STM JOURNALS

Research & Reviews: Journal of
Oncology and Hematology

ISSN: 2319–3387
Volume 15, Issue 1, 2026
January–April
DOI (Journal): 10.37591/RRJOOH

https://journals.stmjournals.com/rrjooh

Review RRJOOH

Cellular Mechanisms of Autophagy in Carcinogenesis: A Narrative Review

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Abstract

Autophagy is a highly conserved lysosomal degradation pathway essential for cellular homeostasis, metabolic adaptation, and survival under stress. In the context of carcinogenesis, autophagy exhibits a paradoxical and stage-dependent role. During early tumor development, autophagy acts as a tumor-suppressive mechanism by limiting genomic instability, oxidative stress, and chronic inflammation. Conversely, in established malignancies, cancer cells exploit autophagy to sustain growth, survive hostile tumor microenvironments, and resist anticancer therapies. Increasing evidence highlights the relevance of autophagy not only as a biological process but also as a diagnostic, prognostic, and predictive biomarker in oncology and pathology. This review comprehensively examines the cellular and molecular mechanisms of autophagy in carcinogenesis, highlighting how autophagy functions as a dynamic and context-dependent biological process during tumor initiation, progression, and metastasis. Emphasis is placed on tumor-specific patterns of autophagic activity across different cancer types and the role of commonly used immunohistochemical markers, such as LC3, Beclin-1, and p62, in evaluating autophagic flux within tissue specimens. The review also discusses the interaction of autophagy with apoptosis, cellular metabolism, hypoxia, and immune modulation within the tumor microenvironment. Furthermore, its diagnostic, prognostic, and therapeutic implications are explored, including resistance to chemotherapy and radiotherapy. Understanding the dual and sometimes paradoxical nature of autophagy – as both a tumor-suppressive and tumor-promoting process – is essential for the rational design and clinical application of autophagy-targeted therapeutic strategies in cancer management.

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Received Date: February 07, 2026
Accepted Date: February 09, 2026
Published Date: March 23, 2026

Citation: Sharique Ahmad, Shekhar Srivastava, Raushan Kumar, Pooja Srivastav, Pushpendra D. Pratap, Faiza Hasan Khan. Cellular Mechanisms of Autophagy in Carcinogenesis: A Narrative Review. Research & Reviews: Journal of Oncology and Hematology. 2026; 15(1): 23–28p.

Keywords: Autophagy, beclin-1, cancer therapy, carcinogenesis, immunohistochemistry, LC3, p62, tumor biology

INTRODUCTION

Carcinogenesis is a multistep and multifactorial process driven by cumulative genetic mutations, epigenetic alterations, metabolic reprogramming, and disruption of cellular quality control systems. Among these systems, autophagy has emerged as a central regulator of cellular integrity and survival. Autophagy enables cells to adapt to nutrient deprivation, hypoxia, oxidative stress, and organelle damage – conditions that are particularly relevant within the evolving tumor microenvironment [1, 2].

In normal tissues, basal autophagy maintains cellular homeostasis and prevents malignant transformation. However, cancer cells frequently reprogram autophagic pathways to meet increased metabolic demands and survive therapeutic stress.

This context-dependent behavior has positioned autophagy as both a tumor suppressor and a tumor promoter, making it a subject of intense investigation in cancer biology and pathology.

TYPES OF AUTOPHAGY AND GENERAL MECHANISM

Autophagy is classified into three major forms: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA). Macroautophagy (hereafter referred to as autophagy) is the predominant form implicated in cancer and involves sequestration of cytoplasmic components within double-membraned autophagosomes that subsequently fuse with lysosomes for degradation [3].

The autophagic process proceeds through tightly regulated stages: initiation, nucleation, elongation, autophagosome maturation, lysosomal fusion, and degradation. These steps are orchestrated by a set of conserved autophagy-related (ATG) proteins. Disruption of autophagy at any stage may significantly influence tumor initiation and progression.

MOLECULAR MACHINERY OF AUTOPHAGY

Initiation and Nutrient Sensing Pathways

Autophagy initiation is regulated by the ULK1 kinase complex, comprising ULK1/2, ATG13, FIP200, and ATG101. Under nutrient-rich conditions, mechanistic target of rapamycin complex 1 (mTORC1) suppresses autophagy by inhibiting ULK1. In contrast, energy stress activates AMP-activated protein kinase (AMPK), which inhibits mTORC1 and directly activates ULK1, thereby initiating autophagy [4–6].

Aberrant activation of the PI3K–AKT–mTOR pathway, a hallmark of many cancers, suppresses autophagy during early carcinogenesis, contributing to genomic instability and malignant transformation [7].

Vesicle Nucleation: Beclin-1 and PI3K Complex

Autophagosome nucleation is mediated by the class III PI3K complex consisting of VPS34, VPS15, Beclin-1 (ATG6), and ATG14. Beclin-1 is a key tumor suppressor and is frequently monoallelically deleted or downregulated in breast, ovarian, and prostate cancers [8].

