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Role of autophagy in the progression and suppression of leukemias

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Contents

Abstract

Autophagy is a physiological process in which cellular components are degraded by the lysosomal machinery. Thereby, organelles are recycled and monomers are produced in order to maintain energy production. Current studies indicate autophagy might suppress or augment survival of cancer cells. Therefore, by elucidating the role of autophagy in cancer pathogenesis, novel therapeutic intervention points may be revealed. Leukemia therapy has advanced in recent years; but a definitive cure is still lacking. Since autophagy often is deregulated in this particular type of cancer, it is clear that future findings will have clinical implications. This review will discuss the current knowledge of autophagy in blood cancers.

Keywords: Autophagy; Leukemia; Cell death; Chemotherapeutic resistance

1. Introduction

Autophagy is a signaling pathway which leads to degradation of cellular components by lysosomal activity. Due to an enhanced supply of monomers originating from the cells own resources, this process is essential for survival during stress. In addition, autophagy has been shown to be important in a variety of other cellular processes including the recycling of aged or damaged organelles, remodeling of cellular structures during development, cell death, and protection against bacterial infection [1]. Since it is important for homeostasis, defects in the autophagy pathway may lead to diseases or malignancies [2]. The exact role of autophagy in carcinogenesis, however, is still unclear but recent work in this field has helped substantially to improve our understanding. Leukemia is cancer of blood forming tissues. According to their hematological origin, leukemia are classified as myeloid or lymphoid. The myeloid lineage is responsible for the production of blood cells other than lymphocytes. In correspondence with the hematopoietic lineage

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in which malignancy has occurred, leukemia are divided into two main groups: acute and chronic. Although there are novel approaches being developed for eradication of leukemic cells, the route to a definitive cure is not easy and requires a better understanding of intricate cellular mechanisms. Accumulating studies provided evidence of alterations in autophagy pathway upon malignant transformation and treatment with chemotherapy [3]. These findings suggest the importance of this process as a possible target for the development of novel therapeutic approaches in malignancies.

This review will compile what is known about the intersection of autophagy and leukemia research in the following sections. Various types and progression pathways of leukemias will be described first, and the mechanisms of autophagy will be briefly presented. Lastly, the involvement of autophagy in hematological malignancies will be discussed.

2. Types and progression pathways of leukemia

Leukemia is the general term for hematological cancers occurring in the tissues responsible for blood formation. Similar to other types of cancers, leukemia are characterized by uncontrolled proliferation of cells, either in bone marrow or the lymphatic system. There are two main classes of leukemia differing in their clinical and pathological properties. The first type, acute leukemia, is known to be more common in children and characterized by the rapid proliferation of immature blood cells. The second type, chronic leukemia, progresses more slowly and involves leukemic cells which are relatively differentiated. Further classification of leukemia is done based on the tissue of origin as lymphoid or myeloid, which are explained in detail below.

Acute lymphocytic leukemia (ALL) occurs in cells called lymphoblasts which normally differentiate into mature white blood cells in healthy individuals. These undifferentiated cells are found in excess numbers in the blood stream while they are confined to the bone marrow in healthy people. The main causes of the majority of ALL cases are not precisely known, but there are some genetic and chromosomal aberrations documented in immature blasts. Key transcription factors or signaling pathways proximal to the membrane are thought to be targets of such aberrations. Translocations observed in ALL lymphoblasts involve the genes *TAL1*, *AML1*, *MLL*, and *TEL* each of which is important in different stages of hematopoiesis [4]. The affected genes determine the subtype of ALL as either B-lineage or T-lineage specific ALL. Burkitt's lymphoma, one type of ALL, involves a translocation between the *MYC* gene and the genes encoding light- or heavy chain immunoglobulin (Ig) proteins [5]. In addition to major chromosomal aberrations, single nucleotide polymorphisms (SNP) were shown to be associated with the development of ALL. For example, SNPs in the genes *ARID5B* and *CEBPE* were found to be significantly related to ALL [6]. In addition to structural changes in the genome, epigenetic mechanisms are also important for ALL. In several studies, unusual levels of DNA methylation in ALL cells were shown to result in the suppression of the WNT pathway, $P15^{INK4B}$ and $P21^{CIP1}$ [7–9] and upregulation of *miR-128* [10].

