



The Role of Autophagy in Acute Myeloid Leukemia

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Abstract

Autophagy is an important biological mechanism to transport proteins in organelles to lysosome for degradation, maintaining a stable physiological balance of the body. Acute Myeloid Leukemia (AML) refers to hematological malignancy caused by a disorder of myeloid hematopoietic stem cells. Recent studies have shown that the expression of some autophagy-related genes in AML patients is closely related to the prognosis and leukocyte formation of AML patients. Therefore, we can use autophagy as a potential target for monitoring, prognosis, and molecular diagnosis of leukemia patients. The study summarized the interaction between AML and autophagy-related signal pathways (such as mTOR and PI3K pathway) and explained the influence of related inhibitors and activators on AML cells in recent years, which laid a theoretical foundation for clinical treatment and research development of AML patients.

Subject Areas

Cell Biology, Oncology

Keywords

Autophagy, Acute Myeloid Leukemia, Signaling Pathway, Clinical Treatment

1. Introduction

Autophagy is the process of transporting proteins and organelles to lysosomes for degradation and recycling. It was proposed by the Belgian scientist Christian de Duve in 1963. In 1977, Yoshinori Ohsumi, a Japanese scientist, first cloned an autophagy-related gene in yeast and named it *Atg1*. In 1999, the *Beclin1* gene, which is

homologous to ATG6, was cloned, allowing autophagy to be studied in mammals. Studies have confirmed that autophagy is closely related to the survival of various tumor cells and the growth and development of normal cells, and the use of autophagy regulation for the treatment of human diseases is a promising strategy [1] [2].

AML is a malignant tumor of hematopoietic stem cells and a common type of acute leukemia, accounting for about 30% of all cases of acute leukemia. Most cases of AML have severe illness and poor prognosis. If they are not treated in time, they can often endanger lives [3]. The traditional treatment of AML mainly relies on the intensive chemotherapy of cytotoxic drugs and hematopoietic stem cell transplantation. However, standard 7 + 3 chemotherapy results are poor, with a complete response (CR) rate of only about 40% and a median overall survival of 12 - 18 months. For allogeneic hematopoietic stem cell transplantation therapy, nearly half of the patients will relapse [4]. In recent years, cytotoxic drugs CPX351, namely the liposome preparation of cytarabine and daunorubicin, have become one of the research hotspots in the treatment of AML patients. In addition, the poor prognosis of the disease has also been confirmed to be closely related to the molecular genetic characteristics of the disease. Therefore, molecular targeted therapeutic drugs for AML patients, such as FLT3 (FMS related receptor tyrosine kinase 3), IDH (isocitrate dehydrogenase), and BCL-2 (BCL-2 apoptosis regulator), have also been closely concerned. However, the clinical effect and drug resistance of each drug that can be obtained at this stage are not satisfactory. We urgently need a more effective and less toxic treatment for AML [5]. Previous studies have shown that autophagy is related to the occurrence and development of AML, and it is double-sided. For example, stimulating hemopoietic stem cells to maintain a certain amount of autophagy can maintain its homeostasis and reduce the possibility of differentiation into leukemia precursor cells; but frequent autophagy may lead to the evolution of leukemia cells' tolerance to a variety of anticancer drugs [6].

This search will analyze the types, molecular mechanisms, regulatory pathways, and regulatory drugs of autophagy and discuss the new trends and possible development directions of AML therapy.

2. The Concept, Classification, and Formation of Autophagy

The main physiological function of autophagy is to maintain homeostasis and normal cell survival. When the cells are induced by external stimuli like starvation, lack of growth factors, microbial infection and so on, the pre-autophagy structure PAS in cells would gradually forms a double-layer material isolation membrane. The membrane continues to extend, wrapping part of the cytoplasm and organelles to form autophagosomes, and the autophagosomes will combine with lysosomes to form the autophagic lysosomes. There are many enzymes in lysosomes, which can degrade the contents of encapsulated proteins and organelles into amino acids or peptides for recycling [7].

