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Cancer Cell Survival Strategies: The Collusion between Autophagy and Immune Evasion in Renal Cell Carcinoma

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Abstract: This review systematically elucidates the core mechanisms and research advancements regarding the role of autophagy in immune evasion in Renal Cell Carcinoma (RCC). Accumulating evidence indicates that autophagy exhibits a typical "context-dependent" dual role in RCC pathogenesis: it may suppress tumorigenesis in early stages, while primarily promoting cell survival and immunosuppressive functions within the established tumor microenvironment (TME). Autophagy facilitates immune escape through multi-dimensional mechanisms, including the precise regulation of PD-L1 stability, degradation of MHC-I molecules and the antigenic peptide pool, remodeling of the metabolic microenvironment, induction of T cell exhaustion, and enhancement of immunosuppressive cell functions. Therapeutically, combining autophagy inhibitors with immune checkpoint inhibitors has demonstrated significant synergistic effects in preclinical studies, and several clinical trials have provided preliminary validation of its safety and efficacy. Future research should focus on integrating multi-omics technologies and advanced disease models to deeply elucidate the autophagy regulatory network, explore its crosstalk with other cell death pathways such as pyroptosis and ferroptosis, and promote the development of personalized treatment strategies based on precise stratification of autophagy activity, thereby offering new avenues to overcome immunotherapy resistance in RCC.

Keywords: Renal Cell Carcinoma; Autophagy; Tumor microenvironment; PD-L1; Immunotherapy

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1. Introduction

Renal Cell Carcinoma (RCC) is a malignant tumor arising from the epithelial lining of the renal tubules, accounting for 80–90% of all primary renal malignancies [1]. RCC is often asymptomatic in its early stages.

Approximately 60% of cases are incidentally detected during routine health examinations or imaging studies for unrelated conditions, while about 30% of patients present with metastatic disease at the time of diagnosis. Only around 10% of patients exhibit the classic triad of symptoms: flank pain, gross hematuria, and a palpable abdominal mass. Furthermore, distant metastasis develops in 20–40% of patients with initially localized RCC following radical nephrectomy (RN) [2]. The management of advanced RCC is challenging due to its inherent resistance to conventional radiotherapy and chemotherapy, as well as its propensity to develop acquired resistance. Consequently, patients with recurrent or metastatic disease generally have a poor overall survival. According to statistics from the SEER database published by the National Cancer Institute (NCI), the 5-year survival rate for RCC confined to the primary site is 93%. Still, this rate drops significantly to 15% once distant metastasis occurs [3]. In recent years, the widespread adoption of screening technologies and advanced imaging modalities has led to a marked improvement in the early detection rate of RCC. Consequently, its incidence has now stabilized, and mortality rates show a declining trend. Nonetheless, due to its high heterogeneity, insidious onset, and difficult treatment, RCC remains a significant disease threatening public health.

The pathogenesis and progression of RCC are not yet fully elucidated. Current evidence indicates strong associations with factors such as smoking, hypertension, obesity, as well as mutations or deletions in the Von Hippel-Lindau (VHL) tumor suppressor gene. Clinically, RN and nephron-sparing surgery (NSS) remain the primary treatment modalities for localized disease. For post-operative management of early to mid-stage patients and as the initial approach for advanced-stage patients, both domestic and international guidelines recommend comprehensive medical therapy. Targeted therapy and immunotherapy have become the cornerstone of treatment for metastatic RCC. First-line regimens include tyrosine kinase inhibitor (TKI) monotherapy, immunotherapy combined with targeted agents, and dual immune-checkpoint inhibition [4]. Although a subset of patients derives significant benefit from these strategies, the administration of systemic therapy must strictly adhere to the principle of individualization. Furthermore, a major clinical challenge is the frequent development of secondary or acquired resistance.

Autophagy, classified as type II programmed cell death, is an intrinsic catabolic process in eukaryotic cells regulated by autophagy-related genes (Atgs). It facilitates the lysosomal degradation of damaged organelles and macromolecules and is categorized into three forms: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA). In its broadest sense, autophagy typically refers to macroautophagy, wherein cells under stress conditions form double-membraned autophagosomes that encapsulate damaged organelles and misfolded proteins. These autophagosomes subsequently fuse with lysosomes for cargo degradation, enabling the recycling of intracellular components and providing energy and biosynthetic precursors for cell survival. Under physiological conditions, basal autophagy occurs at a low level to maintain cellular homeostasis, serving as a core function of all living cells and a vital mechanism for self-protection and metabolic regulation. However, cancer cells frequently upregulate autophagic activity to cope with microenvironmental stress, utilizing the degradation products for biosynthesis and energy production, thereby supporting tumor growth and invasion. Recent research has revealed a context-dependent dual role of autophagy in the pathogenesis and progression of RCC, with its function being determined by the tumor's genetic background and developmental stage. For instance, VHL inactivation leads to the accumulation of hypoxia-inducible factor-1α (HIF-1α), which not only promotes tumor angiogenesis but has also been found to induce autophagy. Elevated autophagy recycles essential nutrients and energy for cancer cells, enhancing their stress tolerance and survival advantage, ultimately contributing to RCC progression, invasion, and mediating therapy resistance [5].

Tumor immune escape refers to the core biological process through which cancer cells dynamically modulate their antigenic profile and the local microenvironment to evade recognition and elimination by the host

immune system, thereby enabling their survival, proliferation, and metastasis within the body. Unlike exogenous pathogens, tumor cells originate from the body's own normal cells, resulting in an antigenic repertoire highly similar to that of healthy tissues. This similarity poses a significant challenge for the immune system in effectively distinguishing "self" from "non-self." In 2002, the "cancer immunoediting" theory, proposed by Robert Schreiber and colleagues, systematically conceptualized tumor development as a process involving three distinct phases: elimination, equilibrium, and escape [6]. The mechanisms underlying tumor immune escape are multifaceted, encompassing impaired tumor antigen presentation, antigen modulation, low immunogenicity, the induction of an immunosuppressive microenvironment, and the formation of physical barrier-like immune-privileged sites. Despite being recognized as an immunogenic tumor, RCC develops sophisticated and highly effective immune escape mechanisms to counteract host anti-tumor immune responses. This paradoxical coexistence of "immunogenicity" and "immunosuppression" makes RCC a prototypical model for studying tumor immune escape. Furthermore, research in this area has driven major breakthroughs in immunotherapy, notably the advent of immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 axis, which have fundamentally transformed the treatment landscape for advanced RCC.