Acute myeloid leukemia (AML) arises from the myeloid lineage. Some myelodysplastic or myeloproliferative disorders may turn into AML [11]. Chemotherapy may also cause predisposition to AML. Especially chemotherapeutic regimens involving topoisomerase II inhibitors [12] or alkylating agents [13] were linked to such a predisposition. Exposure to ionizing radiation also increases the incidence of AML as observed in the surviving population of Japan after atomic bombing [14]. There are also documented cases in which AML was developed by multiple members of a family exceeding the predictions of random chance events suggesting that there might also be a hereditary basis of the disease [15,16]. In part because of these differences, this malignancy is grouped under four categories according to WHO classification [17]: AML with recurrent genetic abnormalities, AML with multilineage dysplasia, therapy related AML; and myelodysplastic syndrome (MDS), and lastly, AML cases that are not suitable for classification in the previously groups. The most common genetic aberrations of AML are t(8;21)(q22;q22) fusing the genes *AML1* and *ETO*; inversion of a portion of chromosome 16 causing the synthesis of MYH11/CBFB fusion protein; t(15;17)(q22;q21) which causes dominant expression of an abnormal retinoic acid receptor by fusing the genes *PML* and *RARα*; and translocations involving the 11q23 locus containing the *MLL* gene. These chromosomal aberrations were observed in nearly 30 percent of AML cases [18,19]. In addition to these major structural aberrations, numerous somatic mutations were found to be associated with AML including mutations in the *NPM1*, *KRAS2*, *CEBPA*, *ETV6*, *JAK2*, and *TET2* genes [20–26].

Besides the acute forms, leukemia can develop chronically in a less aggressive manner. The most frequent form of leukemia is the chronic lymphocytic leukemia (CLL). Incidence of CLL increases with age and is more common in men than women. The disease is manifested by an increased number of CD5-positive B-cells in the bone marrow and blood stream. Uniquely, the accumulated cells are quiescent in the G_0 phase unlike the aggressive nature of most cancerous cells [27]. Yet the presence of increased numbers of those cells in the bloodstream suggests that these cells have a diminished ability for self-destruction through apoptosis. Several studies aimed to shed light on the decreased ability of CLL cells to undergo apoptosis. Overexpression of antiapoptotic BCL-2 is thought to be important in evading apoptosis [28] while cell-to-cell contact [29], and exposure to certain cytokines [30] are also linked to avoiding this type of cell death. Studies in CLL mouse models showed that the Tcl1-Akt, TNF-NF-κB, and Bcl2-mediated antiapoptotic pathways are deregulated [31]. Besides these irregularities, genetic aberrations were also documented in the CLL cases including deletions in the

long arms of chromosomes 13, 11 and 7, and trisomy of chromosome 12 [32]. CLL can be examined in two pathogenetically different classes [33]. The slowly progressing subtype of CLL involves somatic mutations in immunoglobulin variable heavy chain genes. In contrast the subtype with non-mutant immunoglobulin genes has poor prognosis and requires earlier treatments.

Chronic myelogenous leukemia (CML) is the first type of leukemia with pathogenesis resulting from a chromosomal translocation. The resultant translocation structure is called a *Philadelphia chromosome* (Ph) and occurs between the long arms of chromosomes 9 and 22. This translocation drives the transformation to malignancy [34]. In Ph (+) CML, this translocation brings the *BCR* and *ABL* genes together. This fusion gene encodes a constitutive tyrosine kinase that stimulates cell growth and division by phosphorylating downstream targets [35]. Although the results of the translocation are well known, the causative factors have not been yet enlightened. Increased incidence of CML at atomic bombing sites suggests radiation exposure might be partially responsible. The disease exhibits three phases: chronic phase, accelerated phase, and blast crisis [36]. These phases are distinguished from each other by their clinical characteristics and by the results of laboratory tests. The chronic phase is the initial stage and the disease eventually progresses into the accelerated and blast crisis phases if left untreated. With disease progression, novel genetic aberrations and mutations are acquired [37]. One speculation for the mechanism responsible for these changes is that the genomic instability of cancer cells causes new mutations and chromosomal rearrangements. According to another hypothesis, the same mechanisms which cause the translocation itself might also trigger new genetic aberrations. The latter hypothesis is especially supported for cases in which the accelerated phase quickly transforms into the blast crisis phase. The response of CML therapy has improved in recent years with the availability of targeted tyrosine kinase inhibitors (TKIs), including imatinib, nilotinib, and dasatinib. These chemotherapeutic agents bind specifically to the ATP-binding domain of the fusion protein and prevent subsequent phosphorylation of the downstream players, thus directing leukemic cells to programmed cell death. By this mechanism, the numbers of BCR/ABL-positive cells are decreased to undetectable levels in most cases using imatinib treatment, which is the first targeted drug developed. [38].

