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Research Progress on the Role of the Autophagy-Lysosome Pathway in Tumorigenesis, Metastasis, and Therapy

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Abstract: ***The autophagy-lysosome pathway is a highly conserved intracellular degradation system in eukaryotes that is precisely regulated by autophagy-related genes (ATGs). It serves an indispensable role in maintaining cellular homeostasis, and its dysregulation is closely associated with inflammation, neurodegenerative diseases, and tumors. This pathway exhibits a complex dual role in tumorigenesis and progression: during tumor initiation, activated autophagy suppresses tumor development. During tumor metastasis, autophagy shows spatiotemporal specificity. In the early stage, it inhibits epithelial-mesenchymal transition (EMT) to exert anti-metastatic effects. In the late stage, it supplies energy for metastatic cells and promotes distant colonization, thereby exerting pro-metastatic functions. This paper systematically reviews the dual roles and molecular mechanisms of the autophagy-lysosome pathway in tumorigenesis and metastasis, discusses the prospects of targeted therapies against this pathway, and provides a theoretical basis for the precise treatment of malignant tumors including hepatocellular carcinoma.***

Keywords: Autophagy, Lysosome, Cancer, Tumor Metastasis.

1. Introduction

The autophagy-lysosome pathway, as a highly conserved intracellular degradation system in eukaryotic cells, plays a crucial role in maintaining cellular, tissue, and organismal homeostasis by eliminating misfolded proteins, damaged organelles, and pathogens. This process is tightly regulated by a series of autophagy-related genes (ATGs), and its dysregulation is closely associated with the pathogenesis of various human diseases, particularly inflammatory disorders, neurodegenerative diseases, and cancer. In recent years, with increasingly in-depth research, the role of autophagy in tumor biology has become more complex and paradoxical. On one hand, substantial evidence indicates that autophagy deficiency promotes tumorigenesis. For instance, deletion of key autophagy genes such as Beclin1, Atg5, or Atg7 leads to accumulation of protein aggregates and damaged mitochondria, elevates reactive oxygen species (ROS) levels, and induces genomic instability, thereby triggering spontaneous hepatocellular carcinoma in mouse models. On the other hand, autophagy exhibits a dual role in tumor metastasis. Given the complexity of the autophagy-lysosome pathway in tumorigenesis and metastasis, together with its significant potential as a therapeutic target, a deep understanding of its specific mechanisms across different stages of malignancies such as hepatocellular carcinoma (HCC) is particularly critical. Therefore, this review summarizes the dual roles and molecular mechanisms of the autophagy-lysosome pathway in tumorigenesis and metastasis, explores the prospects of targeting this pathway in cancer therapy, and provides a theoretical basis for future precision treatment strategies.

2. Autophagy-Lysosome Dysfunction and Tumorigenesis

The first gene reported to be involved in autophagy-dependent liver tumor formation is Beclin1. In Beclin1 heterozygous mice, autophagy is impaired, leading to a significantly increased incidence of spontaneous tumors including HCC and markedly accelerating malignant lesions induced by hepatitis B virus [1]. Autophagy impairment caused by deletion of Atg5 or Atg7 in mouse liver is typically accompanied by accumulation of denatured protein aggregates, damage to mitochondria, peroxisomes, and lipid droplets, as well as persistent activation of Nrf2, subsequently leading to the development of benign adenomas. The primary cause of this tumorigenesis may be ROS derived from damaged mitochondria or peroxisomes, which induce genomic instability and ultimately result in spontaneous tumor formation. In the livers of mice deficient for Atg5 or Atg7, simultaneous deletion of p62 or Nrf2 suppresses tumor development, suggesting that p62-mediated Nrf2 activation contributes to liver tumor growth in autophagy-deficient mice. Furthermore, in a diethylnitrosamine-induced HCC mouse model, autophagy-mediated clearance of protein aggregates attenuated hepatotoxicity and liver tumorigenesis [2]. Researchers have also found that enhancement of the autophagy-lysosome pathway in HCC promotes p62-mediated ubiquitination and degradation of cyclin D1, thereby inhibiting HCC progression.

3. The Autophagy-Lysosome Pathway and Tumor Metastasis

The role of the autophagy-lysosome pathway in tumor metastasis is complex and context-dependent, exerting dual functions—both promoting and suppressing metastasis — according to tumor type and metastatic stage [3]. It is currently believed that during the early stages of cancer metastasis, autophagy can suppress metastasis by restricting tumor necrosis and inflammatory cell infiltration, as well as by alleviating oncogene-induced senescence. These effects may help reduce the invasion and dissemination of cancer cells from the primary tumor site. In contrast, during the late stages of metastasis, autophagy tends to promote the distant

colonization and survival of metastatic cells that have detached from the extracellular matrix (ECM) [4].