Recent investigations have revealed that dysregulated autophagy serves as a pivotal player in facilitating immune escape in RCC. Its role is dual-faceted: primarily, autophagy sustains metabolic homeostasis within cancer cells, thereby enhancing their proliferative capacity, stress resilience, and therapy resistance. More critically, autophagy modulates the intricate interactions between tumor cells and the immune system. By influencing antigen presentation, immune cell infiltration, and cytokine secretion, it subsequently suppresses anti-tumor immunity and contributes to resistance against immunotherapies. This review aims to systematically elucidate the molecular mechanisms through which autophagy mediates immune evasion in RCC, specifically focusing on how it shapes an immunosuppressive tumor microenvironment and drives therapeutic resistance. This exploration not only deepens our understanding of RCC pathogenesis but also illuminates promising directions for developing novel combination immunotherapy strategies to overcome the challenge of treatment resistance. Specifically targeting tumor-autonomous autophagy pathways may potentially "unmask" cancer cells by dismantling their immune disguise and reprogramming the tumor immune microenvironment, thereby offering new hope for patients with advanced RCC.

2. The promotional role of autophagy in immune evasion of RCC

2.1. Provision of metabolic support and resistance to immune killing

A fundamental distinction between tumor and normal tissues lies in their metabolic pathways. Tumors typically undergo reprogramming towards a more anabolic metabolic state. Metabolic reprogramming represents a core hallmark of malignancy, enabling sustained proliferation under microenvironmental constraints through dynamic adaptation, thereby regulating tumor initiation and progression [7]. Particularly in ccRCC, metabolic reprogramming driven by VHL loss and consequent constitutive activation of the HIF pathway, coupled with autophagy activation, forms a core network that synergistically promotes immune evasion. This metabolic plasticity is characterized by the coordinated rewiring of glucose, amino acid, lipid, and nucleotide metabolism, resulting in a unique metabolic signature that distinguishes ccRCC from normal tissues. Cancer cells exhibit a high dependence on glycolysis and aerobic glycolysis (the Warburg effect) for ATP generation and the production of biosynthetic precursors, even in the presence of ample oxygen. This leads to intense competition for glucose within the tumor microenvironment (TME) and substantial lactate accumulation, which subsequently acidifies the TME and suppresses anti-tumor immunity [8].

Under metabolic stress, autophagy is markedly activated, degrading intracellular proteins, lipids, and other endogenous components to provide cancer cells with essential energy precursors and biosynthetic building blocks

required for survival and proliferation. The mTOR signaling pathway serves as a central hub integrating nutrient sensing and anabolic processes, whose aberrant activation plays a pivotal role in the dual regulation of protein or lipid synthesis and catabolic reprogramming [9] (**Figure 1**). Specifically, mTORC1 promotes fatty acid synthesis by directly phosphorylating and activating SREBPs. Concurrently, it suppresses lipophagy by inhibiting key autophagy regulators ULK1/ATG13, and downregulates CPT1A, impairing mitochondrial function and thereby inhibiting AMPK-mediated fatty acid β-oxidation. Collectively, these actions lead to characteristic massive cytoplasmic lipid deposition, shaping the classic "clear cell" morphology of ccRCC. The accumulated lipids not only serve as a reservoir for energy and biomembrane synthesis but their derivatives, such as phospholipids and signaling lipids, also function as second messengers, further propagating pro-survival signals, suppressing anti-tumor immunity, and ultimately driving the malignant progression of ccRCC.

Furthermore, amino acid metabolism undergoes significant remodeling. mTORC1 upregulates the expression of glutamine transporters, such as ASCT2/SLC1A5, thereby enhancing glutamine uptake. Intracellular glutamine is converted to glutamate by glutaminase (GLS), which is subsequently utilized to generate α-ketoglutarate (α-KG) for the anaplerotic replenishment of the tricarboxylic acid (TCA) cycle. This process provides carbon skeletons for the synthesis of non-essential amino acids and supports the production of high levels of glutathione (GSH), thereby maintaining redox homeostasis and meeting biosynthetic demands. Concurrently, mTORC1 upregulates key rate-limiting enzymes, including phosphoglycerate dehydrogenase (PHGDH), channeling glucose flux into the serine-glycine-one-carbon metabolic network. This pathway supplies precursors for nucleotide synthesis and helps maintain the NADPH/$NADP^+$ and GSH/GSSG redox balances, directly supporting the rapid synthesis of DNA and RNA in cancer cells [10]. This self-replenishing metabolic reprogramming mechanism grants RCC cells a survival and competitive advantage within the glucose-deprived TME, thereby indirectly impairing the tumor-clearing capacity of immune cells.

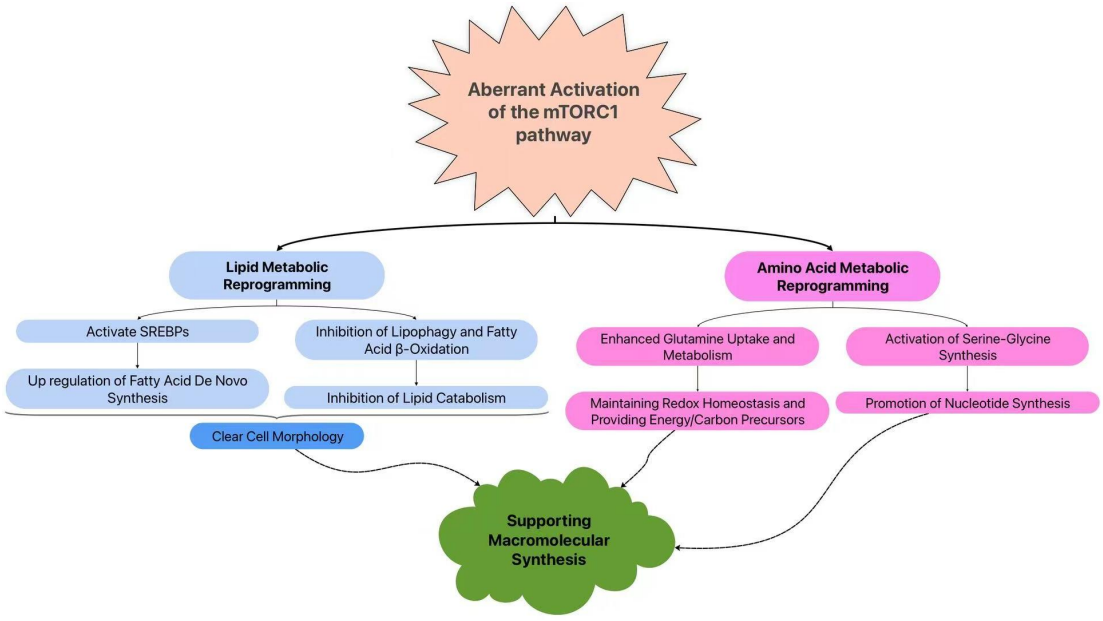

Figure 1. mTOR-mediated metabolic reprogramming inprotein and lipid homeostasis.