Beclin-1 interacts with anti-apoptotic Bcl-2 family proteins, creating a functional link between autophagy and apoptosis. Disruption of this interaction enhances autophagy, whereas its stabilization suppresses autophagy and favors tumor development [9].

Elongation and Autophagosome Formation

Autophagosome elongation requires two ubiquitin-like conjugation systems: the ATG12–ATG5–ATG16L1 complex and the LC3 processing system. LC3 is cleaved to form LC3-I and subsequently lipidated to LC3-II, which integrates into the autophagosomal membrane and serves as a reliable marker of autophagy [10].

Selective autophagy receptors, such as p62/SQSTM1 bind ubiquitinated proteins and LC3, directing cargo to autophagosomes. Accumulation of p62 due to defective autophagy promotes oncogenic signalling, oxidative stress, and inflammation, thereby facilitating carcinogenesis [11].

Autophagosome–Lysosome Fusion and Degradation

Mature autophagosomes fuse with lysosomes through the coordinated action of SNARE proteins, Rab7, and lysosomal-associated membrane proteins (LAMPs). Lysosomal hydrolases degrade sequestered contents, recycling metabolites essential for cell survival [12]. Impaired autophagic flux results in mitochondrial dysfunction, increased reactive oxygen species (ROS), and DNA damage – key drivers of tumor initiation [13].

Tumor-Suppressive Role of Autophagy in Early Carcinogenesis

In normal and premalignant cells, autophagy functions as a critical tumor-suppressive mechanism. By removing damaged organelles and misfolded proteins, autophagy limits oxidative stress, maintains genomic stability, and prevents chronic inflammation [14].

Experimental models demonstrate that deletion of essential autophagy genes, such as ATG5 or ATG7, leads to spontaneous tumor formation, particularly in the liver and lung [15]. Loss of Beclin-1 expression has been associated with increased cancer susceptibility and adverse clinical outcomes [16].

Tumor-Promoting Role of Autophagy in Established Malignancies

Once malignant transformation has occurred, cancer cells often become highly dependent on autophagy for survival. Autophagy supports mitochondrial metabolism, sustains redox balance, and supplies metabolic substrates necessary for rapid proliferation [17].

Oncogenic mutations, such as KRAS and BRAF, are strongly associated with elevated basal autophagy, particularly in pancreatic and colorectal cancers. In these tumors, inhibition of autophagy significantly impairs tumor growth and survival [18].

Autophagy and the Tumor Microenvironment

The tumor microenvironment is characterized by hypoxia, nutrient deprivation, acidosis, and immune pressure, all of which induce autophagy. Hypoxia-inducible factor-1α (HIF-1α) upregulates BNIP3 and BNIP3L, promoting mitophagy and enhancing cancer cell survival under low-oxygen conditions [19].

Autophagy also modulates stromal cells, immune infiltration, angiogenesis, and immune evasion, thereby influencing tumor progression and metastasis [20].

Autophagy in Metastasis and Therapy Resistance

Autophagy facilitates epithelial–mesenchymal transition (EMT), anoikis resistance, and survival of circulating tumor cells, contributing to metastatic dissemination [21]. Furthermore, autophagy enables cancer cells to withstand chemotherapy, radiotherapy, and targeted therapies, making it a major mechanism of treatment resistance [22].

Pathology and Oncology Perspective: Biomarkers and Diagnostic Relevance

From a diagnostic pathology standpoint, autophagy-related proteins have emerged as valuable biomarkers. LC3, p62/SQSTM1, Beclin-1, ATG5, and ATG7 are increasingly evaluated by immunohistochemistry (IHC) in tumor tissues. Punctate cytoplasmic LC3 staining suggests active autophagy, while p62 accumulation indicates impaired autophagic degradation (Table 1)[23].

Interpretation of these markers requires careful correlation with tumor type, stage, and clinical context, as static expression alone does not always reflect autophagic flux.

Table 1. Autophagy markers in human cancers and clinical relevance.

Tumor type	Key autophagy markers	Autophagy pattern	Clinical relevance
Breast carcinoma	Beclin-1 ↓, LC3 ↑, p62 ↑	Reduced early, increased in aggressive tumors	Poor prognosis, high grade, therapy resistance.
Pancreatic ductal adenocarcinoma	LC3-II ↑, ATG5 ↑, ATG7 ↑	Constitutively high autophagy	Metabolic support, poor survival.
Colorectal carcinoma	Beclin-1 ↓ (early), LC3 ↑ (late)	Stage-dependent dual role	Genomic instability, adverse outcome.
Hepatocellular carcinoma	ATG5/7 ↓ (initiation), LC3 ↑ (advanced)	Suppressive early, promotive late	Prognosis, drug resistance.
Lung carcinoma (NSCLC)	LC3 ↑, Beclin-1 ↓, p62 ↑	Hypoxia-induced autophagy	Aggressive behavior, TKI resistance.

