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Cellular Autophagy and Primary Liver Cancer Research Progress

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ABSTRACT

The concept of cellular autophagy is that in eukaryotic cells, there are two significant organelles involved in cellular degradation, namely, lysosomes and proteasomes, whereas proteasomes usually recognize and degrade only ubiquitinated substrates in a highly selective manner, lysosomal degradation has a more complex pattern. Autophagy is a "self-feeding" phenomenon that maintains cellular homeostasis by targeting damaged organelles and misfolded proteins to the lysosome for degradation, i.e., extracellular substances and plasma membrane proteins can be delivered to the lysosome for degradation by endocytosis. In contrast, cytoplasmic components and organelles can be delivered to the lysosome for degradation by autophagy. Therefore, autophagy is an intracellular catabolic process that targets damaged and excess cellular proteins, organelles, and other cytoplasmic components and plays an essential role in maintaining cellular homeostasis and activities.

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The process of cellular autophagy

Autophagy is not only an important life phenomenon in eukaryotic cells but also an evolutionarily conserved multistep process involving a group of conserved gene family members called Autophagy-Associated Gene (ATG), which firstly starts by nucleation of autophagic isolation membranes through the assembly of the ULK1 complex, during which the endoplasmic reticulum, Golgi apparatus, and mitochondria are assembled [1]. The endoplasmic reticulum, the Golgi apparatus, and the mitochondria are assembled. Secondly, ATG12-ATG5 coupling mediated by ATG7 and ATG10 binds ATG16L1 to the phagosome to form a multimer, and LC3, which is widely used as a marker of autophagy, is then processed by ATG4 and ATG7 to produce activated [2]. When the ULK1 complex translocates to the fluorophore, class III phosphatidylinositol 3-kinase is activated by ATG4 and ATG7 to produce activated LC3-I, and LC3-I is inserted into the phagocytosis membrane to assist the extension of the fluorophore. phosphatidylinositol3-kinase (PI3K) complex assembled with form the VPS34-BECLIN1-ATG14L complex promotes membrane nucleation.After nucleation, elongation of the separatrix membrane and completion of autophagosomes occurs. Eventually, these autophagosomes fuse with lysosomal vesicles to form autophagic lysosomes, and the autophagosomal cargo is transported to the lysosomal lumen, where it is degraded by hydrolytic enzymes in this compartment [3,4].

The homeostatic role of cellular autophagy in the liver: The liver, the largest parenchymal organ in the human body, is rich in lysosomes and highly dependent on the energy generated by autophagy to maintain normal metabolic functions. Defects in any form of autophagy may lead to serious liver diseases, such as viral hepatitis, liver fibrosis, cirrhosis, and hepatocellular carcinoma. Therefore, autophagy plays a vital role in precancerous lesions in hepatocellular carcinoma [5,6]. One of the most common causes of hepatocellular carcinoma is infection with hepatitis viruses, and it has been found that reduction of glucosamine modification enhances Hepatitis B Virus (HBV) replication by increasing the formation of autophagosomes, and it has been demonstrated that the X protein of HBV binds to autophagy molecules to induce cellular autophagy. Hepatitis C Virus (HCV) regulates autophagy by controlling intracellular proteins and membrane trafficking to enhance replication and inhibit the host's innate immune response. Both viruses induce autophagy through transcriptional up-regulation of Beclin1. In addition, hepatic autophagy disorders lead to fat accumulation, mitochondrial damage, peroxisomal disruption, and aberrations in membrane structure. Showed that the livers of mice with specific knockout of ATG7 exhibited marked hepatomegaly and were prone to tumor formation [7].

The Relationship between Cellular autophagy and Hepatocellular Carcinoma

Autophagy plays a complex role in hepatocellular carcinoma and promotes cell survival and death through various signaling pathways, mainly involving Bax, Bcl-2, p53, mTOR, PI3K, and Ras-related molecular pathways in tumors. The above signaling

pathways are often associated with each other, and there may be interactions between autophagy-related proteins such as Beclin1, P62, and LC3, which may promote or inhibit the development of tumor cells. Autophagy has a dual role in the development of hepatocellular carcinoma (HCC) [8]. In the early stage of HCC formation, autophagy maintains cell stability and inhibits tumorigenesis; when HCC develops to a particular stage, the tumor cells can use autophagy to adapt to different environments, such as hypoxia or nutrient deficiencies, thus promoting the progression of HCC. In recent years, more and more scholars have found that autophagy can promote the occurrence and development of HCC because some cells can provide amino acids, fatty acids, and energy needed for the survival of the remaining cancer cells after autophagy occurs so that this cell degradation can support the proliferation of cancer cells. This effect can help the tumor cells to survive under the adverse conditions of ischemia, hypoxia, etc. It has been found that, in order to maintain the survival of the tumor cells, autophagy can help the tumor cells to survive [9,10]. In order to maintain rapid proliferation, cancer cells require abundant nutrients and oxygen during progression and metastasis, and growth factor-deprived animal cells need autophagy to maintain cell survival. Increased autophagy response is associated with tumor progression and poor prognosis in HCC.