Leukemic cells may develop resistance to these chemotherapeutic agents, an especially well-documented phenomenon for imatinib therapy. Resistance might be conferred by several mechanisms [39] including BCR/ABL mutations, overexpression of MDR (*M*ulti *D*rug *R*esistance) genes responsible for expelling the drug from the cytoplasm and deregulation of ceramide metabolism [40]. Moreover, a recent study has showed that the BCR/ABL oncoprotein is not absolutely required for the survival of CML stem cells. Therefore, because of this insensitivity tyrosine kinase inhibitors are unlikely to eliminate BCR/ABL(+) progenitors [41]. These findings indicate that there is a need for novel intervention approaches for CML to obtain better leukemic clearance.

3. Autophagy: types and mechanisms

Autophagy is the cellular process in which cellular components are degraded upon activation of the lysosomal machinery. Targets of autophagy might be as small as proteins or as large as organelles. Through this process, building blocks of degraded components are liberated which are then be reutilized for the energy production. Therefore autophagy has importance for survival under stress conditions such as nutrient deprivation [42]. The role of autophagy is not limited to supplying monomers for the production of energy. Autophagy was shown to be important in the recycling of aged organelles, remodeling of cellular structures during differentiation, defense against pathogens, and cell death [1,43,44]. Autophagic morphology was first observed in the mammalian cells but elegant studies involving yeast as a model system have primarily helped to delineate the mechanism [1,2,44]. Our current knowledge indicates that autophagy has essential functions for maintaining homeostasis, and deregulation of this pathway is implicated in the progression of diseases.

Autophagy can be classified into three groups: macroautophagy, microautophagy, and chaperone-mediated autophagy. In macroautophagy, a portion of cytoplasm including cytosolic proteins, protein aggregates and/or organelles is surrounded by a double-membraned structure called the autophagosome (see Fig. 1) [45]. Following fusion with the lysosomal membrane, the previously sequestered materials are enzymatically degraded. TOR (*T*arget *of R*apamycin-one type serine-threonine kinase) and phosphatidylinositol 3-kinase (PI3K) proteins were found to be important for signaling nutrient deprivation, and thus for the induction of macroautophagy [46,47]. Induction of this particular pathway is followed by nucleation, expansion and completion of the autophagosome which is then fused with the lysosome for degradation of autophagic bodies. In each of these stages, distinct sets of ATG proteins (the *Au*T*opha*G*y*-related protein family with at least 16 members in yeast) are involved (see Fig. 1) [2]. Homologs of most of these genes are also present in mammalian species and highly conserved functions. Macroautophagy is a major degradation pathway with a well-defined mechanism and the term "autophagy" is mainly used to address this particular type. Microautophagy refers to direct engulfment of the cytoplasmic portion by the lysosome itself. Therefore the materials to be degraded are not sequestered by the autophagosome; instead, they are internalized to the lysosome by invaginations of the lysosomal membrane. Because the internalized materials are degraded along with portion of the lysosomal membrane, this mechanism might be useful for resizing the lysosome [48]. The third type of autophagy, chaperone-mediated autophagy, is useful for the targeted break-down of long-