Of paramount importance, autophagy can directly suppress anti-tumor immune responses through metabolic regulation. First, aberrantly elevated autophagic activity exacerbates the depletion of critical nutrients, particularly glucose, within the TME, thereby directly impairing the function of effector immune cells such as infiltrating

cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells [11]. The activation and effector functions of these immune cells, including cytokine production and the release of cytotoxic granules, are highly energy-demanding processes that rely heavily on aerobic glycolysis for rapid energy generation. When cancer cells effectively "sequester" and utilize the limited available glucose via autophagy, effector T cells consequently experience "metabolic deprivation," progressively descending into a state of functional exhaustion or anergy. Second, metabolites produced during autophagy, such as lactate, not only directly inhibit the cytotoxic activity and proliferative capacity of T cells and NK cells but also enhance the function of immunosuppressive cells like regulatory T cells (Tregs), further shaping an immunosuppressive microenvironment [12]. Additionally, by selectively clearing damaged mitochondria through mitophagy, autophagy helps maintain the metabolic and redox homeostasis of cancer cells and reduces the production of reactive oxygen species (ROS). This enables RCC cells to evade immunogenic cell death (ICD), which can be triggered by high levels of ROS [13]. This dual activity of autophagy, rooted in nutrient competition and metabolic remodeling, constitutes a pivotal mechanism for immune escape in RCC.

2.2. Modulating the expression of immune checkpoint molecules

Autophagy, an essential intracellular degradation and recycling system, plays a precise regulatory role in the stability, degradation pathways, and membrane localization of key immune checkpoint molecules such as PD-L1 (**Figure 2**). In the TME of RCC, stress signals, including hypoxia and inflammatory cytokines, can concurrently induce both PD-L1 expression and autophagic flux. As a transmembrane protein, PD-L1 undergoes continuous endocytosis and recycling at the plasma membrane. Autophagy directly targets PD-L1 for lysosomal degradation via selective autophagy. This process involves a molecular cascade of "phosphorylation-ubiquitination-recognition": Glycogen synthase kinase 3β (GSK3β) mediates the phosphorylation of PD-L1, which in turn prompts the E3 ubiquitin ligase β-TrCP to catalyze its polyubiquitination. Subsequently, the autophagy adaptor protein p62/SQSTM1 recognizes the ubiquitinated PD-L1 and, through its LC3-interacting region (LIR), docks with LC3 embedded in the autophagosomal membrane. This ultimately loads PD-L1 onto the forming autophagosome for degradation via the autophagosome-lysosome pathway [14]. This classic GSK3β-β-TrCP-p62 ubiquitination-dependent pathway constitutes a fundamental negative regulatory circuit for PD-L1, directly limiting its excessive accumulation on the cell surface. Furthermore, recent research has identified that nucleoporin 2 (NUP2), by interacting with the intracellular domain of PD-L1, anchors it at the plasma membrane, thereby impeding its degradation via the conventional endosome-lysosome pathway. Autophagy activation can alleviate this membrane anchoring by degrading NUP2, consequently promoting PD-L1 internalization and its subsequent degradation via the autophagosome-lysosome pathway [15].

However, a more prevalent and critical mechanism is that autophagy indirectly stabilizes PD-L1 and promotes its membrane localization by maintaining cellular homeostasis. When inflammatory signals, such as interferon-gamma (IFN-γ), strongly induce PD-L1 transcription and synthesis, this often triggers endoplasmic reticulum (ER) stress, leading to the accumulation of misfolded or unfolded proteins. Under these conditions, basal autophagy is feedback-activated, effectively alleviating ER stress and averting global translational inhibition or apoptosis. Thereby, it creates a favorable intracellular environment for the efficient synthesis, proper folding, and subsequent trafficking of PD-L1 [16]. Concurrently, inflammatory cytokines like IFN-γ can also modulate the endocytosis and sorting efficiency of PD-L1. PD-L1 undergoes a continuous dynamic cycle of "internalization-sorting-recycling" between the plasma membrane and endosomal compartments. After internalization into early

endosomes via clathrin-dependent or -independent endocytosis, the majority of PD-L1 is sorted into recycling endosomes under the regulation of Rab GTPases (such as Rab4, Rab11) and is transported back to the cell surface via vesicular trafficking, thereby maintaining its immune checkpoint function. The remaining fraction enters late endosomes, where it is targeted for lysosomal degradation through the formation of multivesicular bodies and the ubiquitin-recognition and sorting machinery of the endosomal sorting complex required for transport (ESCRT) system, constituting another core negative regulatory pathway for PD-L1 [17]. By participating in the regulation of the endocytic-lysosomal system, autophagy can influence the post-internalization fate of PD-L1. For instance, autophagosomes can directly fuse with endosomes or multivesicular bodies to form amphisomes, thereby promoting PD-L1 degradation; conversely, dysfunctional autophagy may disrupt its normal cycling [18]. Furthermore, by clearing dysfunctional proteins, autophagy indirectly sustains the efficacy of molecular chaperone systems, such as heat shock protein HSP90, which in turn enhances PD-L1 stability [19]. These mechanisms collectively consolidate the pivotal role of autophagy in tumor immune escape.