3.1 The Autophagy-Lysosome Signaling Pathway Suppresses Tumor Metastasis

Autophagy can regulate the selective release of the immunomodulator high-mobility group box 1 (HMGB1). Once released, HMGB1 binds to Toll-like receptor 4 (TLR4), activating dendritic cells and thereby triggering a significant anti-tumor immune response that inhibits metastasis [5, 6]. ATG5, a key regulatory protein in the autophagy-lysosome pathway, is significantly downregulated in primary melanoma tissues compared to adjacent normal tissues. Long-term follow-up data from multiple primary melanoma patients revealed that those with low ATG5 expression in tumor tissues had significantly reduced progression-free survival. Studies have shown that knocking down ATG7 in ovarian cancer inhibits autophagy, which promotes the occurrence of epithelial-mesenchymal transition (EMT) by activating the ROS/HO-1 (heme oxygenase-1) pathway [7]. Similarly, impairing autophagy by knocking down ATG5, ATG7, or BECN-1 in glioblastoma induces EMT and promotes cancer cell proliferation [7]. Another study found that the direct interaction of CDH6 with GABARAP, as well as BNIP3 and BNIP3L in thyroid cancer, inhibits the autophagic process, thereby promoting EMT [8]. Twist is a key transcription factor in the EMT process, and research has found that Twist can be degraded by the autophagy-lysosome pathway in cells, inhibiting EMT. Concurrently, studies have shown that the death effector domain-containing DNA-binding protein (DEDD) directly interacts with the PI3KC3/BECN-1 complex, inducing autophagic lysosomal degradation of Snail and Twist, thereby suppressing EMT [9]. The PI3K/AKT/mTOR pathway is a key signaling cascade that inhibits autophagy and promotes cancer progression. Recent studies indicate that due to PTEN loss, PI3K/AKT/mTOR signaling is upregulated in 30-50% of prostate cancers. Inhibiting the PI3K/AKT/ mTOR pathway to increase autophagic flux can promote cancer cell apoptosis [10, 11]. It has been reported that altered expression of different molecules in the PI3K signaling pathway correlates with tumor stage and recurrence risk. Conversely, other studies have found that TAZ, ATP, and BECLIN can promote HCC metastasis by inhibiting autophagy [12, 13]. In terms of pharmacological research, many anti-cancer drugs, such as alisertib, danusertib (Aurora kinase inhibitors), Proscillaridin A, or xanthoangelol, have been found to activate the autophagic pathway in cancer cells while simultaneously inhibiting the EMT process, thereby suppressing HCC metastasis [14, 15].

3.2 The Autophagy-Lysosome Signaling Pathway Promotes Tumor Metastasis

In contrast, numerous studies have also demonstrated that autophagy can promote epithelial-mesenchymal transition (EMT) and facilitate tumor cell migration. Sustained activation of the autophagy-lysosome pathway provides metabolic energy for the survival and proliferation of tumor cells during distant metastasis. Increased punctate LC3II staining correlates with lymph node metastasis and reduced overall survival in human breast cancer [16]. Knockdown of the key autophagy activator BECN1 has been shown to significantly inhibit the EMT process in colon cancer cells [17]. Interestingly, ULK2—an enzyme involved in phosphorylating the BECN1-initiated complex—can also promote EMT in lung cancer cells [18]. Researchers have further indicated that autophagy facilitates tumor metastasis by suppressing pyroptosis. It has been reported that high levels of autophagic activation lead to a significantly increased frequency of RAS mutations in cancer cells. RAS, a small GTPase, is involved in key signaling pathways regulating tumor cell proliferation, survival, and metabolism [19]. Activating RAS mutations upregulate autophagy, thereby enhancing tumor growth, survival, and oncogenesis, and are closely associated with the development of cancers including lung, colon, and pancreatic cancer. In a KRAS-driven non-small cell lung cancer (NSCLC) model, ATG7 deletion significantly reduced tumor growth; furthermore, ATG7 knockout induced regression of K-RAS- mutated adenocarcinomas into benign lesions. Additionally, ATG7 deficiency activates p53, which can further suppress tumor progression. Studies have shown that distinct types of activating RAS mutations can increase intracellular autophagic levels, and cell survival under nutrient deprivation depends on autophagic pathway activation. Further research indicates that inhibiting intracellular autophagic activity via multiple approaches results in the accumulation of damaged and dysfunctional mitochondria, thereby suppressing cell proliferation.

4. Role of Autophagy Activators in Cancer Therapy

Emerging evidence indicates that autophagic activation can induce tumor cell apoptosis, thereby suppressing hepatocellular carcinoma (HCC) progression. The PI3K/ AKT/mTOR pathway is a key regulator of multiple physiological processes in cancer cells. Mammalian target of rapamycin (mTOR) inhibitors exert anti-tumor effects in HCC by activating the autophagy-lysosome pathway. Rapamycin and its analogs are classic mTOR inhibitors that activate this pathway. In a Phase II clinical trial of rapamycin, results demonstrated a significant tumor-suppressive effect in 25 patients with advanced HCC. However, current findings regarding rapamycin and its derivatives in HCC treatment remain inconsistent, highlighting the need for further validation of autophagy-lysosome pathway activators in HCC therapy. Combination therapy has emerged as a critical modality in cancer treatment; therefore, exploring the utility of autophagy-lysosome pathway activators in various combination regimens represents a promising direction for future research.

5. Conclusion and Perspectives

The autophagy-lysosome pathway, a key mechanism for maintaining cellular homeostasis, plays a complex dual role in tumorigenesis, progression, and therapeutic responses. During tumor initiation, autophagy primarily exerts tumor-suppressive effects. In contrast, its role in tumor metastasis is stage-dependent: in the early stages, autophagy can inhibit the epithelial-mesenchymal transition (EMT) process, whereas in the late stages, it provides metabolic support for distant metastatic tumor cells, facilitating their colonization and survival. Future studies are required to

thoroughly elucidate the stage-specific functions of autophagy during hepatocellular carcinoma (HCC) progression, thereby enabling more precise and individualized cancer therapy.

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