Therapeutic Targeting of Autophagy in Cancer

Autophagy has gained considerable attention as a therapeutic target in cancer because of its complex, context-dependent role in tumor biology. While autophagy maintains cellular homeostasis and suppresses malignant transformation in normal tissues, many established cancers exploit this pathway to survive metabolic stress, hypoxia, and exposure to anticancer therapies. This dependence on autophagy, often termed "autophagy addiction," is particularly evident in aggressive tumors and provides a strong rationale for therapeutic intervention aimed at modulating autophagic pathways [24, 25].

Rapidly proliferating cancer cells exist in a hostile microenvironment characterized by nutrient deprivation, poor oxygen supply, and oxidative stress. Autophagy enables tumor cells to adapt to these conditions by recycling intracellular macromolecules, maintaining mitochondrial function, and sustaining energy production. Oncogenic mutations, such as KRAS, BRAF, and MYC, are frequently associated with elevated basal autophagy, especially in pancreatic ductal adenocarcinoma, colorectal carcinoma, and lung cancer. In these settings, inhibition of autophagy disrupts metabolic homeostasis and promotes tumor cell death, highlighting autophagy as a critical survival mechanism in advanced malignancies [26, 27].

The most widely explored therapeutic approach involves inhibition of autophagy at the lysosomal stage. Chloroquine and hydroxychloroquine, originally developed as antimalarial agents, inhibit lysosomal acidification and block autophagosome–lysosome fusion, thereby preventing autophagic degradation. Preclinical studies have consistently shown that lysosomal autophagy inhibitors enhance the cytotoxic effects of chemotherapy, radiotherapy, and targeted therapies by impairing stress adaptation in cancer cells. These findings have led to multiple early-phase clinical trials evaluating hydroxychloroquine in combination with standard anticancer regimens across various solid tumors, including pancreatic cancer, glioblastoma, melanoma, and lung cancer [28, 29].

Although autophagy inhibitors have shown limited efficacy as monotherapy, combination strategies appear more promising. Autophagy blockade sensitizes tumor cells to DNA-damaging agents, kinase inhibitors, and immune-mediated cell death, thereby overcoming therapeutic resistance. Clinical responses, however, have been variable, underscoring the importance of tumor type, genetic background, and degree of autophagy dependence in determining treatment outcomes [30, 31]. These observations emphasize that autophagy inhibition is most effective when used as an adjunct to establish therapies rather than as a standalone approach.

Beyond lysosomal inhibition, novel strategies targeting early components of the autophagy machinery are under active investigation. Small-molecule inhibitors of ULK1 kinase and VPS34 aim to block autophagy initiation and vesicle nucleation, respectively. Preclinical studies suggest that these agents may provide more specific and potent autophagy suppression than chloroquine derivatives. However, given the essential role of autophagy in normal tissue homeostasis, concerns regarding systemic toxicity and narrow therapeutic windows remain significant obstacles to clinical translation [32, 33].

Paradoxically, autophagy induction may also have therapeutic or preventive relevance in selected contexts. By promoting the clearance of damaged organelles and limiting oxidative stress, autophagy activation may suppress tumor initiation in premalignant lesions. Agents, such as mTOR inhibitors, induce autophagy and have demonstrated anticancer activity in tumors driven by dysregulated mTOR signalling, highlighting the need for stage- and context-specific autophagy modulation [34, 35].

A major challenge in autophagy-targeted therapy is the lack of reliable predictive biomarkers. Immunohistochemical markers, such as LC3, p62/SQSTM1, and Beclin-1, are increasingly used to assess autophagy status in tumor tissues. Accumulation of p62 and punctate LC3 staining may indicate impaired autophagic flux or high autophagy dependence and could potentially predict responsiveness

to autophagy inhibition. Incorporation of such biomarkers into clinical trials is critical for patient stratification and personalized therapy [36].

Therapeutic targeting of autophagy represents a promising yet nuanced approach in cancer treatment. While autophagy inhibition can enhance the efficacy of existing therapies in autophagy-dependent tumors, careful patient selection and rational combination strategies are essential. Future advances will depend on improved understanding of tumor-specific autophagy regulation, development of selective inhibitors, and integration of pathological biomarkers to guide precision oncology [37, 38].

CONCLUSION

Autophagy plays a pivotal and context-dependent role in carcinogenesis. While it protects normal cells from malignant transformation, it is frequently co-opted by cancer cells to promote survival, progression, and therapy resistance. Integration of molecular biology with pathology-based biomarkers will be essential for the effective clinical translation of autophagy-targeted strategies. A nuanced, tumor-specific approach is required to harness autophagy for precision oncology.

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