Impact of inflammation and immunotherapy in renal cell carcinoma (Review)

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Abstract. Substantial research attention has been directed at exploring the mechanisms and treatment of renal cell carcinoma (RCC). Indeed, the association between inflammation and tumor phenotypes has been at the center of cancer research. Concomitant with research on the inflammation response and inflammatory molecules involved in RCC, new breakthroughs have emerged. A large body of knowledge now shows that treatments targeting inflammation and immunity in RCC provide substantial clinical benefits. Adequate analysis and a better understanding of the mechanisms of inflammatory factors in the occurrence and progression of RCC are highly desirable. Currently, numerous RCC treatments targeted at inflammation and immunotherapy are available. The current review describes in detail the link between inflammation and RCC.

Contents

1. Introduction

Renal cell carcinoma (RCC) originates from the renal parenchyma and is the most common subtype of kidney cancer (1). According to 2018 GLOBOCAN data, RCC accounts for up to 2.4% of all cancer cases, with an estimated 338,000 patients diagnosed globally each year (2). It has been shown that 25-30% of affected patients have metastatic disease and therefore poor survival outcomes (3). Surgery remains the most effective treatment for both localized and locally advanced RCC, with those patients with RCC who receive surgical excision showing a good prognosis. However, the total recurrence rate after surgical resection is high, estimated at 35% (4).

Although there is now a greater understanding of the occurrence and development of RCC based on previous research, the clinical prognosis of patients with regard to the biological behavioral characteristics of RCC is still unsatisfactory. In recent years, the association between inflammation and tumors has become the focus of cancer research. Inflammation is a fundamental innate immune response to perturbed tissue homeostasis (5). Numerous studies have shown that inflammatory molecules and pathways play an important role in the development of cancer, such as breast cancer, pancreatic cancer, colorectal cancer, colon cancer, rectal cancer, prostate cancer, bladder cancer, lung cancer and ovarian cancer (6-8). Inflammation is highly associated with RCC, and participates in the development of RCC tumors, which are considered to be immunogenic (9,10). The present review summarizes the main inflammatory response features in RCC, focusing primarily on immune-related molecules and immunotherapy to elucidate the association between inflammation and RCC, and its role in the treatment of RCC.

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2. Close association of inflammation with the occurrence and development of cancer

Inflammation is considered a hallmark of cancer development. It is estimated that potential infections and inflammatory responses contribute to 15-20% of cancer-associated deaths globally (11). Evidence shows that the inflammatory response plays a vital role in the occurrence and development of tumors (12). Inflammatory bodies, cytokines, chemokines, transcription factors and immune cells drive the inflammatory tumor microenvironment (TME) through multiple inflammation-associated pathways. It is now increasingly being recognized that inflammation is inextricably linked to cancer (5,13,14). Growth factors alter endocytosis and receptor cycling in cancer cells through several pathways, inhibition of negative feedback mechanisms that attenuate growth and enhancement of receptor-like tyrosine kinases to enrich proliferation-related downstream signaling (15). These changes increase genetic mutations and anti-apoptotic signaling, and promote angiogenesis, thereby promoting cancer progression (6,16,17).

3. Role and mechanism of inflammation in the development of RCC

Inflammation is the natural defense mechanism of the body against microbial infection and other noxious stimuli, which inevitably cause tissue damage. Inflammatory cells accumulate at the site of injury, secrete a large amount of inflammatory mediators, promote tissue breakdown and enhance the defense of the host against potential pathogens (18,19). Inflammation is divided into acute inflammation and chronic inflammation. Acute inflammation contributes to cancer regression (7,20), whereas chronic inflammation promotes cancer progression (21). Currently, details regarding the pathogenesis of cancer arising from inflammation are accumulating at an exponential rate. There are two different modes for the association between inflammation and cancer, namely the intrinsic and extrinsic pathways (22). DNA damage, chromosomal instability and epigenetic changes lead to aberrant gene expression, which is a key feature of intrinsic pathways. Inflammatory signals caused by infections and autoimmune diseases are associated with extrinsic pathways. A variety of important transcription factors, including nuclear factor-κB (NF-κB) and signal transducer and activator of transcription 3 (STAT3) are activated in these two pathways and drive the inflammatory cascade (23,24).

4. Important inflammation-related pathways in the development of RCC

Inflammation and RCC are closely associated, and numerous inflammatory pathways interact with RCC. Four of these pathways that are particularly important include the Von Hippel-Lindau (VHL), mechanistic target of rapamycin (mTOR), tumor necrosis factor (TNF) and STAT pathways.

VHL pathway. VHL is a gene that suppresses the development of RCC and has the highest mutation rate among other genes involved in RCC (25,26). The main function of VHL is to control the oxygen-sensing mechanism of cells by regulating the hypoxia-inducible factor (HIF) α subunits (-1α, -2α and -3α) (27-29). HIF is a heterodimeric transcription factor composed of two subunits, HIF-α and HIF-β (30). Although the β-subunit of HIF is constitutively expressed, HIF-α protein is only expressed under hypoxic conditions and when VHL is inactivated (31). VHL promotes the degradation of HIF-α under normoxic conditions to keep the HIF-α subunit level low (32). Under hypoxic conditions, VHL is inactivated, leading to the accumulation of HIF-α, which binds to HIF-β and forms heterodimers that activate target genes. Therefore, the inactivation of VHL in RCC results in the upregulation of HIF-α isoforms, hence an increase in HIF, thereby activating the downstream carcinogenesis-related genes such as those associated with angiogenesis [vascular endothelial growth factor A (VEGFA) and platelet-derived growth factor β (PDGF-β)], erythropoiesis (erythropoietin) and glycolysis (solute carrier family 2 member 1). This causes tumor development processes such as cell growth, survival (cyclin G2 and transforming growth factor-α are increased) and migration [C-X-C motif chemokine receptor 4 (CXCR4) is increased] to be enhanced (33-35).