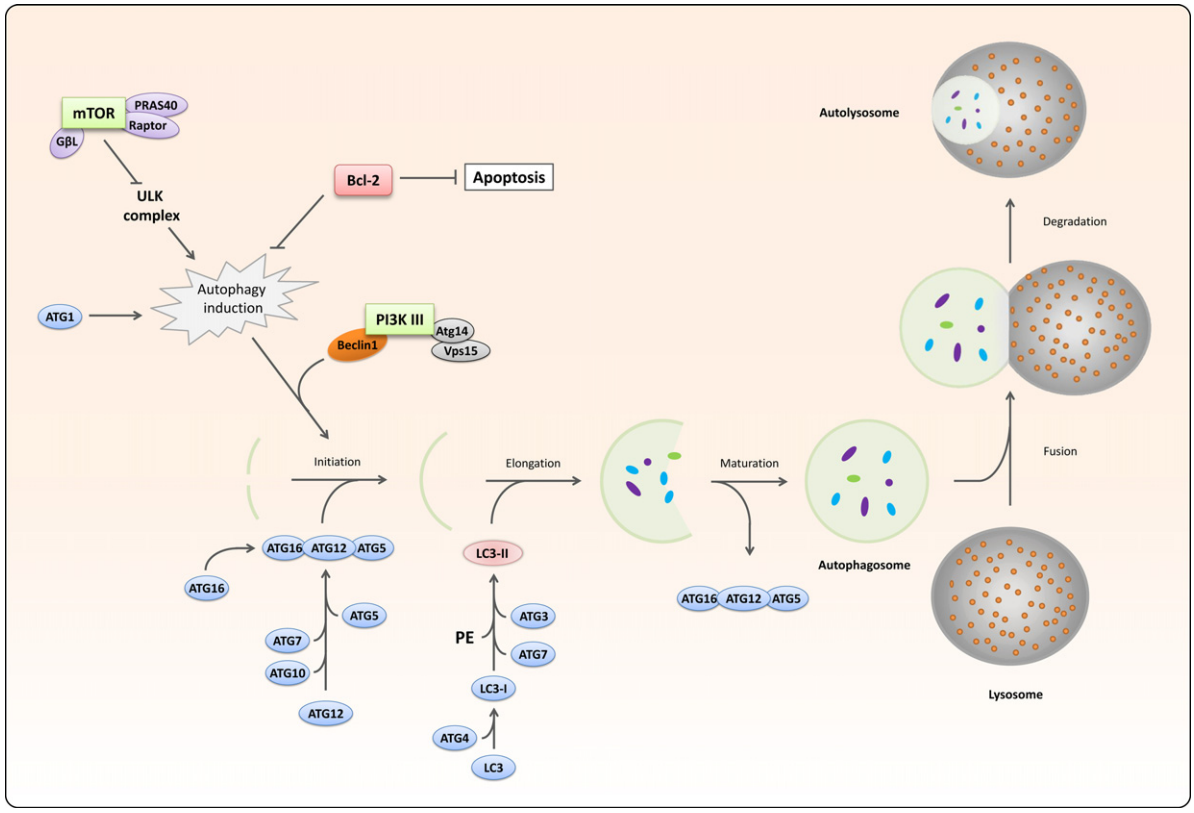

Fig. 1. Signaling pathways regulating autophagy.

The process of autophagy is regulated by Autophagy-related genes (Atg) and their homologs in different eukaryotic cells. There are 35 different Atg family genes discovered in *Saccharomyces cerevisae* and more than 15 in mamalian homologs.

Autophagosome formation

Autophagy begins with the generation of a phagophore assembly sites (PAS). Although the source of the first membrane structure is unclear, thereare strong evidences that it comes from ER. Initiation of the phagophore structure depends on activity of Class-III phosphoinositide 3-kinase (PI3K) Vps34. Vps34 is a protein complex that includes Atg6 (Beclin 1), Vps15 and Atg14 proteins. Besides PI3KII Vsp34, other Atg family proteins (Atg5, Atg12, Atg16) are also involved in the formation of the phagophore structure.

Autophagosome elongation

There are two types of ubiquitylation-like reactions that control autophagy. Atg5 and Atg12 are involved in the first reaction and they are conjugated each other in the presence of Atg7 and Atg10. The formation of this conjugation requires Vps34 activity

The second ubiquitylation-like reaction is the association of microtubule-associated protein 1 light chain 3 (MAP1-LC3; LC3) and phosphatidylethanolamine (PE). The conjugation of Atg5-Atg12 may have roles in L3-I conjugation to PE. LC3-I is generated by Atg4 via cleavage of the C-terminus of LC3. Furthermore, LC3-II is formed by covalent binding of LC3 to PE. Phagophores are extended with Atg5-Atg12-associated membranes which are targeted by LC3. LC3-II is a unique protein that takes part in autophagosomes but not other vesicular structures Assesment of LC3-I to LC3-II conversion results in autophagosome formation which gives an idea about autophagy level. As is mentioned above, there are two types of ubiquitylation that control autophagy and it is known that these two systems are tightly related to each other. For example, Atg10 can ease association of LC3-I to PE.

Autophagosome maturation and fusion

Autophagosomes are transferred to the lysosomes from the cytoplasm via microtubules in a dynein-dependent manner and clumped near the nucleus, microtubule-organising centre. After this transfer, the autophagosome associates with a lysosome and components of the two different compartment are mixed. However, the mechanism of autophagosome and lysosome fusion is still unknown.

lived proteins. Proteins to be degraded are translocated to the lysosome through a protein complex called LAMP-2A (*L*ysososome-*A*ssociated *M*embrane *P*rotein type 2*A*) which is embedded in the lysosomal membrane [49]. Cytoplasmic chaperone Hsp70 and lysosomal chaperone Hsp73 are responsible for unfolding the target protein with a specific motif and translocation into the lysosome [49,50]. This type of autophagy provides another means of protein degradation in addition to the ubiquitin-protease system (UPS) which is a well-characterized mechanism of rapid degradation of short-lived proteins. However, these two mechanisms of protein degradation are not mutually exclusive as shown by hindered UPS activity upon inhibition of autophagy [51,52].