In a mouse model of non-small-cell lung carcinoma, autophagy deficiency inhibits the tumorigenic driving effect of KRAS. In a mouse model of pancreatic carcinoma, autophagy blocks p53, the most critical tumorigenicity component. In a mouse model of pancreatic carcinoma, autophagy blocks p53, the most critical component of tumorigenicity, and autophagy blocks p53. In a mouse model of pancreatic cancer, autophagy blocked the activation of p53, which promoted the growth of RAS-induced cancer cells [11]. Similar studies were also performed in HCC. Liver-specific ATG5 knockout mice induced various oncogenes, including p53 and the knockout of ATG5 in p53-deficient wild-type mice induced the transformation of HCC into benign hepatic adenomas. Sphingosine kinase 1 (SPHK1) induced the TNF receptor-associated factor 2 (TRAF2)-mediated mouse tumorigenesis.

In another study, ATG5 and ATG12mR-N were found in hepatocellular carcinoma cells in combination with hepatitis B. In the same study, ATG5 and ATG12mR-N were also found in hepatocellular carcinoma cells in combination with hepatitis B. In another study, ATG5 and ATG12 mRNA expression in hepatocellular carcinoma cells significantly increased when hepatitis B was combined with hepatitis B. ATG5-ATG12 protein expression in tumor tissues was higher than that in paraneoplastic tissues [12]. The percentage of apoptosis in hepatocellular carcinoma cells was increased by 11.4% in autophagy-activated hepatocellular carcinoma cell lines infected with HBV and then knocking down ATG12. However, the apoptotic ratio did not change when ordinary hepatocellular carcinoma cell lines were treated similarly. ATG12 is a targeting factor for HBV-HCC. The AKT/PI3K pathway has a wide range of effects on tumors.AKT inhibitor 1/2 (AKTi-1/2) induced protective autophagy in cells, and autophagy inhibitor (3-methyladenine, ammonium chloride, and bafilomycin A1) treatment or Beclin-1 siRNA knockdown inhibited autophagy and significantly enhanced AKTi-1/1/1 inhibition. Occurrence and significantly enhanced AKTi-1/2-induced HepG2 cell death and apoptosis indicated that autophagy response was the main resistance factor of AKTi-1/2 in HCC cells [13].

Autophagy Inhibitor Therapy

In HCC, autophagy can maintain intracellular homeostasis, and cancer cells also need autophagy to counteract stress to ensure cell survival. Moreover, this counteracting effect also affects HCC drugs. Autophagy inhibitors can block the pro-tumor survival effect of autophagy and can enhance cytotoxicity when combined with anti-HCC drugs. A high lysosomal inhibitor bafilomycin (BafA1) concentration has shown cytotoxicity in a wide range of cancers. BafA1 was found in the GCC cells and was also shown to be a significant cytotoxic agent in the GCC cells [14]. BafA1 induces cell cycle arrest in the G1 phase, accelerates LC3 transformation, promotes p62/SQSTM1 expression, inhibits lysosomal degradation, and blocks autophagy flow, thereby inducing cell death in HCC cells. Therefore, BafA1 may be a therapeutic tool for HCC. Clinical trials have been conducted on combining anticancer drugs and autophagy inhibitors such as Chloro Quine (CQ) and Hydroxychloroquine (HCQ) for treating various cancers. It has been found that CQ and HCQ can increase the pH of lysosomes by precipitating protons, thus preventing acidic lysosomal degradation, the final stage of autophagy.

The combination of oxaliplatin, cisplatin, 5-fluorouracil, and sorafenib in HCC xenografts showed a more pronounced tumor suppressor effect compared with either agent alone. Similarly, co-administration of CQ and sorafenib in HCC cell lines resulted in significant tumor suppression, and silencing of Atgs in HCC cell lines inhibited specific autophagy and promoted chemotherapy-induced cell death [15].

Recently, it has been shown that heat shock transcription factor 1 (HSF1) enhances the transcriptional activity of the Atg4B gene promoter (-1429 to -1417), and researchers have further demonstrated that knockdown of HSF1 or Atg4B enhances the anti-HCC Effect of Epirubicin (EPI) in vivo in nude mice. These results suggest that HSF1 promotes the expression of Atg4B and reduces HCC through the enhancement of protective autophagy. These results suggest that HSF1 can promote Atg4B expression and reduce the sensitivity of HCC cells to EPI by enhancing protective autophagy, which suggests that the "HSF1/Atg4B/protective autophagy" pathway may be a new target for the development of sensitive chemotherapeutic agents for hepatocellular carcinoma. It has also been found that hanchusonin, combined with sorafenib, can inhibit autophagy induced by hanchusonin and thus kill human HCC cells more efficiently. Antitumor agents such as oxaliplatin, 5-fluorouracil, and piroxicam (THP) have also been shown to induce LncRNA HULC expression and protective autophagy significantly.