There are three known forms of autophagy: Microautophagy, Macroautophagy,

gy, and chaperone-mediated autophagy (or CMA). Autophagy in most cases usually refers to Macroautophagy. Microautophagy is the process of lysosomal membrane invagination, warping substrates, and degradation. Macroautophagy involves the ATG (Autophagy-related) genes. It relies on the bilayer membrane structure of the cell membrane or other organelles to wrap substances to be degraded and then fuse with lysosomes [8]. CMA only exists in mammalian cells and it has certain selectivity. It needs Chaperone HSC70 to recognize the soluble cytoplasmic protein substrate with the KFERQ sequence and degrades autophagy [9]. **Figure 1** shows the types of autophagy and its processes.

3. Molecular Mechanism of Autophagy

Autophagy plays an important role in the development of targeted drug therapy, disease prevention, and research.

Cells are regulated by a variety of autophagy-related genes (or ATG). Beclin1 is very important in the initial stage of autophagy. It is located on human chromosome 17q21 and is a homologous gene of yeast gene *ATG6*. The proteins UVRAG, AMBRA, and BIF1 in PI3K complex II can bind with Beclin1 to activate Beclin1 and further activate autophagy, then Beclin1 forms trimers with PI3K (hvps34) and Atg14, and constantly recruits autophagy-related proteins to start this process [11].

LC3, as a homologous gene in yeast *Atg8*, includes type I and type II, respectively. Before autophagy, cytoplasmic LC3 (LC3-I) was dispersed in the cytoplasm. When autophagy occurs, LC3-I is liposomes, which means a small polypeptide is enzymatically hydrolyzed to form membrane-type LC3 (LC3-II). LC3-II binds with phosphatidyl-ethanolamine (PE) under the action of ATG4 and adheres

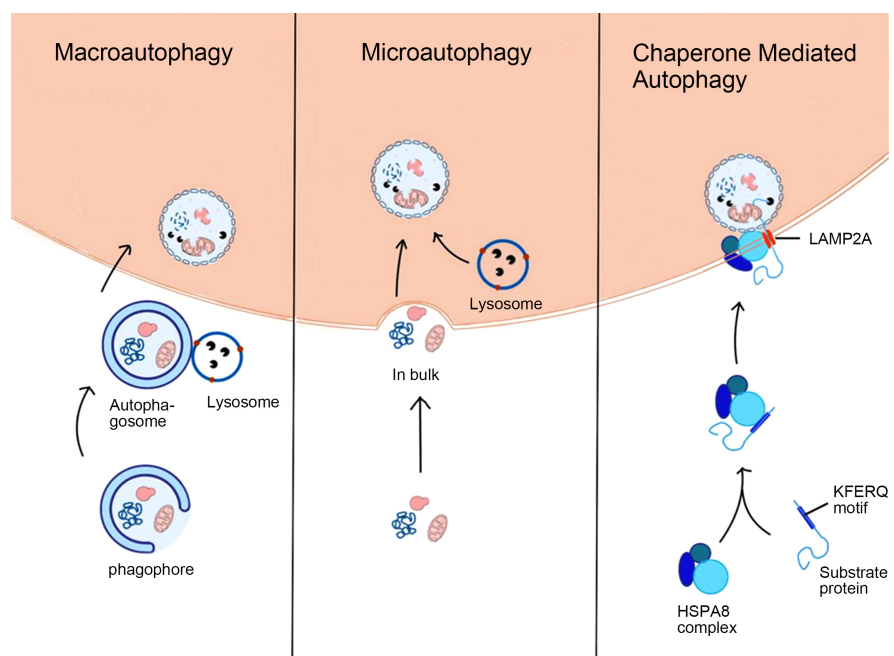


Figure 1. The types of autophagy and its processes [10].

closely to the autophagosome membrane. After the formation of autophagosomes, they fuse with lysosomes to form autophagic lysosomes. At the same time, ATG12-ATG5 and ATG16 are depolymerized. LC3-II is cut from the lipid layer by atg4 and released into the cytoplasm to promote the formation of autophagic lysosomes and degrade the contents into nutrients for recycling. Finally, LC3-II bound to PE on the autophagosome membrane is always fixed on the cell membrane. In experiments, we rely on fluorescent-labeled LC3-II to observe autophagy. **Figure 2** shows the basic regulation of autophagy and outcome.

