Asian Science Bulletin

OPEN ACCESS

Modulating Autophagy as an Attractive Strategy to Treat Renal Cell Carcinoma

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ABSTRACT

Autophagy is a key major mechanism by which cancer cells are able to survive periods of therapy-induced stress that result in drug resistance, autophagy is crucial for mediating cellular stress and damage. Renal Cell Carcinomas (RCC) make up about 90% of kidney cancer cases. Modulating autophagy has been demonstrated to increase the cytotoxicity of authorized Renal Cell Carcinoma (RCC) therapies and combat drug resistance in recent years. Autophagy activation inhibits malignancies by removing damaged organelles and proteins while shielding certain tumor cells from low oxygen levels and starvation, which are primary features of tumor microenvironments. It is unknown why autophagy has two effects, despite evidence that it controls both cell death and survival. Research has shown that autophagy regulators can treat RCC by controlling the PI3K/Akt/mTOR and AMPK/mTOR signaling pathways. On the other hand, the relationship between autophagy and immune cell activation, especially in RCC, is unclear. Early studies suggest inhibiting autophagy can affect hematopoiesis and systemic immunity, suggesting immune checkpoint inhibitor therapy may not be beneficial. Recent studies show autophagy inhibition does not stop T-cell activation. It is noteworthy that studies examining the connection between autophagy and RCC are becoming more popular. Autophagy-related proteins have been shown in earlier research to be interesting prognostic indicators for Renal Cell Carcinoma (RCC) treatment. Therefore, to determine the therapeutic relevance of autophagy activators and inhibitors in Renal cell carcinomas (RCC), more investigation is required. This study explores the therapeutic alternatives for the current situation and potential future directions of autophagy targeting as a potential alternative and successful treatment for renal cell carcinoma.

KEYWORDS

Autophagy, renal cell carcinoma, hematopoiesis, immune checkpoint, cytotoxicity, cell death

INTRODUCTION

Primarily formed from renal tubular epithelial cells, renal cell carcinoma (RCC) is thought to be the most prevalent kind of malignant kidney tumor. The most prevalent subtype of RCC is reportedly renal clear cell carcinoma (ccRCC)[1]. The biology, pathogenesis and treatment of RCC have advanced, but the incidence of the disease is still rising. More than 200,000 new cases are reported globally each year and their incidence has been rising at a rate of roughly 2% each year[2]. Even though there are numerous targeted medications and biologicals for ccRCC that are now in the research and development stage, it is still unknown whether they are effective. Nevertheless, numerous research has lately revealed close

ISSN: 1813-0070 (Online)
https://doi.org/10.3923/asb.2024.290.297

Received: 25 Oct. 2023
Accepted: 04 Apr. 2024
Published: 31 Dec. 2024

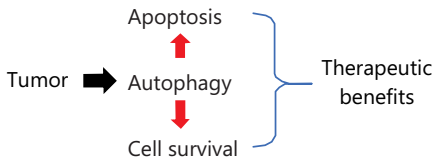

Fig. 1: Autophagy in the development and treatment of cancer

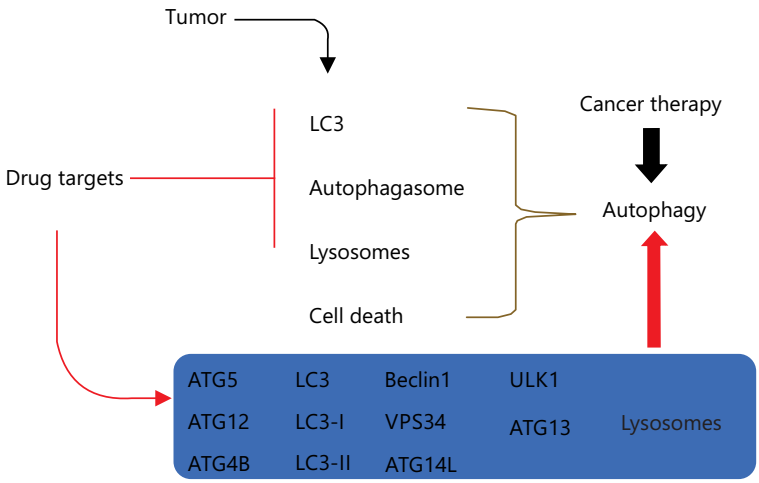

Fig. 2: Different gene targets involved in the process of autophagy which can lead to decreased auto phagosome formation inhibiting lysosomes
ATG: Autophagy related gene, VPS34: Vacuolar protein sorting 34, LC3: Microtubule-associated protein 1A/1B-light chain 3 and ULKI autophagy

connections between autophagy and RCC, which may present fresh therapeutic possibilities for RCC[3]. It is important to note that studies on the connection between autophagy and RCC have drawn attention (Fig. 1). Therefore, autophagy-related proteins may serve as promising prognostic indicators for the therapy of RCC, according to prior research (Fig. 2)[4-6].