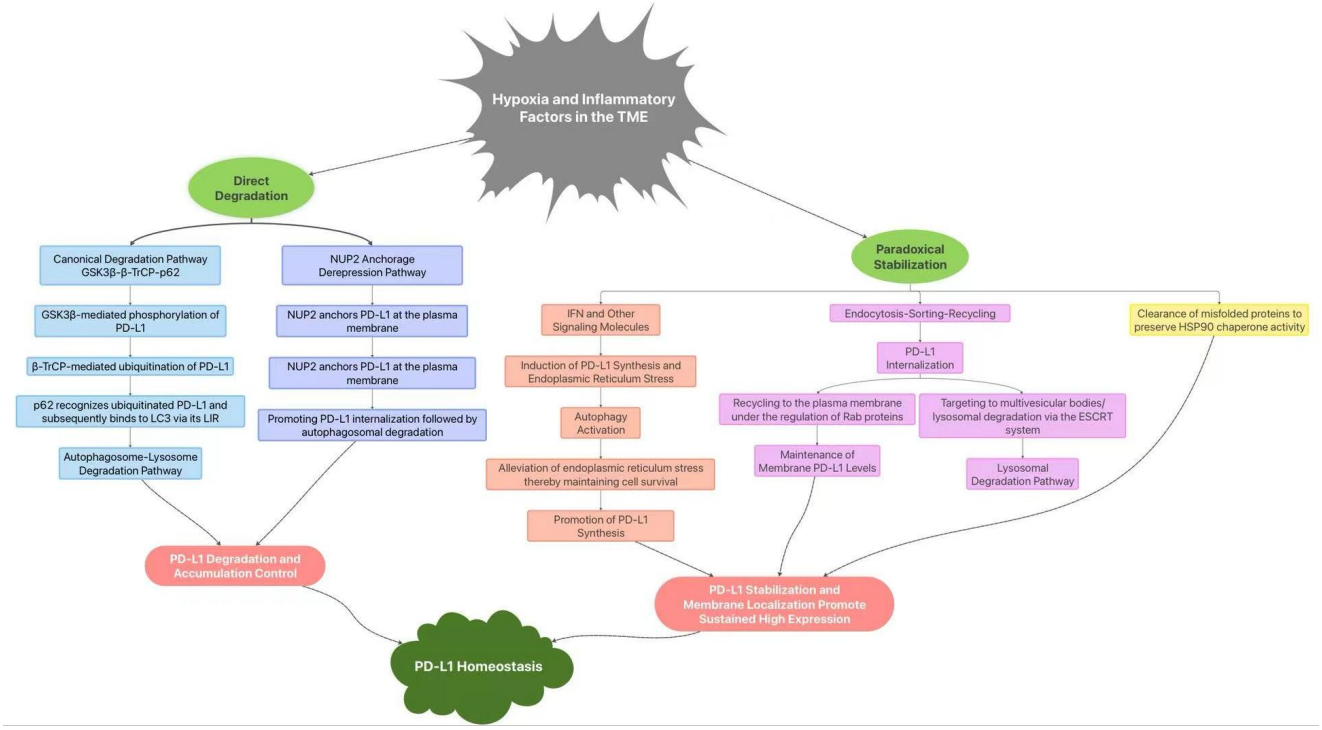

Figure 2. Autophagy-mediated tripartite regulation of PD-L1.

In RCC, characteristic genetic mutations or deletions and autophagic activity converge to form a core regulatory network that mutually reinforces and collectively drives tumor immune escape. The deletion or inhibition of autophagy-related genes (such as ATG7, Beclin-1) exacerbates the unfolded protein response and increases apoptotic susceptibility, providing counterevidence that basal autophagy is critical for maintaining RCC cell survival and PD-L1 protein homeostasis [20,21]. In ccRCC, the loss of function of VHL, a key component of an E3 ubiquitin ligase complex, leads to constitutive activation of HIF-α under normoxic conditions. This not only transcriptionally upregulates PD-L1 expression but also cooperatively enhances autophagic flux [22]. Specifically, HIF-1α directly binds to hypoxia-response elements in the promoter regions of multiple autophagy-related genes, leading to the transcriptional upregulation of core autophagic components, including BNIP3, BNIP3L/NIX, ATG5, and LC3. Among these, BNIP3 and BNIP3L function as pro-autophagic proteins that directly initiate

autophagy by disrupting the inhibitory complex between Beclin 1 and Bcl-2 [23]. Consequently, HIF-α signaling and autophagy activation establish a positive feedback loop, which collaboratively shapes an immunosuppressive tumor microenvironment conducive to the stable high expression of PD-L1. This effectively shields tumor cells from CTL-mediated attack and reinforces their immune evasion capability.

Consequently, autophagy regulates PD-L1 in a seemingly paradoxical, "double-edged sword" manner. On one hand, it directly degrades PD-L1 to prevent its aberrant accumulation and subsequent over-activation of immune recognition. On the other hand, it functions as a cellular "stabilizer," establishing a dynamic "degrade-first, sustain-later" homeostatic balance. This mitigates excessive endogenous stress that could trigger cell death, thereby indirectly facilitating the sustained high expression of PD-L1. Under the persistent stress of TME, the latter pro-survival function often predominates. By ensuring the stable expression and membrane localization of PD-L1, autophagy maximizes its binding efficiency with the PD-1 receptor on T cells, ultimately promoting tumor immune escape.

2.3. Impacting the processing and presentation of tumor antigens

2.3.1. Metabolic exhaustion of antigenic substrates

Autophagy constitutively degrades intracellular protein components, directly depleting the pool of antigenic peptides available for MHC class I presentation. Within the unique metabolically stressed microenvironment of RCC, aberrantly activated autophagic flux, via pathways such as macroautophagy and chaperone-mediated autophagy, extensively degrades endogenous tumor antigens, significantly reducing the substrate availability for proteasomal antigen processing [24]. This clearance of "antigenic precursors" leads to a drastic reduction in the quantity of peptides transported into the ER lumen by the transporter associated with antigen processing (TAP). Consequently, the efficiency of TAP-dependent peptide loading within the ER is markedly diminished, ultimately resulting in the exhaustion of antigenic resources at their source.

2.3.2. Functional disruption of the antigen processing machinery

At the level of antigenic peptide transport, p62/SQSTM1-mediated selective autophagy recognizes and targets the ubiquitinated TAP1/TAP2 heterodimer, directly impairing the peptide-translocating capacity of the ER membrane. Studies have confirmed that in VHL-deficient RCC cells, the turnover rate of the TAP complex is accelerated and positively correlates with enhanced autophagic flux [25]. Regarding antigenic peptide processing, the endoplasmic reticulophagy (ER-phagy) pathway, via the Sec62 receptor, recognizes aberrantly folded ERAP1/2, leading to their autophagic degradation. This results in abnormal C-terminal trimming of antigenic peptides, generating peptide fragments with lengths incompatible with the binding groove of MHC class I molecules, significantly reducing the stability of the pMHC complex [26]. Concurrently, autophagy disrupts the assembly of the peptide-loading complex (PLC): calnexin is cleared via ER-phagy, endoplasmic reticulum oxidoreductase 1 alpha (ERp57) is degraded through the CMA pathway, and the ubiquitination of tapasin promotes its binding to p62, enhancing its autophagic degradation [27]. At the proteasomal level, autophagy selectively removes immunoproteasome subunits PSMB8, PSMB9, and PSMB10, promoting the dominance of standard proteasome subunits. This alters the cleavage specificity of antigenic peptides, shaping their C-terminal anchor residue characteristics to favor immune escape [28].

At the transcriptional regulatory level, autophagy synergizes with HIF-1α: by degrading histone deacetylase 4 (HDAC4), it alters chromatin accessibility, maintains HIF-1α stability, and enhances its binding to the MHC-I promoter region. Concurrently, autophagy suppresses MHC-I translation efficiency via the mTOR-4EBP1 pathway. These concerted actions ultimately disrupt the proper formation of the MHC-I heavy chain–β2-

microglobulin dimer [29]. At the endoplasmic reticulum-to-Golgi transport stage, autophagy disrupts the normal trafficking of MHC-I molecules through a dual mechanism: it degrades the Sec23/Sec24 complex to hinder COPII vesicle transport by modulating Rab GTPase activity, and it captures transport vesicles at ER exit sites via the interaction of ATG8 proteins with ERGIC53 [30].