4. Autophagic Cellular Pathways and Autophagic Inhibitors

Under physiological conditions, there is only a small amount of autophagy to maintain cell homeostasis. When stimulated by conditions, such as starvation, growth factor deficiency, microbial infection, organelle damage, protein folding error or aggregation, DNA damage, radiotherapy, chemotherapy, etc., a large amount of autophagy is induced by cell signal transduction.

The mammalian target of rapamycin (mTOR) is one of the most important signaling pathways regulating autophagy. mTOR can sense a variety of stimuli and combine signal transduction of many upstream pathways at the molecular level. For example, it can regulate protein synthesis and survival by affecting Phosphoinositide-3 Kinase (PI3K)-Akt and Amp-activated Kinase (AMPK) pathways. mTOR complex 1 (mTORC1) is the main checkpoint for regulating the autophagy signaling pathway, while its corresponding pathway mTORC2 is not a regulatory site, and its function has not been determined. Therefore, current drugs often take mTORC1 as an effective target for drug activation therapy [12] [13]. Rapamycin is a natural and the most typical autophagy inhibitor acting on mTOR. It belongs to the PI3K protein kinase family and has a highly conserved structure. Rapamycin can form a complex with FKB12 (a glycoprotein) in cells. This complex can allosteric mTORC1 and inhibit its kinase activity,

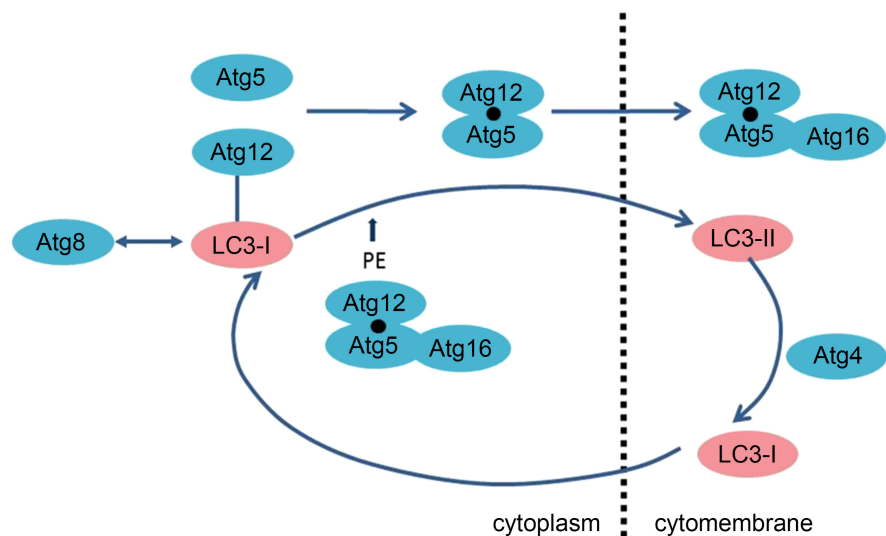


Figure 2. The basic regulation of autophagy and outcome [11].

resulting in autophagy inhibition. Rapamycin is widely used to inhibit autophagy and slow down cell proliferation. Its function has been developed as one of the potential anti-cancer drugs. In addition, since autophagy inhibition itself belongs to immunosuppressive, rapamycin has been used as an immunosuppressant in organ transplantation [13].