4. Autophagy and cancer

The relationship between autophagy and cancer has been a hot topic for years, and currently there are numerous studies shedding light onto different aspects of this relationship. As controversial as it sounds, there is evidence that autophagy might have roles in both tumor suppression and

tumor progression as extensively reviewed in other papers [3,53–55]. Some studies have shown that the activity of the autophagic pathway decreases in most cancerous cells [56,57], suggesting that autophagy might be a suppressive mechanism for cancer progression. The tumor-suppressive effect of autophagy might be conferred by increased protein degradation and/or by the clearance of damaged organelles from the cytosol. Increased protein degradation might be useful for diminishing the amounts of proteins stimulating cell growth which may lead to uncontrolled cell division. Autophagic disposal of organelles such as mitochondria and peroxisomes that contain reactive oxygen species (ROS) reduces the risk of mutations and genomic instability; therefore it might be acting by preventing a tumor initiation. Promotion of tumorigenesis in several tissues of transgenic mice with a disrupted *Beclin-1* gene (*ATG6*), and a high proportion of monoallelic *Beclin-1* deletion in breast and ovarian cancers agree with this hypothesis [58,59]. *Beclin-1* was also shown to interact with regulatory proteins of the apoptotic pathway [60,61], and this raises questions that the tumor suppressive function of *Beclin-1* might not necessarily result from its involvement in autophagic activation. Instead it might be regulating apoptosis to some extent. On the other hand, it is evident that other autophagy-specific genes exert tumor suppressive functions in the cell. One example is the *ATG4C* gene which encodes a protease required for the processing of LC3. Experiments with mice deficient in *ATG4C* have increased risk of developing fibrosarcomas along with reduced autophagic activity induced upon starvation [62].

In contrast to tumor suppressive effects, autophagy might also contribute to cancer cell survival. Especially for rapidly growing, solid tumors, autophagy might provide cells with necessary nutrients from their own resources in an environment where nutrients and oxygen are scarce due to poor vascularization [63]. The same hypothesis is valid for metastasizing cells that experience nutritional deficiencies during the process of migration. In support of this hypothesis, studies showed that autophagic induction occurs upon detachment from the extracellular matrix [64], which is precisely what happens for metastasizing cancer cells. Autophagy might also be useful for cancer cells by allowing disposal of damaged mitochondria that would otherwise produce ROS and harm the cell in such unfavorable conditions [65]. In addition, autophagy might also be involved in aggressiveness and chemotherapeutic resistance of malignancy [66]. Suggesting a possible role in the chemotherapeutic response, autophagosomes were detected in cancer cells upon treatment with various chemotherapeutic agents including tamoxifen, temozolomide and resveratrol [67–69].

Because autophagy may act for the benefit of cancer cells, the possibility of targeting this pathway arises for a novel cancer therapy. Some preliminary studies with cell lines have shown that blockage of the autophagy pathway may sensitize cancer cells of different origins to chemotherapy and radiotherapy [70–73]. However, autophagy is a useful and necessary mechanism for the turnover of cellular components and clearance of protein aggregates that might cause cell death in healthy cells. This latter case is especially important in neurons. When the dual effects of autophagy in tumor suppression and progression are taken into consideration; its usage in cancer therapy remains to be elucidated. If autophagy is to be employed as a common therapeutic approach, alteration of autophagy should probably be targeted manner to cancer cells to prevent undesired effects on healthy cells.

