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The Controversial Role of Autophagy in AML/ Cancer: Review Article

Salma G. Morsy*[1], Asmaa M. Zahran[2], Nivin A. Hassan[3], Omnia El-Badawy[4], Mahmoud N. El-Rouby[5]
Departments of [1]Cancer Biology (Cancer Immunology and Virology),
[2]Clinical Pathology, [3]Cancer Biology (Pharmacology and Experimental Oncology),
South Egypt Cancer Institute, Assiut University, Assiut, Egypt
[4]Department of Medical Microbiology and Immunology, Faculty of Medicine, Assiut University, Assiut, Egypt
[5]Department of Virology and Immunology Unit, Cancer Biology,
National Cancer Institute, Cairo University, Cairo, Egypt
***Corresponding author:** Salma G. Morsy, **Mobile:** (+20) 0109289225, **E-Mail:** Salmagamal@aun.edu.eg

ABSTRACT

Background: A catabolic process that has been preserved throughout evolution, autophagy sends cytoplasmic proteins, organelles, and bacteria to lysosomes for destruction. Within its subtypes, acute myeloid leukaemia (AML) exhibits a significant lot of variety, and autophagy's complex function in the disease's genesis and development is also evident. Chromosome translocations and rearrangements, which are often seen in AML, have been discovered to be related with heterozygous deletions and missense mutations of important autophagy genes.

Objective: In this review we aimed to discuss the dual role of autophagy in cancer and focusing on the relation between autophagy and acute myeloid leukemia.

Methods: PubMed, Google scholar and Science direct were searched using the following keywords: Autophagy, Cancer, Acute myeloid leukaemia and Chromosomal translocations. The authors also screened references from the relevant literature, including all the identified studies and reviews, only the most recent or complete study was included between December 2001 and May 2022. Documents in a language apart from English have been excluded as sources for interpretation. Papers apart from main scientific studies had been excluded as well as documents unavailable as total written text, conversation, conference abstract papers and dissertations.

Conclusion: It is now understood that the process of autophagy has a dual role in the initiation and progression of cancer. In terms of using autophagy in modern treatment modalities like cancer immunotherapy and precision medicine in AML, this might be advantageous. Additionally, the utilization of autophagy biomarkers for clinical response and therapeutic effectiveness prediction would eventually result in better results and the best possible care for AML patients.

Keywords: Autophagy, Cancer, Acute myeloid leukaemia, Chromosomal translocations.

INTRODUCTION

During stressful situations like nutrition shortages and infections, autophagy, a highly conserved catabolic process, sends cytoplasmic proteins, damaged organelles, and microorganisms to lysosomes for breakdown [(1)].

Hematopoietic stem cells (HSCs) require autophagy for maintenance. Numerous studies showed how the deletion of essential autophagy genes like TG7 or ATG5 in animal models disrupted the normal metabolic activity of HSCs, led to a buildup of mitochondrial superoxide, caused DNA damage, and encouraged a pre-leukemic state. Additionally, according to extensive genomic investigations of human tumours, oncogenic events that may activate autophagy have been seen, although deletion or mutation of essential autophagy genes is not prevalent[(1-3)].

An aberrant buildup of immature hematopoietic progenitor cells in the bone marrow and peripheral blood is a hallmark of acute myeloid leukaemia (AML), a malignant tumour of the bone marrow myeloid lineage that manifests clinically and genetically as a heterogeneous malignancy [(2)].

Multiple studies have shown that AML is characterised by a variety of intricate molecular pathways, therefore the present biomarkers may not be useful or appropriate for all patients. Therefore, it is imperative to look for a new biomarker that can aid in more accurate AML patient classification and, ultimately, clinical treatment [(3)].

In this review we aimed to discuss the dual role of autophagy in cancer and focusing on the relation between autophagy and acute myeloid leukemia.