However, rapamycin alone has poor selective activity, and direct use of it will produce more adverse prognostic reactions, resulting in poor clinical treatment. This suggests that autophagy needs to be regulated in coordination with other small molecule compounds or induced signal pathways against specific mTORC1 inhibitors. mTOR inhibitors developed by relevant research groups at home and abroad can directly target the kinases of mTORC1 and mTORC2 and change their activities. These inhibitors are ATP analogs, collectively referred to as ATP competitive mTOR inhibitors or mTOR kinase inhibitors (mTOR KIS). Some of these inhibitors have dual inhibitory effects on mTOR and PI3K due to their similarity in kinase structure. Compared with rapamycin, specific inhibitors such as mTOR-KI-Torin-1 blocked the substrate-level phosphorylation of mTORC1 and produced a relatively stable autophagy inhibitory effect. A large number of studies have shown that specific mTOR inhibitors in conjunction with traditional chemotherapy drugs can simultaneously activate targeted autophagy, promote AML cell apoptosis, and enhance the efficacy of chemotherapy drugs [14].

Besides, some drugs may not inhibit autophagy through the mTOR pathway, such as chloroquine. As a classic drug for the prevention and treatment of malaria, it has immunosuppressive properties and is used to treat autoimmune diseases in some areas. In autophagy, it can directly inhibit the fusion of autophagosomes and lysosomes. When combined with some cytotoxic drugs, chloroquine can increase the efficacy of the latter. There is also a lot of evidence that chloroquine makes cancer cells sensitive to radiation and other anti-cancer drugs. Similar autophagy inhibitors, such as Bafilomycin A1, 3-methylidene, and Pepsin A, also have been used for anti-tumor. Some scholars believe that these drugs, including chloroquine and its derivatives, are not specific regulators of autophagy activity. They also have other effects on cell functions (such as lysosomal function and endocytosis). Therefore, it can only be used as an alternative drug for anti-tumor, but not as an autophagy regulator [15]. However, the exact mechanism of the anticancer effect of chloroquine is not obvious; only its anti-autophagy activity is known. There are few reports on how chloroquine can inhibit the malignant proliferation of tumor cells by regulating autophagy activity.

5. The mechanism of Autophagy with AML Pathogenesis

Acute myeloid leukemia is a common kind of leukemia and is common in adult patients. It is mainly characterized by the abnormal proliferation of primitive immature lymphocytes in the bone marrow and peripheral blood. Its clinical manifestations are anemia, hemorrhage, infection and fever, organ infiltration, metabolic abnormalities, etc. Most cases are in acute condition and have a poor

prognosis. Autophagy is closely related to fusion genes and carcinogenic mutations in AML [16]. Currently, autophagy is believed to have two functions in AML cells: one is to protect AML cells from damage caused by stimulus conditions and maintain cell survival and proliferation. For example, the treatment of AML cells with catalytic mTOR inhibitors will induce autophagy and promote the survival of leukemia cells [17]. In acute promyelocytic leukemia (APL), PML-RAR α degradation was promoted in ATRA-induced human bone marrow cells and the differentiation of bone marrow cells was regulated [18]. The second is to induce AML cells to promote apoptosis through autophagy, such as basal autophagy as a death-promoting (tumor suppressive) mechanism, to ensure the clearance of damaged organelles, such as the possible production of a large number of ROS, and protect cells from genomic instability and inflammation, to prevent the occurrence of cancer [19].

