promotes apoptosis in leukemia [148].

The KDM3B is another autophagy regulator in leukemia that accelerates transcription of GABARAPL1 in autophagy induction [149]. The targeted regulation of autophagy in tumor cells can provide new insights in their treatment. Here, two notes are important that A) autophagy regulates chemotherapy response and therefore, its regulation is invesitable; and B) therapeutic targeting of autophagy regulators requires new approaches. For instance, autophagy induction mediates doxorubicin resistance in leukemia. However, when self-assembled leucine polymer is utilized, it impairs autophagy to increase response to doxorubicin in leukemia [150]. After protective autophagy is suppressed in leukemia, the potential of PI3K inhibitors in apoptosis induction in leukemia increases [151]. However, this concept should be considered that PI3K/Akt/mTOR axis is a regulator of autophagy in leukemia. 1-Methoxyerythrabyssin II accelerates autophagy in leukemia and this is pertained to the suppression of PI3K/Akt/mTOR axis [152]. Both interactions in cytoplasm and nucleus are vital for regulation of autophagy in leukemia. The cytoplasmic TP53INP2 is a regulator of autophagy. However, from the first, TP53INP2 is not present in the cytoplasm. FTO promotes transcription of TP53INP2 through the function of m6A and then, it is transferred into cytoplasm by the function of NPM1-mA to induce autophagy through interaction and upregulation of LC3 and ATG7, causing leukemia survival [153].

An important aspect in recent years is the interaction of autophagy and endoplasmic reticulum (ER) stress. Moreover, ER stress can regulate autophagy. On the other hand, both autophagy and ER stress can be regulated by therapeutic compounds [154,155]. The recent studies have highlighted the function of ER stress in regulation of leukemia progression. The stimulation of mitochondrial dysfunction and ER stress by shikonin can cause apoptosis in leukemia [156]. Furthermore, signatures have been developed based on ER stress in understanding the prognosis and immune cell infiltration in leukemia [157,158]. In terms of interaction of autophagy and ER stress, Chang and colleagues have provided a new hypothesis. They have shown that PERK-mediated suppression of Hsp90 can increase ATF4 and CHOP expression to cause IRE1α degradation and dephosphorylation of elF2α. As a result, the change occurs in the activity of UPR and it causes apoptosis. Moreover, ER stress in leukemia cells can cause autophagy. However, it is of importance that repression of autophagy downregulates GRP78 expression and promotes phosphorylation of elF2α in causing ER stress-mediated apoptosis in leukemia [159]. Table 4 provides a summary of the autophagy regulation in leukemia.

Table 4
The pathways regulating autophagy in leukemia.

Molecular target	Remark	Ref
FAPP2	FAPP2 depletion impairs PI3K/Akt/mTOR axis and promotes autophagy in leukemia	[160]
JNK mTOR	Polyphyllin I causes apoptosis and autophagy in leukemia through suppression of Akt/mTOR axis and JNK upregulation	[161]
Casein kinase 1α	P53 inhibition to prevent apoptosis and autophagy	[162]
Circ-PRKDC	Silencing circ-PRKDC promotes apoptosis and autophagy through miR-653-5p upregulation and subsequent inhibition of RELN-induced PI3K/Akt/mTOR	[163]
Naja atra Cardiotoxin 3	Acceleration of apoptosis and autophagy through regulation of Ca2+/PP2A/AMPK Axis	[164]
AMPK	AMPK upregulates NOXA and Beclin-1 expression to mediate autophagy-induced apoptosis	[165]
miR-143	Downregulation of ATG7 and ATG2B to disrupt autophagy	[166]
METTL3	Increase in PSMA3-AS1 stability to induce autophagy	[167]
IER3	Akt/mTOR suppression to induce autophagy	[168]
NPM1	Mutant NPM1 increases RASGRp3 through MID1 interaction in autophagy and growth acceleration	[169]
miR-454-3p	Downregulation of Akt/mTOR and ZEB2 to induce apoptosis and autophagy	[170]
KIT	KIT mutations increases STAT3-induced autophagy to promote growth	[171]
STAT3	Furowanin A-mediated suppression of STAT3/Mcl-1 increases autophagy	[172]
IRF2	IRF2 increases INPP4B expression to induce autophagy and suppress apoptosis	[173]
WAVE1	Silencing WAVE1 reduces autophagy and increases apoptosis	[174]