5. Role of autophagy in leukemic cell death and survival

5.1. Contribution of autophagy to cell death

In several studies, induction of autophagy was shown to be important for the death of leukemic cells. In most of these studies, autophagy was manifested upon treatment with different chemotherapeutic agents (Table 1). The widely used tyrosine kinase inhibitor imatinib was shown to induce cellular autophagy in a dose-dependent manner in a variety of cell lines [74]. This observation might be indicative of a novel mechanism of action for clearance of the malignant cells by imatinib. However, the effect of autophagy in imatinib therapy must be further delineated further because increased autophagy was not directly related to cytotoxicity in the cell lines used for this study. However, the ability of imatinib to induce autophagy is exciting for providing novel aspects for research to reveal what is happening at the cellular level. The mTOR inhibitor everolimus (RAD001) is another chemotherapeutic agent that was documented to kill childhood ALL cells through activation of autophagy and was also shown to provide a survival advantage to mice with ALL by reducing the mass of leukemic cells [75,76]. A naturally occurring phytoalexin called eupalinin A inhibits growth of acute promyelocytic leukemia (APL, a subtype of AML) cells by initiating autophagy which is independent of Beclin-1 but triggered by mitochondrial damage [77]. By a similar mechanism, an extract of the recreational herb khat (*Catha edulis*) causes cell death via autophagy in AML cells by damaging mitochondria [78]. Induction of autophagic cell death due to the loss of functional integrity of mitochondria was also documented by other groups. Some triterpenoid derivatives, novel anticancer drug candidates, were shown to induce autophagic death in CML cells by causing mitochondritoxicity [79]. Brevinin-2R, one type of defensin isolated from the skin of frog *Rana ridibunda*, kills T-cell leukemia and B-cell lymphoma cells selectively through autophagy, again with the involvement of mitochondria [80]. Some novel quinoline-like molecules with anti-cancer potential were also found to be important for initiation of autophagy. This study, mitochondrial deformations were a concurrent with autophagic induction, possibly indicating that mitochondria are also involved in this scenario [81]. Novel anti-cancer therapeutic compounds activating the autophagic pathway are not limited to the species previously stated. In addition to these,

Table 1
Effect of autophagy on cell death or survival/drug resistance with different chemotherapeutics and leukemia models.

Autophagic cytoprotection and drug resistance		Autophagic cell death	
Type of leukemia	Drug treatment	Type of leukemia	Drug treatment
Childhood ALL	Everolimus (RAD001) (75,76)	CML	INNO-406 (103)
APL (a subtype of AML)	Eupalinin A (77)	CML	Imatinib (104)
AML	*Catha edulis* extract (78)	CML	SAHA (HDAc inhibitor) (105)
CML	Triterpenoids (79)	APL	Sodium selenite (106)
T-cell leukemia and B-cell Lymp.	Brevinin-2R (80)	T-cell ALL	Triciribine (107)
Murine lymphoid leukemia	Naphthalimides (82)	B-cell CLL	Dasatinib (112)
Human myeloid leukemia	Vitamin D3 and K2 (83, 84)		
Lymphoid leukemia	Dexamethasone (85,86)		
APL	Platonin (87)		
APL	Arsenic tri-oxide (89,90)		
Myeloid leukemia	2′-Deoxy-5-azacytidine (92)		
B-cell CLL	APO866 (93)		
AML	GX15-070 (94)		
TKI resistant CML	Resveratrol (96,97)		

some derivatives of naphthalimide were found to be potent inhibitors of lymphoid leukemia in murine models [82] while vitamins D3 and K2 were shown to inhibit human myeloid leukemias [83,84]. Glucocorticoids such as dexamethasone also contributed to autophagic death in leukemia of lymphoid origin [85,86]. In addition to these compounds, platonin, a photosensitizing compounds used in photodynamic therapy, was also found to induce cell death in several leukemic cell lines independent of the caspase pathway as is characteristic of autophagy [87]. In another study, autophagy was shown to be an important mechanism for cell death due to extensive recycling of cellular organelles damaged from photodynamic therapy in mouse lymphocytic leukemia cells [88]. Arsenic tri-oxide is another compound which was shown to induce cell death in APL cells via autophagy [89,90]. However some other arsenicals did not show tumor suppressive effects by activation of the autophagic pathway in a promyelocytic leukemia cell line [91].

Epigenetic alterations were also found to be important for inducing cell death through autophagy. In a recent study, prolonged exposure of myeloid leukemia cells to the DNA demethylating agent 2′-deoxy-5-azacytidine (DAC) resulted in increased erythroid and megakaryocytic differentiation as well as increased leukemic cell death by promoting the autophagic pathway [92]. APO866, an inhibitor of nicotinamide phosphoribosyl transferase, was shown to contribute to autophagic cell death synergistically with apoptotic activator TRAIL in B-cell CLL [93]. In this recent report, APO866 resulted in the depletion of NAD and cellular ATP levels leading to induction of autophagy. This process did not take place in healthy leukocytes suggesting that such a combination therapy might be a selective approach for CLL treatment. The Bcl-2 homology domain 3 (BH3) mimetic, GX15-070, was shown to induce autophagic cell death along with increased apoptosis in AML cells [94]. However in breast and cervical cancer cell lines, another BH3 mimetic, gossypol, was shown to induce autophagy, leading to cytoprotection, suggesting that targeting similar mechanisms may have opposite outcomes in different cell types [95]. Tyrosine kinase inhibitor sensitive and resistant CML cells were shown to undergo autophagic cell death after treatment with resveratrol, a naturally occurring plant phytoalexin. This cell death occurred JNK-mediated overexpression of p62 and activation of AMPK [96,97]. This suggests that autophagy might be an important pathway for cell death in different chemotherapeutic modalities. Indeed, in a recent study, genome-wide analysis of DNA methylation patterns revealed that hypermethylation of autophagy-related genes correlated with poor prognosis in CML cells indicating that blocking autophagy reduces the leukemic cell clearance [98]. Refractory ALL was sensitized to glucocorticoids and other cytotoxic drugs by Bcl-2 antagonists in a process involving rapid activation of autophagy-dependent necroptosis which overcame the block in mitochondria-dependent apoptosis. These results suggested that manipulation of autophagy could have a translational aspect for multi-drug resistant leukemias [99].