Autophagy is a tightly regulated catabolic system for self-preservation that involves the breakdown of extraneous or malfunctioning parts[7]. Autophagy-related (ATG) genes play a significant role in controlling this process, which enables cells to adapt to a variety of conditions such as nutrition deprivation, endoplasmic reticulum (ER) stress, pathogen infection, or hypoxia, which is thought to be a survival mechanism[8,9]. However, autophagy can take part in cell death under severe or protracted stress or in cells lacking in apoptosis[10]. The ROS is a crucial regulator of both apoptosis and autophagy, however, both processes are accompanied by excessive overproduction, phosphatidylinositol 3-kinase inactivation and mitogen-activated protein kinase (MAPK) activation[11-13].

As a result, once autophagy is initiated, it can shield cells from harm caused by aging organelles and damaged macromolecules that can be broken down by lysosomal enzymes. Autophagy, however, appears to be a double-edged sword that can both cause autophagic cell death (type II programmed cell death) and cell survival[14] depending on the situation (Fig. 2). The C-terminal peptide of LC3B, a microtubule-associated protein light chain 3, is often the first part of the autophagy process to be broken down by the cysteine protease ATG4 to produce LC3B-I, which is subsequently conjugated to phosphoethanolamine to produce LC3BII. Furthermore, LC3BII can join forces with ATG5, 7 and 12 to create autophagosomes that contain phospholipid bilayers[15]. In order to degrade macromolecules and

damaged organelles, ubiquitin-binding protein p62/sequestosome-1(SQSTM1) interacts with LC3 simultaneously. The AMPK (increased ratio of AMP/ATP, nutrient deficiency) can activate autophagy induction, whereas pmTOR suppresses it. Under conditions of nutrient deficiency, AMPK will be phosphorylated/activated to trigger autophagy initiation, whereas pmTOR, a cell survival signaling, can suppress autophagy formation[15]. Similarly, these two mechanisms frequently use a variety of paths in response to a single stress. The new target mechanism for chemotherapy-resistant cancer therapy is therefore autophagy/apoptosis[16,17].

Depending on the kind, grade, stage and depth of the tumor, autophagy's effect in cancer can either be tumor-suppressive or tumor-promoting[18]. Metastatic RCC cells may use autophagy as a means of cell survival and inhibiting it in ccRCC may increase the cytotoxicity of mTOR inhibitors, according to certain studies[19,20]. When ccRCC patients use pazopanib, autophagic gene polymorphisms are linked to progression-free survival (PFS). Therefore, it is hypothesized that autophagy regulation and function are probably related to the preservation of kidney cancer cell homeostasis, disease etiology and therapeutic resistance.

AUTOPHAGY IN RENAL CELL CARCINOMA

The connection between autophagy and RCC has attracted attention. As a result, investigating the molecular basis of autophagy in RCC may serve as a therapeutic target[15]. According to research by Radovanovic *et al.*[21], the role of autophagy in ccRCC is independent of AMPK/Mtor transcriptional regulation of autophagy. In ccRCC tumors, the mRNA levels of pro-autophagic ATG4, p62 and UVRAG were higher than those of pro-apoptotic BAX, anti-apoptotic BCL-XL, pro-apoptotic ATG4 and BCL-XL. A rise in phospho-ULK1 and the degradation of the autophagic substrate p62, while leaving apoptotic PARP cleavage unaffected, served as evidence that autophagy had been induced. The AMPK phosphorylation was reduced and 4EBP1 phosphorylation was increased in ccRCC tissue[21].

The expression of apoptosis regulators did not correlate with clinicopathological features of ccRCC. On the other hand, higher levels of the mRNA for ATG4, GABARAP and p62 were linked to earlier tumor stages, smaller tumors and improved disease-specific 5-year survival (ATG4 and p62). Therefore, lower tumor stage, less metastasis and improved 5 year survival were related to decreased p62 protein levels, which correspond to greater autophagic flux. In a different study, Deng *et al.*[22] discovered that sinomenine inhibited the PI3K/Akt/mTOR signaling pathway, which caused ACHN cells to undergo cell death and autophagy. Additionally, Antonaci *et al.*[23] demonstrated that PI3K/AKT/mTOR/p70S6K pathways were involved in dimethyl sulfide (DMS)-induced autophagy in Caki-1 cells. Autophagy has been activated *in vivo* and *in vitro* by sunitinib inhibiting the Akt/mTOR/p70S6K pathway[24]. The literature reviewed above demonstrates that autophagy and the PI3K/Akt/mTOR signaling pathway may serve as therapeutic targets for the prevention and treatment of RCC. The basal amount of autophagy is inherently higher in RCC cell lines. One study found that between 30 and 60% of growing cells in different RCC cell lines have LC3-II puncta[25].