2.3.3. Coordinated control of MHC class I stability and membrane trafficking

Autophagy cooperatively reduces the surface abundance of MHC class I molecules through dual direct and indirect mechanisms. The direct pathway is characterized by the recognition of newly synthesized MHC class I heavy chains in the ER via the ER-phagy pathway [31], in which p62/SQSTM1-mediated selective autophagy plays a pivotal role. The indirect pathway operates through the regulation of membrane protein recycling: MHC class I molecules already expressed on the cell surface undergo clathrin-dependent endocytosis into early endosomes and are subsequently degraded through the aforementioned "endocytic-lysosomal" system. This process significantly diminishes the pool of functional MHC class I molecules available for recycling back to the plasma membrane, leading to impaired antigen presentation capacity. Ultimately, this weakens the specific recognition of tumor antigens by $CD8^+$ T cells via the T cell receptor (TCR) and their subsequent immune activation [32].

In summary, in RCC, autophagy synergistically inhibits MHC class I-mediated antigen presentation through multiple mechanisms. On one hand, by regulating the HIF-α and mTOR signaling pathways, it drives metabolic reprogramming, leading to the accumulation of aberrant proteins, which in turn negatively regulate the expression levels of molecules associated with antigen processing. On the other hand, the selective clearance of damaged organelles such as mitochondria reduces the release of tumor-associated antigens and damage-associated molecular patterns (DAMPs), thereby limiting the generation of immunogenic signals. These mechanisms collectively result in a significant reduction in the density of MHC-I-antigen peptide complexes on the surface of tumor cells, impair the recognition and activation of $CD8^+$ T cells, and ultimately promoting tumor immune escape.

2.4. Shaping the immunosuppressive tumor microenvironment

In the immunosuppressive TME of RCC, autophagy induces T cell exhaustion and promotes tumor immune escape. First, autophagy exerts dual regulation on PD-L1: on one hand, it degrades excessively accumulated PD-L1 via p62-mediated selective autophagy; on the other hand, it ensures its continuous synthesis by maintaining cellular proteostasis, ultimately achieving stable expression of PD-L1 on the tumor cell surface. This dynamic equilibrium enables PD-L1 to persistently engage with the PD-1 receptor on T cells, initiating an SHP2-mediated phosphorylation cascade that inhibits the activation of key TCR signaling molecules (such as ZAP70, PKCθ) [33–35], thereby impeding T cell proliferation and effector functions. Second, autophagy-activated RCC cells upregulate indoleamine 2,3-dioxygenase (IDO) expression through enhanced tryptophan metabolic reprogramming, leading to tryptophan depletion and accumulation of kynurenine metabolites in the microenvironment [36]. Tryptophan deficiency activates the GCN2 kinase, triggering the integrated stress response and inhibiting T cell proliferation [37]; while kynurenine promotes T cell apoptosis and drives Treg cell differentiation via the aryl hydrocarbon receptor (AhR) signaling pathway [38]. Concurrently, autophagy-mediated activation of the ATP-adenosine metabolic pathway results in extracellular adenosine accumulation, which suppresses T cell receptor signaling through A2A receptor activation [39]. Third, autophagy promotes the infiltration of Treg cells into the TME by regulating the secretion of chemokines such as CCL22 and TGF-β [40-41]. Autophagy deficiency experiments have confirmed that ATG5 knockout significantly reduces the immunosuppressive function of Treg cells [42]. Furthermore, autophagy

maintains the metabolic adaptability of M2-type tumor-associated macrophages (TAMs) through mitochondrial quality control, facilitating the sustained secretion of immunosuppressive factors like IL-10 and TGF-β [43]. Fourth, autophagy, in conjunction with persistent antigen exposure and the inhibitory microenvironment, induces epigenetic alterations in T cells. Histone modification analyses reveal significant changes in chromatin accessibility at key genetic loci of exhausted T cells, accompanied by reprogramming of transcription factor expression profiles (such as TCF1, TOX), leading to a gradual loss of memory phenotype and stable acquisition of exhaustion characteristics [44]. Finally, autophagy, by regulating nutrient competition within the TME, impairs mitochondrial biogenesis in T cells. Exhausted T cells exhibit reduced mitochondrial mass, decreased membrane potential, and accumulated ROS, with insufficient ATP production directly affecting the bioenergetic supply required for T cell activation. The PGC1α-mediated mitochondrial biogenesis pathway is persistently suppressed, further exacerbating T cell functional exhaustion [45]. These mechanisms collectively form an autophagy-driven positive feedback loop: the autophagy-maintained immunosuppressive microenvironment promotes T cell exhaustion, while functionally exhausted T cells are unable to effectively eliminate tumor cells with enhanced autophagic activity, ultimately resulting in a vicious cycle of immune escape in RCC.

Beyond inducing $CD8^+$ T cell exhaustion as described above, autophagy remodels the TME through multiple additional mechanisms, coordinately regulating the functional states of tumor-infiltrating immune cells. At the level of Treg cells, autophagy activation enhances their CTLA-4-mediated suppression of dendritic cell (DC) function and their secretion of IL-10/TGF-β, further impairing effector T cell function [46]. In myeloid immune cells, autophagy maintains the oxidative metabolic advantage of M2-type TAMs by clearing damaged mitochondria and promotes the secretion of immunosuppressive factors such as CCL2 and IL-10 via modulation of the HIF-1α/NF-κB signaling axis, thereby driving TAM polarization towards the M2 phenotype [47]. Concurrently, autophagy stabilizes the immunosuppressive function of myeloid-derived suppressor cells (MDSCs) by enhancing the expression of arginase-1 and inducible nitric oxide synthase (iNOS), thus reinforcing their ROS/NO-dependent T cell suppression capacity [41]. Regarding DC, autophagy deficiency can impair lysosomal stability and reduce the efficiency of MHC class II antigen presentation [32]. Furthermore, autophagy weakens DC cross-presentation efficiency and type I interferon production by modulating the STING-IRF3 signaling pathway, affecting their maturation status and immunostimulatory capacity [48]. Metabolically, autophagy-driven glutaminolysis and fatty acid oxidation intensify nutrient competition within the microenvironment, limiting the biosynthesis and signal transduction of immune cells. Additionally, autophagy finely regulates the secretion dynamics of key cytokines like IL-1β and IL-18 by modulating NLRP3 inflammasome activity and the proteolytic processing of TGF-β precursors [49]. These mechanisms collectively constitute an autophagy-centric immunoregulatory network. By directly intervening in immune cell function and indirectly reshaping microenvironmental properties, they synergistically promote the process of immune escape in RCC.