Alexandre's research team found that autophagy has a certain relationship with leukemia [20]. Autophagy is very important to maintain hematopoietic stem cells (HSCs) and also has a certain impact on the production of leukemia and drug resistance: the change of autophagy activity in HSCs may promote the occurrence and development of leukemia and it may have secondary drug resistance to first-line therapeutic drugs due to the role of protective autophagy. Functional autophagy enables HSCs to differentiate into multiple lineages (mainly myeloid and lymphoid cells); Autophagy damage leads to the accumulation of mitochondrial reactive oxygen species and DNA damage and may activate downstream signal pathways, such as the Notch pathway, blocking the differentiation of normal HSCs, and convert normal HSCs into pre-leukemic HSCs (pre-leukemic stem cells [LSCs]). This unstable pre-leukemic state is conducive to the dominant transformation of leukemia, such as the BCR-ABL or PML-RARA translocation of HSCs to LSCs. In this case, the reduction of autophagy will make these proto-oncoproteins more stable. Studies have also shown that some nodes also affect the progression of AML through autophagy, for example, CASP3 controls AML1-ETO driven leukocyte generation through ULK1-dependent mode, reduced expression of BECN1 leads to poor prognosis of AML patients, and TSC2 inhibits mTOR signal transduction through phosphorylation and AKT inhibition. The mTOR signaling is also associated with the proliferation of leukemia tumor cells through mediating cell energy metabolism [21]. Thus, as previously mentioned, nodal induction of autophagy in some diseases may improve drug efficacy. Therefore, autophagy inhibitors such as 3-methyl adenine (3-MA), hydroxychloroquine (HCQ), and bafilomycin A1 (Baf-A1) can enhance the anti-leukemia effect and promote cell apoptosis when used in combination (Chart 1).

Similarly, autophagy has also been confirmed in animal experiments to be crucial for the maintenance and dependence of HSCs in mice [22]. The deletion of autophagy-related genes such as *ATG7* or *ATG5* will damage the physiological function of normal HSCs and lead to hematopoietic dysfunction. When the

Chart 1. Maintenance of HSCs is dependent on autophagy and its deficiency lead to leukemia.

	Active Autophagy	Defective Autophagy	Induced Autophagy
HSCs status	Normal hematopoietic differentiation	Multilateral differentiation stopped and abnormal proliferation occurred; Transformed into pre leukemic cells	Abnormal HSCs began to apoptosis
Cell function	Normal DNA transcription and replication	Abnormal DNA transcription and replication, and error accumulation; Transformation of HSCs into leukemic cells induced by proto oncogenes	Normal HSCs cells were preserved, and abnormal HSCs were phagocytized by protective autophagy

mouse cells induced mitochondrial superoxide and DNA damage and showed the characteristics of malignant tumor proliferation, the phenotypic characteristics of early leukemia appeared. Bone marrow cells of mice have higher IC-NOTCH1 values (representing the specific protein in the ich Notch signal is activated) than normal mice. Inhibition of autophagy and active inhibition of Notch signal can observe the recovery of the differentiation ability of mouse HSCs. So, when autophagy is induced, it can regulate the downstream signal pathway (Notch) and control the proliferation and differentiation of HSC. When autophagy is impaired, HSCs change from a normal state to a preleukemic state, which promotes the occurrence of AML [20].

6. Effect of Autophagy on the Treatment of AML

As mentioned earlier, autophagy often has two sides in the process of leukemia: on the one hand, it promotes autophagy of mutant somatic cells and makes them apoptotic to maintain the homeostasis of the body; on the other hand, it shows the effect of anti-tumor drugs for AML cells to avoid the damage of stimulation conditions [23]. The former is the research basis of treating AML through drugs, and it is also the main direction of drug application in recent years; The latter is called protective autophagy because autophagy can protect leukemia cells from chemotherapy. At present, another key to the research of AML drugs is to reduce or inhibit the body's protective autophagy against leukemia cells to increase the efficacy of cytotoxic antitumor drugs. In addition, many experiments have observed abnormal activation of mTOR and related signal pathways in hematological malignancies. Therefore, mTOR inhibitors originally developed as immunosuppressants (rapamycin as a typical representative) inhibit autophagy and cooperate with various cytotoxic drugs has become the key to the treatment of AML diseases [24], which leads to drug tolerance by resisting protective autophagy. In the clinic, autophagy inhibitors have been studied in many preclinical disease models and clinical trials, which are of great significance for the targeted

treatment of AML.