8. Therapeutic interventions for regulation of autophagy

Maybe the spotlight of the studies is that fact that there have been efforts for introduction of new therapeutics for regulation of autophagy in treatment of leukemia. Before the detailed analysis of autophagy regulation in leukemia, it should be highlighted that various kinds of drugs including synthetic and natural based drugs have been utilized for regulation of autophagy in leukemia. Moreover, if a drug stimulates autophagy in leukemia, it does not mean that function of toxic and after inducing or suppressing autophagy, its role in leukemia can be understood. An example for confirming this statement is that asparaginase is capable of inducing both apoptosis and autophagy in leukemia, but the function of autophagy in this case is protective and can increase carcinogenesis [175]. Bafilomycin A1 is a promising compound in treatment of leukemia and it may disrupt autophagy to impair tumorigenesis. Bafilomycin A1 prevents the formation of autophagosomes and through downregulation of mTOR and increasing dissociation of Beclin-1 and Vps34, it suppresses both early and late stages of autophagy for the treatment of leukemia and also, it promotes apoptosis [176]. The regulation of autophagy by these drugs can affect the interaction of apoptosis and autophagy in leukemia that was discussed in earlier sections of this paper. Pyrimethamine is able to downregulates Bcl-2 expression through STAT5 suppression to impair autophagy and increase apoptosis in leukemia [177]. However, occurrence of apoptosis and autophagy by these drugs in leukemia has no relationship sometimes. Punicalagin has shown potential in reducing Bcl-2 expression and upregulation of caspase-3/-8/-9 to induce apoptosis in leukemia, while it reduces mTOR expression and upregulates ULK1 to induce autophagy in leukemia [178].

The increase in ROS generation by TMQ0153 can cause necroptosis in leukemia and the interesting point is stimulation of autophagy that has a protective function and if the Beclin-1 siRNA is used to suppress autophagy, the leukemia cells are sensitized to the necroptosis [179]. However, there are some limitations with a number of studies in evaluation of autophagy regulation in leukemia that in many cases, they have simply evaluated the autophagy induction, but no investigation of the function of autophagy and if it is suppressed, it can affect the progression of cancer or no. The CDK9 inhibitor has been utilized in treatment of leukemia and through upregulation of LC3-II, it stimulates autophagy. Moreover, it stimulates apoptosis through caspase-upregulation and downregulation of Mcl-1 [180]. The previous studies highlighted the role of HMGB1 in regulation of autophagy and inducing this mechanism in tumorigenesis in leukemia. Since its function is oncogenic, its suppression has been followed in treatment of leukemia. The use of corilagin can increase miR-451 expression to suppress HMGB1 for autophagy suppression and acceleration of apoptosis in leukemia [181]. However, induction of both apoptosis and autophagy in the leukemia at the same time can suppress progression. Niclosamide is able to increase caspase-3 and LC3B expression levels to induce apoptosis and autophagy in the treatment of leukemia [182].

In another situation, it has been revealed that Akt/mTOR can regulate autophagy in leukemia. Akt/mTOR upregulation suppresses autophagy in leukemia. As a drug, hesperetin promotes AMPK expression to suppress Akt/mTOR axis in induction of autophagy through increasing Beclin-1/ATG5/p62 complex upregulation and also, it mediates late apoptosis to impair tumorigenesis in leukemia. However, the function of autophagy is related to increasing proliferation and viability of leukemia cells and therefore, autophagy suppression using inhibitors can provide new insights in the treatment of leukemia [183]. Based on this fact, if the protective autophagy is controlled, the anti-cancer activity of drugs may change. The inhibition of PI3K/Akt/mTOR axis by tigecycline can induce autophagy in leukemia. However, when autophagy is suppressed, the ability of tigecyclin in overcoming chemoresistance in leukemia increases [184]. The upregulation of CD147 in leukemia can enhance the growth rate of leukemia. However, AC-73 as a therapeutic compound targeting CD147 is able to suppress ERK/STAT3 axis in autophagy stimulation and facilitating response of cancer cells to chemotherapy [185]. When the cytotoxic autophagy is induced by anti-cancer drugs, it can accelerate cell death and this prevents the emergence of multidrug resistance in leukemia (Fig. 5) [186]. Table 5 provides an overview of the autophagy regulation by pharmacological compounds in leukemia.