3. The enhancing role of autophagy in immune surveillance against RCC

3.1. Induction of immunogenic cell death

In RCC, the regulation of ICD by autophagy exhibits a homeostatic, biphasic nature. Under basal conditions, autophagy attenuates therapy-induced immunogenicity by maintaining cellular homeostasis; whereas under specific stress conditions, it synergistically enhances immune surveillance efficacy through multiple mechanisms. Specifically, autophagy promotes the specific translocation of calreticulin (CRT) from the endoplasmic reticulum

lumen to the cell surface by regulating ER-mitochondria interactions, thereby enhancing DC recognition and phagocytosis of RCC cells [50]. Concurrently, autophagy-mediated programmed secretion of ATP activates the purinergic receptor P2RX7, promoting NLRP3 inflammasome assembly and IL-1β maturation, thereby optimizing the formation of an inflammatory microenvironment [51]. Regarding the release of DAMPs, autophagy limits excessive ROS production by selectively clearing damaged mitochondria, ensuring the timed release of high mobility group box 1 (HMGB1) during the paraptosis phase. The released HMGB1, upon binding to Toll-like receptor 4 (TLR4), effectively promotes DC maturation and antigen presentation efficacy [52]. In antigen quality control, autophagy optimizes the antigen repertoire by regulating the degradation balance of immunogenic proteins, selectively retaining highly immunogenic antigen fragments while clearing immunosuppressive protein components. This enhances DC cross-presentation efficiency and promotes the activation of tumor-specific $CD8^+$ T cells. Furthermore, autophagy maintains intracellular energy homeostasis, preventing ATP depletion-induced secondary necrosis and promoting immunogenic apoptosis. This death modality calibration ensures the orderly release of immunogenic signals, averting immune tolerance caused by cytokine storms [53].

It is noteworthy that within the unique context of VHL-deficient RCC, the constitutive activation of the HIF-α signaling pathway can upregulate regulators such as BNIP3, enhancing mitophagy efficiency and further optimizing the quality control of immunogenic cell death [54]. This finely calibrated immunogenic cell death program, orchestrated by autophagy, not only preserves essential intracellular homeostasis but also maximizes the activation of the antitumor immune response.

3.2. Restricting tumor-associated inflammation

In the context of tumor-associated inflammation, chronic inflammatory factors induce the accumulation and activation of MDSCs and M2-type TAMs, while promoting the proliferation and function of Treg cells, through the activation of STAT3 and NF-κB signaling pathways. This inflammatory milieu also upregulates the expression of immune checkpoint molecules such as PD-L1 and fosters angiogenesis and tissue remodeling. Furthermore, inflammatory mediators collectively establish an immunosuppressive microenvironment by interfering with antigen presentation and inducing T cell exhaustion, ultimately undermining the antitumor immune response and promoting tumor progression.

Autophagy, however, precisely regulates RCC-associated inflammation through multi-layered mechanisms, thereby fostering a microenvironment conducive to immune surveillance. Firstly, by selectively clearing damaged mitochondria and intracellular debris, autophagy significantly reduces the release of inflammasome activators such as ROS and mitochondrial DNA (mtDNA), effectively curbing the overactivation of the NLRP3 inflammasome. This leads to decreased maturation and secretion of pro-tumorigenic inflammatory cytokines like caspase-1-dependent IL-1β and IL-18, thereby blocking the amplification cascade of pro-tumor inflammatory signaling [55].

At the molecular pathway level, p62-mediated selective autophagy facilitates the lysosomal degradation of key components of the NF-κB signaling pathway, such as the IκB kinase complex. Concurrently, autophagy suppresses persistent STAT3 phosphorylation by maintaining cellular homeostasis, significantly reducing the production of pro-inflammatory cytokines like IL-6 and IL-11 [56], thereby effectively inhibiting chronic inflammation-driven tumor proliferation.

In the VHL-deficient RCC microenvironment, autophagy remodels the expression gradient of CXCL1/CXCL5 and CXCL9/CXCL10 chemokines by balancing HIF-2α stability. This promotes the infiltration of CTLs into the tumor core while restricting the excessive accumulation of neutrophils and monocytic myeloid cells [57],

optimizing the spatial distribution of antitumor immune cells.

Moreover, autophagy restricts the sustained release of DAMPs like HMGB1 and ATP, preventing TLR4- and P2X7 receptor-mediated chronic inflammatory responses [58], and averting DC dysfunction and T cell immune tolerance.

Finally, autophagy degrades hypoxia-inducible factors in M2-type TAMs, suppressing the expression of ARG1 and vascular endothelial growth factor (VEGF), while concurrently modulating tryptophan metabolism to reduce the abnormal accumulation of kynurenine. These actions collectively reverse the immunosuppressive inflammatory environment. This strategy not only controls the damaging effects of tumor-promoting inflammation but also preserves the alarm signals necessary for antitumor immunity, ultimately enhancing the body's immune surveillance capability against RCC.

3.3. Eradication of oncogenic viruses

Epidemiological studies have established a significant association between chronic infections, such as Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV), and an increased risk of RCC development [59,60]. Viral oncoproteins, exemplified by the HBV-encoded HBx protein, promote tumorigenesis by interfering with the functions of key tumor suppressor proteins, including p53 and Rb, thereby inducing genomic instability and dysregulation of the cell cycle [61].

Within this context, autophagy directly recognizes and encapsulates intracellular viral particles and viral proteins via the xenophagy pathway, targeting them for lysosomal degradation [62]. This process significantly reduces the intracellular viral antigen burden and blocks the sustained activation of virus-associated oncogenic signaling pathways. Furthermore, by maintaining mitochondrial membrane integrity, autophagy prevents aberrant mtDNA release, thereby suppressing hyperactivation of the cGAS-STING pathway. Simultaneously, by clearing damaged endosomal membranes, it enhances the oligomerization of the MAVS protein in the RLR signaling pathway, promoting a type I interferon response [63]. These mechanisms collectively optimize the antiviral immune response.