IMBALANCE IN AUTOPHAGY MARKERS IN RENAL CELL CARCINOMA (RCC)

Beclin1 participates in the formation of Beclin 1-Vps34-Vps15 core complexes and the start of autophagy, especially in unfavorable conditions[26]. It was discovered that RCC tissues and cell lines (A498 and ACHN) express Beclin 1 at high levels[4]. Reduced expression of ATGs, which are essential for the process of autophagy nucleation, is associated with a poor prognosis in RCC[27,28]. According to Liu *et al.*[29], the majority of ccRCCs show allelic loss and/or mutations of ATG7 p62/SQSTM1, a conventional macroautophagy substrate, interacts with LC3 directly to digest ubiquitinated protein[30]. Autophagy decreased p62 levels in RCC and additionally, p62 amplification on chromosome 5 was linked to the development of kidney carcinoma[31].

Studies have shown that the ccRCC, A498 and ACHN cell lines' up-regulated expression of LC3 encourages cell motility[4]. According to two investigations, LC3-II levels in RCC tissues and cells were lowered by boosting autophagy-related apoptosis[24,32]. However, Wang *et al*.[33] discovered that LC3-II expression levels in RCC cell lines (786-O, 769-P, OS-RC-2 and ACHN cells) were lower than those in a control cell line (HK-2 cell).

AUTOPHAGY CONTROLS BOTH CELL DEATH AND SURVIVAL

It is unclear why autophagy has two effects. Numerous investigations have shown that autophagy regulates both cell survival and death (Fig. 2). Reduced and aberrant autophagy gene and protein expression may have an effect on RCC illness. The autophagy-related proteins Beclin-1 and LC3B-II have been demonstrated to be downregulated in kidney cancer cells by the cytoprotective enzyme heme oxygenase-1 (HO-1)[33]. Wang *et al*.[33] found that Atg7 and LC3-II overexpression suppressed cell proliferation in the human RCC cell lines 786-O, 769-P, OS-RC-2 and ACHN both *in vivo* and *in vitro*. However, autophagy protects some tumor cells against nutrient deprivation and low oxygen levels, which are the two main characteristics of tumor microenvironments[34]. In RCC cells lacking VHL, EPAS1, a type of hypoxia-inducible factor, builds up and targets ITPR1. In the interim, ITPR1 regulates the recognition of an unidentified signal coming from NK cells that initiates autophagy. Granzyme B (GZMB), a substance that NK cells make, is destroyed as a result of autophagy activation in RCC cells, which reduces NK's capacity to eradicate tumor cells[35,36]. Furthermore, it has been shown that ITPR1 regulates the induction of autophagy in the NK-mediated killing of RCC cells[36].

IMMUNE SYSTEM AND AUTOPHAGY

Despite the fact that it is uncertain how autophagy suppression affects the effectiveness of chemotherapies, clinical trials have started utilizing CQ or HCQ, primarily in conjunction with them, to treat cancer patients[37-39]. These combinations, which are mostly used to treat cancer in xenograft mouse models, have demonstrated some promise in suppressing tumor growth and extending host survival[40-42]. However, to prevent tumor rejection in these studies, immuno-deficient animals were used, therefore there was no chance to assess how autophagy inhibitors affect immune system cells directly and indirectly[43]. Further studies employing immune-competent mice have shown that the loss of essential autophagy-relevant gene products such as autophagy-related (ATG) 5 or Beclin 1 (BECN1) reduces the effectiveness of radiotherapy or chemotherapy in immune-competent mice, even though these treatments have a greater anti-cancer effect *in vitro* and *in vivo* in immune-deficient mice[44].

The study's finding highlights the essential role that the immune system plays in effective anticancer treatment when autophagy is being altered. The immune system may be stimulated by immunogenic cell death (ICD), which was demonstrated to be produced by a number of substances released by cancer cells as they died following chemotherapies or when exposed to the environment on their surface[45,46]. The Damage Associated Molecular Patterns (DAMPs) exposed on the surface of dying lymphoma cells treated with bortezomib were Calreticulin and Heat Shock Protein (HSP) 90 and that the receptor molecule involved in dendritic cells' (DCs') recognition of these DAMPs was CD91[47,48]. This protein was found to be significant in the study. Strong antigen-presenting cells (APCs) called DCs are necessary for inducing a specific immune response and destroying cancer cells that have undergone apoptosis[49]. Therefore, it is now plainly clear that the immune system's participation is necessary for effective anticancer therapy.