9. Conclusion and perspective

Among the haematological tumors, the role of autophagy in progression of leukemia has been evaluated in details providing a comprehensive discussion of the process of tumorigenesis. A summary of the current findings is that autophagy has interaction with other cell death mechanisms including ferroptosis and apoptosis. The suppression or induction of ferroptosis and apoptosis depends on the exact role of autophagy as a tumor-promoting factor or a tumor-suppressor activity. The hallmarks of leukemia including growth and invasion can be regulated by autophagy during the tumorigenesis process. The regulation of autophagy in leukemia is a complicated and conversely maintained that can occur by the function of non-coding RNAs, epigenetic factors, histone transferase, STAT3 and mTOR, among others. Moreover, the regulation of autophagy by pharmacological compounds has provided new insights in the treatment of leukemia.

The function of autophagy in the regulation of leukemia progression has been significant. The various hallmarks and biological behaviors of tumor cells can be modulated by this cell death mechanism. Interestingly, the autophagy-related genes can be considered as prognostic factors in leukemia and therefore, this improves the clinical application of targeting autophagy in the treatment of patients [209]. Since protective autophagy can increase progression of leukemia, the application of autophagy inhibitors along with therapeutic compounds such as E35 as a derivative of emodin is suggested [210]. Noteworthy, the studies have evaluated both apoptosis and autophagy status in leukemia that downregulation of USF2 impairs autophagy, while it promotes apoptosis [211]. The regulation of autophagy by affecting the related molecular pathways including PI3K/Akt/mTOR and MAPK can change the process of drug resistance in leukemia [212]. Although the exact regulation of autophagy-related pathways by nanostructures has not been evaluated, it appears that autophagy modulation by nanostructures can improve the immunotherapy. The stimulation of autophagy by biomimetic MOF platforms can stimulate dissolution of AFMMB to impair DNA methylation and increase levels of MHC-I complex, mediating anti-leukemia immunity [213].

Recently, immunotherapy has been emerged as a new kind of treatment modality for leukemia. The dysregulation of pathways can cause immune resistance in leukemia. The STAT5 upregulates PD-L1 to increase immunosuppression in leukemia through increasing histone lactylation [214]. On the other hand, autophagy has been considered as a regulator of immune system in cancers [215]. The upregulation of ATG16L1 as an autophagy regulator can impair anti-tumor immunity [216]. The downregulation of YAP1 disrupts autophagy ad enhances the potential of anti-PD-1 in cancer immunotherapy [217]. Although it has been ignored, the interaction of autophagy and immune system can occur in the cancer cells. Therefore, the studies should be directed towards understanding the role of autophagy in the regulation of immunosuppression in leukemia. Moreover, autophagy can regulate the infiltration of immune cells. The polarization of macrophages can also be regulated by autophagy that requires investigation in the treatment of leukemia.