The autophagy pathways:

Microautophagy, chaperone-mediated autophagy, and macroautophagy are the at least three recognised mechanisms that make up autophagy. Microautophagy is the process of cytosol-containing vesicles budding into the lysosomal lumen. Chaperone-mediated autophagy is the mechanism by which the cytosolic and lysosomal HSC70 chaperones assist the LAMP-2a transporter in moving unfolded proteins across the lysosomal membrane [(4)].

However, the term "macroautophagy" refers to the degradation of the cytoplasm via unique cytosolic vesicles that finally bind to lysosomes. Mammals initially undergo macroautophagy in reaction to famine, and this is followed by chaperone-mediated autophagy as a second response [(5)]. Identification of cellular components to be destroyed, labelling of these components to be recognised by the

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autophagy mechanism, formation of an autophagosome that surrounds them with a double membrane, and finally formation of an autolysosome by fusion of the autophagosome with the acidic compartment of the endolysosomal system. All are steps in the complex process known as macroautophagy [6].

The main nutrition sensor mTORC1 is one of the most significant stimuli. Another significant cause is the concurrent stimulation of endosomal microautophagy brought on by hunger. Loss of GSK3-beta signaling and the activation of The AMP-activated protein kinase (AMPK) and hypoxia-inducible factor (HIF) signaling are other related processes [7].

The dual role of autophagy in cancer:

Genome stability and anti-inflammatory signaling pathways have been found to contribute to autophagy's involvement in tissue homeostasis and preventing pro-oncogenic conditions. Although autophagy genes have been discovered to be maintained in malignancies, autophagy protein polymorphisms and altered levels of expression may still occur. Additionally, it has been shown that autophagy genes may both promote and prevent tumour growth [8].

The research on the autophagy modulator Beclin-1 highlighted the function of autophagy in relation to human malignancies (BECN1). Although BECN1 is engaged in several vital cellular processes, its initial tumour suppressor roles are still up for debate [9]. The theory's proponents cite BECN1 as a "haploinsufficient" tumour suppressor gene since it has been found to be deleted in a significant proportion of breast, ovarian, and prostate cancers. Furthermore, heterozygote BECN1 mice have shown increased susceptibility to hepatic, mammary, and lymphoid neoplasia [10, 11].

A supporting investigation used knock-in mice with an active variation of Beclin-1 (BECN1F121A/F121A) to focus on the in vivo removal of the relationship between endogenous Beclin-1 and the negative regulator of Beclin-1-dependent autophagy, Bcl-2 [12]. Additionally, it has been demonstrated that tissues from BECN1 mutant mice with higher autophagic flux levels had longer life spans, better health, and a lower incidence of age-related spontaneous cancer [13] . Additionally, it was discovered that endogenous HER2 and Beclin-1 can interact to suppress autophagy and promote carcinogenesis. Increased basal autophagy was anti-tumorigenic and inhibited the development of HER2-mediated cancer in BECN1F121A animals. The autophagy-inducing peptide (Tat-Beclin-1) inhibited tumour development in mice with HER2-breast cancer xenografts, suggesting a potential therapeutic approach for HER2-positive breast cancer [14]. Colon cancer has been shown to have mutations in UVRAG, another autophagy regulator, indicating that it is another haploinsufficient tumour suppressor [15].

Tumorigenesis showed a growing association with the lack of autophagy. In a phase known as "replicative crisis," autophagic cell death significantly reduces chromosomal instability [16, 17]. Continual division of precancerous cells throughout this process results in increasing telomeric DNA shortening and apoptosis due to dysregulated cell cycle checkpoints. Chromosome instability might result from autophagy-deficient cells with disrupted cell cycle checkpoints avoiding replicative crisis and cell death. Cytosolic chromatin fragments created by DNA telomere damage trigger cGAS-STING (cyclic GMP-AMP synthase-stimulator of interferon genes) signaling and the activation of the autophagy machinery [18].

According to this data, autophagy rather than conventional apoptosis may be the cause of cell death during a replicative crisis. Similarly, targeted hepatic ablation of Atg5 in mice resulted in hepatotoxicity, inflammation, and the growth of benign liver tumours [16]. Similar conditional studies have demonstrated the benefits autophagy has on the pancreas [19].