5.2. *Importance of autophagy in leukemic cell survival and drug resistance*

Because autophagy acts to the benefit of cells under normal physiological conditions, it may also provide advantages to cancerous cells. There are reports indicating that autophagy acts as a pro-survival mechanism and may contribute to chemotherapeutic resistance in various leukemias. In some studies, it was shown that inhibition of autophagy enhanced the therapeutic potential of tyrosine kinase inhibitors in Ph (+) malignancies [100–102]. In another study, the autophagic response upon application of the second-generation tyrosine kinase inhibitor INNO-406 was protective for BCR/ABL positive cells [103]. Experiments done in various leukemia cell lines and mouse fibroblasts have revealed that imatinib treatment increases the amount of autophagosomes which provide a cytoprotective effect [104]. In this study, knockdown of autophagy-specific genes did not result in complete loss of the protection, suggesting that autophagy

was partially responsible for this observation. Targeting autophagy in experimental settings involving chemotherapeutics other than tyrosine kinase inhibitors was also shown to have potential to enhance the chemotherapeutic outcome. The tumor-suppressive efficacy of the histone deacetylase inhibitor, SAHA was augmented when applied in combination with autophagy inhibitors in CML cells [105]. Selenium is another chemotherapeutic agent for which the exact mechanism of action is currently the focus of active research. While application of sodium selenite resulted in downregulation of autophagy in APL cells, selenium-induced apoptosis was shown to be enhanced upon suppression of autophagy [106]. In this study, PI3K/Akt was found to be upregulated in autophagy and downregulated in apoptosis in the APL cell line NB4. Moreover, autophagy was linked to the survival of NB4 cells. A recent report indicated that the Akt inhibitor triciribine increased apoptosis in T-cell ALL by a process in which autophagy played a defensive role as shown by increased apoptosis when autophagy was inhibited [107]. Similarly, suppression of autophagy with shRNAs and specific inhibitors resulted in blocking of PML-RARα oncoprotein degradation and granulocytic differentiation in myeloid leukemia cells [108]. CML cells expressing BCR/ABL oncoprotein at high levels were shown to induce autophagy in order to recover from targeted and nontargeted treatment options, indicating the protective effect of autophagy in CML [109]. These findings are supported by another recent report that indicated that the release of specific damage-associated molecular pattern molecules (DAMPs) after chemotherapy conferred drug resistance to leukemic cells by activating the autophagic pathway [110,111]. In addition to these findings, B-cell CLL was also shown to develop resistance to the tyrosine kinase inhibitor dasatinib by activating autophagy [112] In another report, overexpression of the melanoma differentiation-associated gene-7/interleukin-24 (mda-7/IL-24) was shown to induce autophagy and confer survival advantage to leukemic cells [113]. Mda-7/IL-24 and suppression of autophagy may have potential for leukemia therapy since it selectively induces apoptosis in a variety of cancer cells. In addition, autophagy was shown to exert protective functions on cellular physiology upon photodynamic therapy (PDT). However, it was also shown that extensive recycling of cellular components might cause cell death if the PDT dosage is increased [114]. In the light of the current literature, the cytoprotective effect of autophagy might also be important for conferring chemotherapeutic resistance. Thus targeting autophagy might provide novel approaches to overcome the resistance frequently observed in the clinic. This phenomenon is addressed by various other studies and review papers [100,101,115–118].