A new perspective for the treatment of leukemia can be the regulation of stemness and cancer stem cells (CSCs) by autophagy. Until now, there has been lack of significant attention to the role of autophagy in the regulation of stemness in leukemia. However, this gap could be exploited as a promising insight for the treatment of leukemia. According to the studies, the CSCs play a significant role in the progression of leukemia. The ALKBH5 has ability of increasing self-renewal ability of

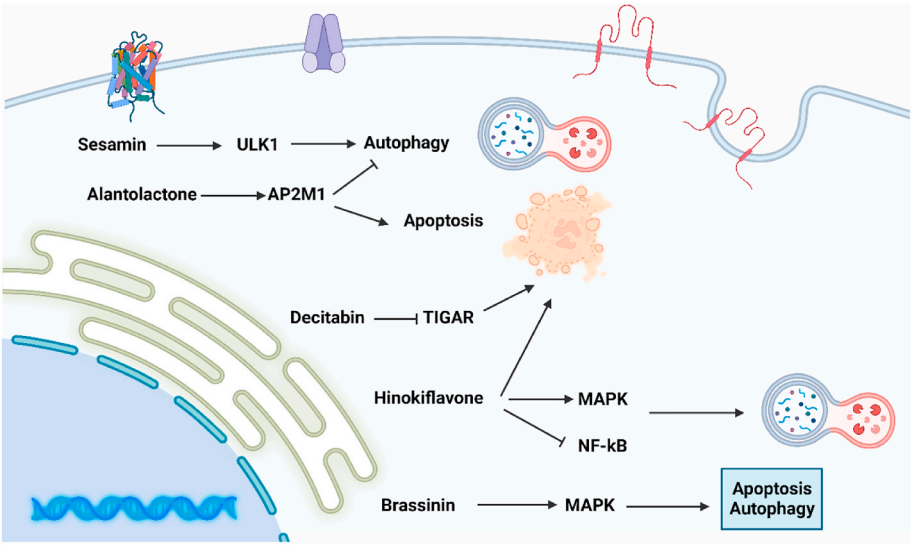

Fig. 5. The regulation of autophagy by pharmacological compounds. ULK1 and MAPK are the common pathways affected to regulate autophagy in leukemia. Sometimes, both apoptosis and autophagy occur that may show their interaction. Moreover, upregulation of AP2M1 and downregulation of NF-kB and TIGAR can regulate autophagy in leukemia therapy. However, autophagy induction by pharmacological compounds does not render its suppressor activity.

CSCs in leukemia [218]. Furthermore, the overexpression of CD9 can increase the self-renewal ability of cells and they demonstrate chemoresistance [219]. CD90 and CD110 are other factors regulating CSCs in leukemia [220]. On the other hand, autophagy regulates CSCs and stemness in different cancers [221,222]. According to this, the autophagy and CSCs have high association. Therefore, the impact of autophagy on the stemness in leukemia should be evaluated in future studies. Moreover, the interaction of autophagy with CSC makers and related pathways such as hedgehog, CD133 and ALDH1 requires investigation in leukemia.

Regarding the fact that autophagy regulation can provide new insights in the treatment of leukemia, there has been interest in the targeted regulation of autophagy. Currently, the pharmacological compounds utilized for the regulation of autophagy lack targeted delivery and their poor pharmacokinetic profile can restrict their ability in autophagy modulation in leukemia therapy. Based on the previous studies, the nanoparticles can regulate autophagy for improved cancer chemoimmunotherapy [223] and regulation of related molecular pathways such as PI3K/Akt/mTOR (inhibition) [224]. Furthermore, the autophagy modulators can be loaded with other therapeutic compounds on nanostructures in cancer therapy [225]. The regulation of autophagy by nanostructures is not limited to a certain type of cancer and also, several types of nanocarriers such as lipid and polymeric nanoarchitectures can regulate autophagy in cancer [226]. Hence, the nanoparticles with ability of regulating autophagy and related mechanisms and pathways such as ROS and PI3K/Akt can be introduced for the treatment of leukemia. Finally, the autophagy modulators and pharmacological compounds can be loaded on the nanostructures for the targeted regulation of autophagy and improving eradication of leukemia.