In contrast, malignant cells utilize autophagy to their advantage. In pancreatic cancer, KRAS mutations leads to 95% of PDACs which is autophagy-dependent tumorigenic growth [20]. Genetic ablation of mutant KRAS or inhibition of ERK expression in PDAC cells lead enhance autophagosome flux, overexpression of Beclin-1, high transcription of autophagy-related genes and downregulation of mTOR signalling [21]. In addition, Energy metabolism is regulated by the microphthalmia/transcription factor E (MIT/TFE) family of transcription factors through the control of autophagy associated genes expression and lysosomal biogenesis. These transcription factors have role in tumorigenesis [22].

Autophagy and AML:

Within its subtypes, acute myeloid leukaemia (AML) exhibits a significant lot of variety, and autophagy's complex function in the disease's genesis and development, which is also evident. Chromosome translocations and rearrangements, such as t(8;21), t(15;17), inv(16), t(6;9), t(9;11), or t(6;9), frequently result in genetic abnormalities in AML (11;19). These particular anomalies might lead to a certain prognosis of AML subtype. Mutations in receptor kinases, important signaling mediators, proto-oncogenes, or epigenetic enzymes, such as FLT3-ITD, TP53, c-KIT, or IDH1/2 mutations, have been demonstrated to affect the course and severity of AML [23-27].

Key autophagy genes frequently have heterozygous deletions, missense mutations, or copy number alterations in AML patients. This was found using in silico analyses and sequencing, and it mostly applies to AML patients with complicated karyotypes[28].

In the same context, it has been demonstrated that elevated ROS levels, reduced autophagic flux, and poor expression of a number of autophagy genes, including ATG10, ATG5, ATG7, BECN1, GABARAP, GABARAPL1/2, and MAP1LC3B that are present in human AML blasts. Additionally in the same study, it was demonstrated that heterozygous deletion of Atg5 or Atg7 in an MLL-ENL AML mice model caused more rapid leukaemia development, pointing to the tumor-suppressive function of autophagy [29, 30].

According to a research by **Jin *et al.*** [28], Ficoll-enriched leukemic blasts from AML patients had lower transcription levels of ULK1, FIP200, ATG14, ATG5, ATG7, ATG3, ATG4B, and ATG4D than granulocytes from healthy donors. **Rudat *et al.*** [31] showed in a research using a wide RNAi screen for "rearranged during transfection" receptor tyrosine kinase (RET) effectors that RET inhibition increased autophagy and resulted in FLT3 depletion. Whereas, mTORC1-mediated autophagy suppression can maintain mutant FLT3 in AML. Instead, **Heydt *et al.*** [32] demonstrated that FLT3-ITD-enhanced autophagy in patient and AML cell lines through ATF4, and that inhibiting autophagy or ATF4 eliminated FLT3 inhibitor resistance. Additionally, **Folkerts *et al.*** [33] study's was able to reveal that a variety of leukemic cell lines and isolated CD34+ cells from AML patients displayed varying degrees of basal autophagic flux, particularly high in young ROS low LSC blasts and unfavourable AML risk groups, such those with TP53 mutations. Additionally, they were able to demonstrate that the impairment of human cell engraftment in immunodeficient NSG mice was caused by the suppression of ATG5 in primary AML cells. This is noteworthy because it suggests a stronger tumor-promoting role for autophagy instead of the suggested tumor-suppressor role [3, 33].

CONCLUSION

It is now understood that the process of autophagy has a dual role in the initiation and progression of cancer. To define the involvement of autophagy in various AML subtypes, more research is required.

This could be helpful in terms of using autophagy in modernised treatment modalities like cancer immunotherapy and precision medicine, as well as the use of autophagy biomarkers for treatment efficacy and clinical response prediction, which would ultimately result in better outcomes and more effective care.

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