In other aspects, autophagy research has also made great progress. Piya *et al.* [25] found that mice can significantly increase the cytotoxic effect of cytarabine on AML cells after knocking out *Atg7* gene or blocking autophagy with baflomycin A1 or chloroquine [26]. Therefore, hydroxychloroquine can promote the apoptosis of cytarabine resistant leukemia cells. Yang *et al.* pointed out that statins reduce cholesterol levels by inhibiting 3-hydroxy-3-methylglutaryl CoA reductase, which limits the biosynthesis of cholesterol [27]. The decrease of intracellular cholesterol level stimulated cytoprotective autophagy and induced the inhibition of leukemia cells. At the same time, the inhibition of autophagy enhances the anti-leukemia effect of statins. Hendrik *et al.* observed that the basic autophagy variability between different AML cells in the same patient is very large [28]. Compared with AML cells from patients at moderate risk, the autophagy flux in AML cells at low risk is higher. These AML flux changes are usually related to TP53 gene mutations. AML CD34+ cells with TP53 gene mutations are more sensitive to the autophagy inhibitor hydroxychloroquine (HCQ). HCQ treatment of AML cells without TP53 mutation can trigger PUMA (p53 up apoptotic factor) which depends on the apoptotic response. Knockdown of ATG5 can inhibit the survival of AML CD34+ cells in NSG mice. Autophagy promotes the apoptosis of tumor cells in AML and enhances the killing effect of drugs on AML cells, indicating that autophagy has a protective effect on AML patients to a certain extent.

Activating autophagy to promote AML cell apoptosis has become an important way to study malignant hematological tumors. Bonapace *et al.* found that low-dose Bcl-2 antagonist methanesulfonate can dissociate *Beclin1* gene and reduce mTOR activity. Everolimus, an mTOR inhibitor, has also been shown to cause autophagic apoptosis [28]. Cheng *et al.* treated U937 and HEL cell lines with cytarabine at increasing doses and different action times [29], and found that the expression of LC3 and Beclin1 in AML cells was induced after treatment with low doses of cytarabine (50 nm), which increased with time, and showed the characteristics of autophagy after 24 hours of treatment [30] [31]. They believe that low-dose cytarabine can induce autophagy of AML cells and play an important role in their differentiation and apoptosis. At the same time, the downregulation of the Akt-mTOR pathway was also observed, which was considered one of the reasons for its antitumor effect. And Larry *et al.* found in the experiment that FLT3-ITD mutant acute myeloid leukemia is highly sensitive to proteasome inhibitors [32]. FLT3-ITD mutant AML refers to the continuous occurrence of tandem repeats (ITDs) within the FMS like tyrosine kinase-3 receptor (FLT3). Autophagy inhibitors were used to act on such mutant AML cells, and specific downregulation of key autophagy proteins [including Vps34, autophagy genes (*ATG5*, *ATG12*, *ATG13*, etc.)] was found, proving that proteasome inhibitors can induce cytotoxic autophagy in AML cells. Similarly, ha *et al.* induced protective autophagy and apoptosis in *flt3-itd* positive AML cells by using pe-

tropurin C (an *Aspergillus albus* isolated from marine fungal extract) [33]. The autophagy induction marker lc3b was quantified by Western blotting. It was found that petropurin C significantly inhibited the formation of autophagy vesicles in the cytoplasm. In China, Li qiu *et al.* used daunorubicin (DNR) to liposome LC3-II and induce the formation of autophagosomes, confirmed that two AML cell lines HL60 and U937 can effectively induce autophagy by DNR, and observed that mTOR-ULK1 signal is inhibited, suggesting that ULK1 pathway is one of the important strategies to treat the above two AML cell lines by autophagy [34].