The silencing of HULC inhibited protective autophagy, and the sensitivity of HCC cells to the three drugs was enhanced after the inhibition of autophagy. Ectopic expression of HULC induced autophagy in HCC cells, which was closely related to the stabilization of Sirt1. In addition, HULC up-regulated the expression of ubiquitin-specific peptidase 22 (USP22), which decreased the ubiquitin-mediated degradation of the Sirt1 protein [16]. Therefore, it has been suggested that the activation of the "HULC/USP22/Sirt1/protective autophagy" pathway would reduce the sensitivity of HCC cells to chemotherapeutic drugs. Doxorubicin (Dox) is also known to induce autophagy, and inhibition of Dox-induced autophagy could promote apoptosis in HCC cells. In 30 HCC patients, the expression of miR-26a/b was significantly downregulated in tumor cells and negatively correlated with the expression level of the autophagy initiator protein ULK1. miR-26a/b inhibited the autophagic flux at the initial stage by targeting ULK1, and in vitro experiments demonstrated that the overexpression of miR-26a/b enhanced the sensitivity of HCC cells to Dox and promoted cell apoptosis through the

inhibition of autophagy. Moreover, it promotes apoptosis by inhibiting autophagy.

Autophagy Activator Therapy

Many studies in HCC have focused on the protective effects of autophagy on tumor cells, leading to drug-related experiments. pI3K/Akt/mTOR pathway is a significant regulatory pathway for cell proliferation, growth, survival, protein synthesis, and glucose metabolism in cancer cells. mTOR inhibitors have shown antitumor activity in HCC, suggesting that targeting this pathway may benefit HCC treatment. Rapamycin and its derivatives act as mTOR activators. Rapamycin and its derivatives, as mTOR inhibitors, are common autophagy inducers. A phase II clinical trial found that rapamycin showed antitumor effects in 25 patients with advanced HCC. A rapamycin-based immunosuppressive regimen after liver transplantation improved the OS of patients with HCC. However, due to the need for clinical data on each drug, it is premature to promote rapamycin and its derivatives. Everolimus (a drug that is a significant regulator of glucose and glucose metabolism) may be a valuable target for HCC. It was suggested that everolimus (RAD001) showed antitumor activity in a xenograft model of human HCC; however, it was shown to have no benefit on survival and disease progression in a phase III trial.

In contrast, more mTOR-targeted dual inhibitors with RAD001 and PI3K/mTOR increased tumor autophagy/mitochondrial autophagy, decreased tumor size, and demonstrated greater tumor size in a mouse model of HCC [17]. Recently, a CDK4/6 inhibitor, Palbociclib, has been clinically significant for treating HCC. Palbociclib has been shown to induce autophagy and apoptosis in HCC cells by activating AMP-Activated Protein Kinase (AMPK) and inhibiting Protein Phosphatase 5 (PP5). Another study found that polyamine spermidine induced autophagy in tumor cells and initiated oxidative stress-induced cell death, thus preventing liver fibrosis and hepatocellular carcinoma. Researchers found that MAP1S positively regulated the flow of autophagy in cells, and MAP1S-deficient mice had a 20% reduction in median survival and progressed to severe liver fibrosis and HCC in response to stress. Wild-type mice or cells treated with spermine increased MAP1S stability and autophagy signaling by depleting the solute HDAC4. Oral administration of spermine prolonged the lifespan of mice by 25% with lifelong administration and reduced chemical-induced hepatic fibrosis and hepatocellular carcinoma foci [18]. More importantly, the effects of spermine were dependent on MAP1S-mediated autophagy. This study provides an opportunity for the treatment of oral spermine. This study provides preclinical evidence for the treatment of oral spermidine.

Summary and Prospects

Autophagy plays a dual role in Hepatocellular Carcinoma (HCC), which may be related to the heterogeneity of HCC tumors, the state of tumor cells, and the environment in which the tumors exist. Cellular autophagy is crucial in hepatocellular carcinoma genesis, metastasis, targeted therapies, and drug resistance. On the one hand, autophagy plays an inhibitory role in Hepatocellular Carcinoma (HCC) by eliminating oxidative stress, maintaining genome stability, and preventing HCC inflammation in the early stage of HCC. On the other hand, it can promote HCC cellular growth in the tumor microenvironment during the formation of malignant tumors. Therefore, the complexity of autophagy in HCC may require individualized management. Although studies have shown that autophagy modulators can be a high-potential therapeutic approach for HCC, the efficacy and safety of these autophagy modulators still need to be verified by clinical data. Autophagy may be an ideal candidate for tumor immunotherapy. Therefore, with further research on the mechanism of autophagy in hepatocellular carcinoma, it is possible that autophagy could be an ideal candidate for tumor immunotherapy. Therefore, with further studies on the mechanism of autophagy in hepatocellular carcinoma, the combination of autophagy modulators, multiple kinase inhibitors, signaling pathway inhibitors, and immunotherapy may play a synergistic therapeutic role in patients with advanced hepatocellular carcinoma.

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