TARGETING AUTOPHAGY IN RENAL CELL CARCINOMA

Cancer cells can provide alternate energy sources in times of stress by recycling nutrients via autophagy, a critical lysosomal breakdown mechanism[50,51]. Numerous recent studies have suggested that changes in the autophagy pathway may be particularly significant for patients with RCC and affect overall survival[52,53]. For the treatment of cancer, some substances pharmacologically target autophagy. Additionally,

lucanthone is being researched as a cancer preventative. In tests using cell culture, lucanthone revealed lysosomal disruption and suppression of autophagy[53]. Furthermore, cathepsin D, a lysosomal protease, was discovered to be an important mediator of lucanthone's powerful pro-apoptotic actions in a number of breast cancer cell lines. Researchers have developed new, lysosome-targeting medications with the use of insights from the chemical composition of lucanthone. The STF-62247 specific substance is thought to trigger autophagy in cancer cells since it has strong lethal effects on VHL-deficient cancer cells but is ineffective against wild-type (WT) VHL cells. Treatment results in huge, cytoplasmic vacuoles in both WT-VHL and VHL-deficient cells. The molecular connections between VHL and autophagy, however, have not yet been thoroughly clarified[53].

Both chloroquine (CQ) and hydroxychloroquine (HCQ) substances function by building up in lysosomes and then deacidifying them[54]. This deacidification prevents autophagy from taking place because lysosomes' low pH is necessary for the cargo to degrade. The CQ and HCQ have been repurposed to pharmacologically target autophagy in a range of cancer types for more than 10 years[55]. However, there haven't been many clinical investigations that have looked at HCQ in RCC patients. The HCQ and lucanthone core motifs were designed into the dimeric compound ROC-325. Similar to HCQ, ROC-325 concentrates on the late stages of autophagy. Instead of impairing the growth of autophagosomes, ROC-325 assembles in the lysosome and deacidifies it. The indicators LC3-II and p62 stabilize when ROC-325 is applied *in vitro*, which is consistent with autophagy suppression. At half maximum inhibitory concentrations (IC_{50}) of 2-10 vs. 50-100 M, ROC-325 dramatically decreased cell viability in RCC cell lines as compared to HCQ. Another study found that the suppression of autophagy with 3-methyladenine (3-MA) and bafilomycin dramatically boosted paclitaxel-activated apoptosis in FLCN-deficient RCC cells[56,57].

Interestingly, bafilomycin A1 was found to disrupt autophagy by inhibiting the union of the autophagosome and lysosome. These results imply that while these drugs partially inhibit the lysosomal degradation of cellular components, they might not be potent enough to completely inhibit the degradation of autophagy. It is essential to create new, more potent autophagy inhibitors in order to increase the efficacy of treatments.

CONCLUSION AND FUTURE PERSPECTIVE

Autophagy has recently been found to be the main mechanism by which cancer cells can endure periods of therapy-induced stress that lead to drug resistance. The progression of clear cell renal cell carcinoma (ccRCC) continues to be a significant clinical issue and understanding the molecular triggers of malignancy progression is necessary to creating effective therapy targets. The connection between autophagy and immune cell activation, particularly in RCC, is poorly understood. However, preliminary outcomes from a number of cancer models have given conflicting outcomes. Early studies indicate that inhibiting autophagy can have an impact on hematopoiesis and systemic immunity, indicating that using immune checkpoint inhibitor therapy in conjunction with autophagy may not be beneficial. However, recent studies indicate that inhibiting autophagy does not stop T-cell activation. This underlines the requirement for developing and evaluating medicines that modulate autophagy in addition to the expanding list of approved RCC therapies.

SIGNIFICANCE STATEMENT

Renal Cell Carcinoma accounts for malignant renal tumors and its occurrence has been rising at a pace of roughly 2% per year. Consequently, it is essential to create new targets for RCC. However, several recent research has revealed close connections between autophagy and RCC, which may present new avenues for the disease's treatment. Autophagy inhibits the growth of tumors by removing oxidative stress, preserving genomic stability and lowering malfunctioning proteins in RCC. While, RCC-specific

chemotherapy stimulates autophagy, which results in medication tolerance and accelerates the growth of the tumor. This suggests that medications that inhibit autophagy may be useful in the treatment of RCC. In other words, especially for RCC that is resistant to chemotherapy, chemotherapies in combination with autophagy inhibitors may prove more efficacious.

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