In terms of inflammation regulation, autophagy selectively degrades viral nucleic acid fragments, limiting the sustained activation of pattern recognition receptors and preventing hyperactivation of the NF-κB signaling pathway. This significantly reduces the aberrant secretion of pro-inflammatory factors such as IL-6 and TNF-α, effectively halting the progression of virus-associated chronic inflammation toward malignant transformation [64]. Reportedly, autophagy promotes the efficient loading of viral antigenic peptides onto MHC class I molecules by optimizing the processing of viral antigens and enhancing the cross-presentation capacity of DCs. Thereby, it facilitates the activation and clonal expansion of virus-specific $CD8^+$ T cells [65], strengthening immune surveillance against virus-infected cells. Another study revealed that autophagy degrades components of the virus-activated NLRP3 inflammasome, controlling the aberrant release of pro-carcinogenic factors like IL-1β. Simultaneously, through metabolic reprogramming, it sustains the long-term survival of virus-specific memory T cells, establishing durable immune surveillance capabilities. These defensive mechanisms collectively block the malignant transformation pathways of virus-associated RCC. Consequently, autophagy, via multiple routes including clearance of oncogenic viruses, precise regulation of antiviral immunity, and optimization of immunological memory, significantly enhances the body's immune surveillance capacity against RCC.

4. Synergistic autophagy and immunotherapy

Although ICIs have demonstrated significant clinical success in various cancers, their application in RCC therapy continues to face substantial challenges, including limited response rates and acquired resistance. Recent research has revealed that autophagy, a core regulatory mechanism of cellular homeostasis, plays a dual role in shaping the TME and facilitating immune escape in RCC. On one hand, autophagy promotes immune tolerance by degrading MHC class I molecules and tumor antigens, thereby impairing antigen presentation efficiency, and through various mechanisms such as regulating PD-L1 stability, mediating T cell metabolic reprogramming, and enhancing the function of immunosuppressive cells. On the other hand, its role in maintaining the stress adaptability of tumor cells also offers potential targets for enhancing anti-tumor immune responses. This functional duality has spurred in-depth exploration of synergistic strategies that combine autophagy targeting with immunotherapy.

4.1. Evidence from preclinical studies

In RCC xenograft models, autophagy inhibitors (such as chloroquine derivatives) induce transient accumulation of PD-L1 on the tumor cell surface by blocking its lysosomal degradation pathway [66]. This dynamic process, characterized by an initial increase followed by a subsequent decrease, significantly prolongs the therapeutic window for ICIs such as anti-PD-1/PD-L1 antibodies. Concurrently, autophagy inhibition stabilizes MHC class I molecule expression, enhancing the recognition and activation of tumor antigen-specific T cells, and markedly improves the response rate to PD-1 blockade therapy [67]. In terms of TME remodeling, autophagy modulation reduces cancer cell dependence on fatty acid oxidation by inhibiting mitophagy, thereby reversing the metabolically suppressed state of $CD8^+$ T cells. Furthermore, by obstructing amino acid recycling pathways, it restricts the nutrient competitive advantage of tumor cells, improves the metabolic fitness of T cells, and modulates the adenosine metabolic pathway to reduce extracellular adenosine accumulation, thereby alleviating the suppression of T cell function [68].

Further investigations in genetically engineered mouse models have revealed that autophagy inhibitors significantly enhance radiotherapy/chemotherapy-induced immunogenic cell death and promote DC cross-presentation. The underlying mechanism involves the modulation of the STING signaling pathway to augment type I interferon responses, thereby promoting T cell infiltration into tumor sites. Concurrently, by inhibiting the autophagy-dependent function of Tregs cell, they effectively alleviate the immunosuppressive microenvironment [69]. Single-cell RNA sequencing analyses confirmed that the combination therapy significantly reduces the expression levels of T cell exhaustion markers (such as TIM-3, LAG-3), maintains the activity of key transcription factors in effector T cells, and promotes the expansion of stem-like T cell subsets, thereby establishing durable antitumor immune memory [41].

These systematic preclinical investigations comprehensively elucidate the synergistic effects of the combination therapy, spanning from molecular mechanisms to cellular dynamics. They provide a solid theoretical foundation and experimental support for advancing clinical trials of autophagy-targeting agents combined with immunotherapy.

4.2. Active clinical trials

Multiple ongoing clinical trials are systematically evaluating the synergistic effects and clinical benefits of combining autophagy inhibitors (hydroxychloroquine/HCQ, chloroquine/CQ) with ICIs in advanced RCC. A representative Phase II clinical study (NCT04028245) demonstrated that the combination of HCQ and nivolumab was manageable in safety profile for patients with pretreated metastatic clear cell RCC, achieving an

objective response rate (ORR) of 35%. Furthermore, the PD-L1 positive subgroup exhibited a degree of benefit significantly superior to historical data from monotherapy with immune checkpoint inhibitors [66]. Mechanistic exploration revealed that the combination therapy group showed an increased density of $CD8^+$ T cell infiltration and a decreased proportion of regulatory Tregs cells within the TME. These changes were accompanied by the accumulation of the autophagy marker p62 and alterations in PD-L1 membrane expression patterns, providing evidence that autophagy inhibition likely enhances treatment efficacy by modulating immune cell balance and checkpoint molecule expression.

Another Phase Ib study (NCT04314137) confirmed that the regimen combining CQ with pembrolizumab significantly increased the density of tumor-infiltrating $CD8^+$ T cells while reducing the proportion of MDSCs [33]. Multi-omics analysis revealed a dual mechanism of action: the autophagy inhibitor, on one hand, prolongs the duration of action of ICIs by blocking the lysosomal degradation pathway of PD-L1; on the other hand, it improves the metabolic fitness of T cells by modulating tryptophan and arginine metabolism within the TME. Single-cell RNA sequencing (scRNA-seq) results further validated that the combination therapy significantly downregulated the expression of T cell exhaustion markers and concurrently promoted the expansion and functional maintenance of stem-like T cell subsets.

Notably, radiomics-based predictive models have demonstrated significant potential for clinical application in this field. Computed tomography (CT) radiomics analysis revealed a significant correlation between tumor texture features on pre-treatment contrast-enhanced CT scans and autophagy-related gene expression profiles [70]. This finding provides a novel biomarker strategy for screening potential beneficiaries through non-invasive imaging methodologies. These preliminary findings collectively indicate that autophagy modulation can effectively enhance the anti-tumor activity of ICIs in advanced RCC, establishing a solid theoretical foundation and clinical rationale for understanding the central role of autophagy in tumor-immune interactions and for developing novel combination therapeutic strategies.

However, the precise clinical implementation of this combination strategy requires reliable biomarkers to guide patient selection and dose optimization, particularly through stratification based on tumor autophagy activity. Currently, multiple confirmatory clinical trials, including Phase III randomized controlled studies, are underway. These trials aim to further elucidate the clinical value and optimal application modalities of this combination therapy, thereby providing more robust evidence-based medical support for the establishment of personalized treatment strategies.