In addition to the above, there is also a lot of evidence that the application of cytotoxic drugs to cancer cells will induce protective autophagy and secondary drug resistance. Different anticancer drugs induce different subtypes of AML with different autophagic effects [35]. Autophagy is an important mechanism to maintain body protection, but it is detrimental to the automatic repair of the body in the case of AML. Autophagy inhibitors can prevent or delay the occurrence of protective autophagy, and induce autophagy in the absence of specific genes, directly inducing apoptosis of target cells. The use of autophagy regulating drugs not only increases the antitumor effect of cytotoxic drugs, but also helps to overcome drug resistance, improve clinical results, and reduce the side effects of cytotoxic drug therapy. It can be seen that autophagy provides a new idea for the treatment of various subtypes of AML.

7. Expectation

AML is a clonal haematopoietic disease with myeloid differentiation blockage and haematopoietic function impairment, and it is the most frequent form of acute leukemias in adults [36] [37]. Autophagy is a cellular stress response that maintains homeostasis by lysosomal degradation and recycling of damaged organelles and protein aggregates which is of great significance for the treatment of AML [38]. On the one hand, this catabolic process suppresses tumors by degrading damaged organelles and misfolded proteins in the early stages of cancer. Conversely, it also gives cancer cells the ability to survive under stressful conditions as they form and progress to terminal stages, as in mature tumor cells [21]. Therefore, it is crucial to clarify how autophagy affects the occurrence and development of tumors in the treatment of AML. How to exert autophagy to induce and regulate tumor cell apoptosis, how to inhibit protective autophagy from making tumor cells no longer produce drug resistance, and how to improve the efficacy of other anti-tumor drugs are urgent issues to be studied and paid attention to. After the German pathologist Rudolf Virchow put forward the concept of “leukemia” in 1847, the emergence, development and treatment of leukemia have been concerned. With the development of life medicine omics, various molecular biology and precision targeted therapy research methods are constantly updated. The development and approval of novel substances have resulted in substantial improvements in the treatment of acute myeloid leukemia

[39]. Autophagy in AML treatment has made quite gratifying research progress, but the specific molecular mechanism of many drugs affecting AML through autophagy has not been clarified; most of the drugs used in clinic also show problems such as drug resistance, poor prognosis, and ineffective treatment. Therefore, it is necessary to explore new and more effective treatment methods, further clarify the molecular pathogenesis of AML, improve the quality of life of patients and reduce their pain.

It is gratifying that the drug dose, pressure concentration and the effect of various RNAs have an impact on the survival of tumor cells and some related signal pathways, which provides a new research direction for the future treatment of AML, RNA therapy. Nevertheless, in the context of therapy, in AML, as well as in other cancers, autophagy could be either cytoprotective or cytotoxic, depending on the drugs used [40]. At present, although a large number of small molecular compounds that inhibit autophagy against treating tumors have entered clinical trials, they are not targeted at specific AML cases [41]. This requires us to further study the mechanism of these drugs to further clinical practice. Experts and scholars have provided many new ideas, which provide good reference schemes and guidance for AML precision treatment.

The mechanism and treatment of autophagy on AML still need to be studied, and we still have a long way to go.

Project

National Innovation and Entrepreneurship Training Program for College Students, Stable expression of autophagy-labeled LC3 acute myeloid leukemia cells and their biology, 202013023018. Zhejiang Education Department, Study on hemophylline-mediated autophagy in acute myeloid leukemia, Y201942573. Zhejiang Provincial Administration of Traditional Chinese Medicine Science and Technology Project, Study on the mechanism of antitumor hemophysis mediated mitochondrial autophagy on apoptosis of acute myeloid leukemia cells through oxidative stress, 2021ZB081. Zhejiang Province University Laboratory Work Research Project, Exploration and research on the safety system of laboratory animals in colleges and universities under the background of COVID-19 prevention and control, YB20207.

Conflicts of Interest

The authors declare no conflicts of interest.

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