In spite of significant advances in the treatment of leukemia by affecting autophagy, the current limitations of studies can be summarized as follows:

A) The interaction of autophagy with apoptosis and ferroptosis has been evaluated. However, what about other types of cell death mechanisms including necrosis, necroptosis and immunogenic cell death regulated by autophagy in leukemia? Maybe the further studies should put more attention on this.
B) The apoptosis regulation by autophagy has been limited to the intrinsic pathway of apoptosis. However, the extrinsic pathway that involves death receptors is of importance and its regulation by autophagy in leukemia should be investigated.
C) The autophagy regulation by various molecular pathways in cancer has been evaluated. However, studies should focus on the status of autophagy in different stages of leukemia progression.
D) Autophagy-regulated chemoresistance has been shown in leukemia, but only one experiment has evaluated its potential in radioresistance control that still requires more attention.
E) The regulation of autophagy by pharmacological compounds and synthetic drugs has been evaluated in leukemia. However, a new emerging concept is targeted regulation of autophagy by nanoparticles that has been evaluated in other cancers [227–229], but it needs too much evaluation in leukemia.

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Data availability statement

The data presented in this study are available on request from the corresponding author.

CRediT authorship contribution statement

Young Yun Jung: Investigation, Conceptualization. **Kwang Seok Ahn:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization. **Mingzhi Shen:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Table 5
The pharmacological intervention for regulation of autophagy in leukemia.

Drug	Molecular profile	Remark	Ref
Sesamin	Caspase-3 ULK1	Upregulation of caspase-3 and ULK1 in autophagy and apoptosis induction	[187]
Alantolactone	AP2M1	AP2M1 upregulation to induce apoptosis and suppress autophagy	[188]
Decitabine	TIGAR	TIGAR downregulation to facilitate apoptosis and autophagy	[189]
Hinokiflavone	MAPK/NF-κB	Stimulation of apoptosis, autophagy and cell cycle arrest through MAPK upregulation and NF-κB downregulation	[190]
Brassinin	MAPK	Stimulation of apoptosis, autophagy and paraptosis through MAPK upregulation	[191]
Tanshinone IIA	PI3K/Akt	Reduction in PI3K/Akt expression to accelerate apoptosis and autophagy	[192]
20(S)-Ginsenoside Rh2	–	The protective autophagy may reduce apoptosis	[193]
Detoxified pneumolysin derivative ΔA146Ply	mTOR	Stimulation of mTOR to induce apoptosis and disrupt autophagy	[194]
Compound C	ROS/p38 MAPK/AMPK/ TET2/FOXP3	Autophagy stimulation	[195]
Leelamine	STAT5	STAT5 inhibition to induce apoptosis and autophagy	[196]
Alisertib	AKT/mTOR/ AMPK/p38	Suppression of AKT/mTOR/ AMPK/p38 axis to mediate apoptosis and autophagy	[197]
Thymus vulgaris and Arctium lappa Extract	–	Stimulation of apoptosis, autophagy and ferroptosis	[198]
Ungeremine	–	Suppressing drug resistance Stimulation of ferroptosis, necroptosis and autophagy through caspase induction, MMP loss and ROS overproduction	[199]
GX15-070	–	Stimulation of apoptosis and autophagy to reverse glucocorticoid resistance	[200]
Chidamide	Akt	The reduction in Akt expression to regulate autophagy in suppressing chemoresistance	[201]
Betulinic Acid-Brosimine B Hybrid Compound	–	Stimulation of autophagy through upregulating Beclin-1 and LC3-II	[202]
Chloroquine	–	Autophagy suppression to increase potential of chemotherapy	[203]
Obatoclax and lapatinib	NOXA	Regulation of NOXA to increase dissociation of Bcl-2 and Beclin-1 in autophagy induction	[204]
Arsenic trioxide	S100A8	SiRNA suppressing S100A8 can suppress autophagy in increasing potential of cancer therapy	[205]
Spautin-1	–	It is a novel autophagy suppressor that promotes apoptosis induction by imatinib	[206]
SAHA	–	Therapeutic regulation of autophagy can increase potential of SAHA in suppressing chemoresistance	[207]
BIIB021	mTOR/ULK1	Autophagy suppression promotes apoptosis induction	[208]

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.canlet.2023.216518.

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