4.3. Current challenges and future perspectives

Currently, although autophagy inhibitors show significant therapeutic potential in RCC, their clinical translation in combination with ICIs faces multiple challenges. First, cancer cells develop adaptive resistance through complex mechanisms, including the activation of ULK1-independent alternative autophagy pathways and enhanced proteasome activity to compensate for autophagy inhibition [71]. Furthermore, tumor heterogeneity leads to spatial variations in autophagy dependency, with some subclones maintaining an immunosuppressive microenvironment via alternative signaling pathways such as Wnt/β-catenin [72]. Second, techniques for dynamically monitoring autophagic flux remain suboptimal, hindering precise patient stratification. Existing biomarkers like LC3B-II/p62 detection by immunohistochemistry are significantly limited by tumor sampling bias and spatiotemporal heterogeneity [73], while the specificity and sensitivity of novel PET tracers such as [^{18}F]FEBTS require further validation [74]. Third, a pharmacokinetic-pharmacodynamic (PK-PD) mismatch creates a “therapeutic window

dilemma." Autophagy inhibitors often fail to reach effective concentrations in tumor tissues comparable to those in preclinical studies, while dose-limiting toxicities (such as retinopathy, gastrointestinal effects) restrict long-term dosing. Conversely, intermittent dosing may result in incomplete autophagy suppression [75]. Fourth, autophagy inhibition may trigger compensatory immunosuppressive mechanisms, including upregulation of indoleamine 2,3-dioxygenase (IDO1), compensatory proliferation of regulatory Tregs cells, and remodeling of the ATP-adenosine pathway [12], potentially undermining the sustained efficacy of combination therapy. Fifth, preclinical models have species-specific limitations. Existing mouse models cannot fully recapitulate the complexity of the human TME, and patient-derived organoids often fail to reconstitute a complete TME. Sixth, autophagy inhibitors may exacerbate immune-related adverse events (irAEs), particularly by impairing autophagy-dependent intestinal epithelial barrier function and disrupting cardiomyocyte homeostasis, thereby increasing the risk of gastrointestinal toxicity and myocarditis [76], further narrowing the therapeutic window. These challenges urgently need to be addressed through the development of tumor-targeted inhibitors, the establishment of dynamic monitoring systems, and the optimization of clinical trial designs.

Future clinical research on combination therapy targeting autophagy and immunotherapy should focus on establishing a multi-dimensional precision treatment system. The primary task is to develop an autophagy activity grading system based on multi-omics profiling, integrating transcriptomic (autophagy-related gene expression signatures), proteomic (LC3-II/p62 ratio), and metabolomic (amino acid metabolic profiles) data to construct mathematical models predictive of treatment response [77]. Concurrently, dynamic monitoring of plasma autophagosome-related markers via liquid biopsy techniques should be implemented to enable real-time efficacy assessment. Secondly, significant efforts should be directed toward developing novel tissue-specific autophagy modulators. This includes selective ULK1/2 inhibitors targeting the autophagy initiation phase, allosteric VPS34 inhibitors [42], tumor-targeted nanocarrier delivery systems [48], and dual-functional molecules capable of simultaneously targeting autophagy pathways and immune checkpoints [78]. Third, there is a need to optimize chronotherapeutic strategies based on the oscillatory patterns of autophagy. This involves exploring sequential therapies with epigenetic modulators (such as HDAC inhibitors, DNMT inhibitors) [79], multi-targeted approaches combining metabolic regulators (such as IDO inhibitors, adenosine receptor antagonists), and spatiotemporally synergistic protocols integrating localized treatments such as radiotherapy and oncolytic virotherapy.

Concurrently, the biomarker platform should be refined by developing molecular imaging biomarkers such as specific autophagy-targeting PET probes, digital pathology biomarkers based on artificial intelligence (AI) analysis of spatial distribution of tumor-infiltrating lymphocytes, immunometabolic biomarkers detecting metabolic fitness of peripheral blood T cells, and microbiome biomarkers reflecting the association between gut microbiota and autophagy activity. In terms of clinical trial design, adaptive platform trials should be adopted, incorporating enrichment designs based on patient selection using autophagy signatures, basket designs for cross-cancer investigation of autophagy dependency, umbrella designs for parallel evaluation of multi-target inhibitors, and integration of real-world data for long-term efficacy and safety monitoring.

Furthermore, single-cell multi-omics technologies should be employed to deeply decipher the evolutionary dynamics of resistant clones, with a focused investigation into key mechanisms such as the autophagy-apoptosis switch, compensatory mitochondrial quality control pathways, immune editing-driven alterations in antigen presentation, and the autophagy dependency of cancer stem cells. A predictive and management system for specific toxicities must be established, encompassing screening for retinal toxicity-associated gene polymorphisms, detection of early biomarkers for cardiotoxicity, preventive interventions modulating gut microbiota, and

computational models for individualized dosing regimens. By integrating breakthroughs in basic research with the demands of clinical practice, a novel paradigm of autophagy-based precision immunotherapy can be established, specifically addressing core challenges including tumor heterogeneity, the narrow therapeutic window, and the evolution of drug resistance, ultimately maximizing the clinical value of combination therapeutic strategies.

5. Conclusion

This review systematically elucidates the core mechanistic roles and research advancements of autophagy in immune escape in RCC. Compelling evidence indicates that autophagy plays a "context-dependent" dual role during RCC progression: it may exert a tumor-suppressive function in the early stages of tumorigenesis, whereas its pro-survival and immunosuppressive functions become predominant within the established TME. Specifically, autophagy coordinately promotes the immune escape process in RCC through multiple pathways, including the precise regulation of immune checkpoint molecule dynamics such as PD-L1, limiting the efficiency of antigen processing and presentation, remodeling the metabolic microenvironment, and inducing T cell functional exhaustion.

Regarding future research directions, several priorities emerge. First, there is a need to integrate cutting-edge technologies like multi-omics with novel model systems such as patient-derived organoids to deeply delineate the specific regulatory networks of autophagy pathways across different RCC subtypes and within various TME cell populations. Second, research should focus on investigating the crosstalk mechanisms between autophagy and other modes of cell death, such as pyroptosis and ferroptosis, in immune regulation, aiming to clarify the molecular basis of how coordinated multi-modal cell death regulates anti-tumor immune responses. Finally, there is an urgent need to advance the clinical translation of personalized treatment strategies. This can be achieved by establishing dynamic monitoring systems for autophagy activity, developing highly selective autophagy modulators, and strategically integrating them with existing immunotherapeutic regimens. These efforts are expected to provide novel therapeutic paradigms for overcoming immunotherapy resistance in RCC.

In summary, a deeper dissection of the autophagy-immune regulatory network and its precise intervention will open new avenues and strategies in the field of RCC immunotherapy, ultimately realizing the goal of personalized treatment based on the precise stratification of autophagy activity.

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