6. Conclusion and future directions

Autophagy is currently one of the hottest topics in the scientific arena, and more specifically, in cancer research. Accumulating evidence indicates that this process is involved in numerous physiological and pathophysiological conditions. Increasing numbers of studies in this area are currently unable to solve the controversial nature of autophagy from the perspective of development of novel cancer therapeutics. Our current knowledge leaves no doubt that autophagy has great potential for the development of novel therapeutics. However, further research should be done to delineate the role of autophagy in cancer cell death and cell survival. One important point to be elucidated is the determination whether autophagy is directly responsible for the reported observations, or if it is a secondary response of cells to the specified conditions. In addition, we need to gain a deeper understanding of autophagy in the discrimination of cell death and cell survival. By achieving this, manipulation of autophagy might emerge as a future cancer therapeutic. Indeed, there are three phase II clinical trials that are currently recruiting patients and which investigate the efficacy of hydroxychloroquine, an inhibitor of autophagy [119], in CML (clinical trial identifier NCT01227135); in relapsed refractory multiple myeloma (NCT00568880); and in untreated B-CLL (NCT00771056). The latter trial will indicate the potential of autophagy inhibition itself as an anticancer approach because B-CLL patients who have not previously received any chemotherapy or immunotherapy are being included in the trial. The other two trials aim to inhibit autophagy along with the application of previously known chemotherapeutic drugs to determine whether the refractory phenotype of leukemia can be reversed by altering the autophagy pathway. In addition to trials, there are numerous others that test the effects of inhibition of autophagy in various cancer models other than leukemias (reviewed in [120]).

For more than a decade, autophagy has been thought to be an important process in cancer biology. Numerous studies have shown that autophagy contributes to both cancer cell survival and cell death. This multifaceted feature of autophagy is contributed by two factors: the complexity of the system which has numerous critical regulators and cross-talk with other cellular processes which determine cell survival. The functions of autophagy seem to differ among cell types of different origin as similar experimental designs yielded completely different observations when cellular origin was altered. This suggests that different cellular pathways might be modulating autophagy to some extent rendering it either as a pro-survival or toxicity mechanism. More research should be done to dissect such mechanistic differences between various forms of cancer cells and non-malignant cells in the body. As appealing as it sounds for cancer therapy, altering autophagy could possibly have undesired outcomes for healthy cells if it is nor regulated in a specific manner. The search for autophagy-activating pathways that are selectively activated in cancer cells would provide potential targets for the development of selective therapeutics. One good example for this approach is the search for hypoxia-inducible pathways that activate autophagy [121,122]. Such research might provide a selective means for eradication

of solid tumors since such tumors experience hypoxia and nutrient deprivation in poorly vascularized tumor tissue and during metastasis. Similarly, understanding the distinct pathways activating autophagy in different forms of leukemia is likely to produce novel targets for leukemia therapies, and there is a need for more detailed studies that shed light on cross-talk in malignancy. Another important future perspective for this area would be discriminating the involvement of autophagy in different stages of leukomogenesis. Before inhibiting the pathway, one would want to know which stage of malignancy requires autophagy for cytoprotective effects. Moreover, there might be a need for novel powerful tools to assess whether autophagy is the causative factor for the observed effects or if it is a secondary response of cells and not particularly important for the decision of cellular fate. In the latter case, drug resistance may appear simultaneously with autophagic induction; but inhibition of this pathway might not be an efficient intervention since the main pathways driving the process are not blocked. This suggests that we need to know more about other cellular processes that interact with autophagy and to decipher the cross-talk among different mechanisms in order to develop an efficient approach to increase leukemic cell death and reversal of drug resistance. With this knowledge and understanding of the molecular genetics underlying this complex process, clinicians could identify patients who might benefit from an approach involving alteration of the autophagy pathway with inhibitors.

Conflict of interest

None of the authors have any interests which might influence the compilation of the current literature in this subject. We apologize to the authors whose valuable studies were not included here due to space limitations and the concentrated scope of the review.

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Biography

Yusuf Baran has been working as an associate in the Department of Molecular Biology and Genetics, at İzmir Institute of Technology. His career in cancer research began at Middle East Technical University (METU) which is especially renowned in the area of molecular biology. Understanding cell death mechanisms in leukemias constituted the particular aim of his masters and doctoral education both of which were completed at METU. During his PhD education at METU, he worked in the Medical University of South Carolina; Holling Cancer Center, USA. After earning his PhD degree, he worked as a visiting researcher in Gulhane Medical School, Medical and Cancer Research Laboratory. Thereafter he joined the Department of Molecular Biology and Genetics of İzmir Institute of Technology where he became associate professor. He established the "Cancer Genetics Research Laboratory" in this university. Currently, he has seven graduate students working in my lab and he is the principal investigator of six ongoing projects. He was also awarded with an "Outstanding Young Scientist Award" in 2010 by the Turkish Academy of Sciences.