mTOR pathway. mTOR is a member of the protein kinase phosphatidylinositol 3-kinase (PI3K)-associated kinase family, which plays a key role in cell growth, cell proliferation, cell motility, cell survival, protein synthesis, autophagy and transcription (36). mTOR is composed of two complexes, mTOR complex 1 (mTORC1) and mTORC2, containing two different scaffolding proteins (37,38). mTORC1 can be activated by growth factors and amino acids to promote cell growth (e.g., increases in cell size and mass) and cell proliferation. Activation of mTORC2 contributes to the regulation of cell polarity and the actin cytoskeleton (39,40). mTOR is closely associated with the incidence of RCC. AKT, a molecule with an important role in the mTOR pathway, can be activated by inflammation, which causes tumorigenesis through mTOR signal transduction (41). Mutations in associated genes and inflammation lead to an increase in the incidence of metastatic RCC after an increase in mTOR activity (Fig. 1). Functional deletion mutations of the mTOR negative regulator PTEN, via the PI3K/AKT pathway, occur in ~5% of patients with RCC (42,43). Furthermore, the increased constitutive activity of mTORC1 promotes the proliferation and invasiveness of metastatic RCC (44). This is since the increased activity of mTORC1 promotes cell growth and proliferation (45). In addition, mTORC1 increases the level of HIF-1α in cells, thereby activating the production of proangiogenic factors such as VEGF, PDGF-α and TNF-α (46). In certain patients with RCC, activation of mTORC1 is mediated by a phosphatase PTEN loss-of-function mutation, which negatively regulates mTORC1 via the upstream PI3K/AKT pathway (47). Additionally, the occurrence of RCC in patients with tuberous sclerosis is due to mutations in tuberous sclerosis complex interfering with its negative regulation of mTORC1 activity (48,49).

TNF pathway. TNF is a multifunctional pro-inflammatory cytokine secreted by macrophages and is the core driver of inflammatory responses (50). TNF binds and functions through its two different receptors, TNF receptor 1 (TNFR1)

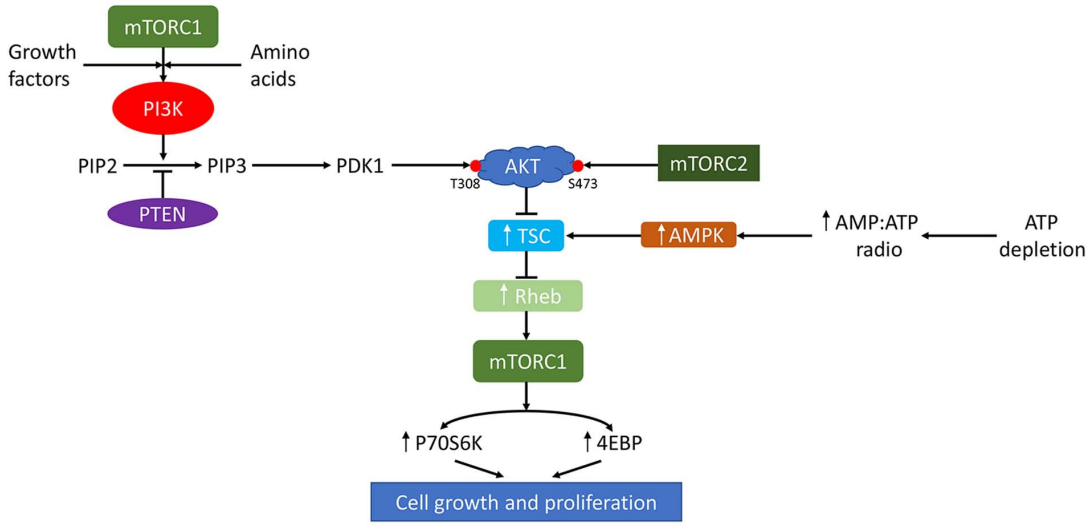

Figure 1. mTOR pathway affects tumor cell growth and proliferation. mTOR consists of two intracellular complexes, mTORC1 and mTORC2. Growth factors and amino acids activate mTORC1, thereby activating lipid kinase PI3K. Phosphorylation of PIP2 by PI3K then produces PIP3, which phosphorylates and activates AKT via the intermediate kinase PDK1. PTEN is a phosphatase that negatively regulates PI3K to dephosphorylate PIP3 back to PIP2. Once this pathway is activated, AKT phosphorylates and inhibits the TSC phosphorylation (AKT can also be activated by mTORC2). TSC is able to negatively regulate mTORC1 by inhibiting Rheb, a GTP-binding protein. AKT can disable this inhibition and activate the mTOR pathway. AMPK reduces cellular ATP storage and increases the AMP:ATP ratio, inhibiting mTOR by the phosphorylation and activation of TSC2. After AKT is activated, mTORC1 phosphorylates p70S6K and 4EBP to promote protein translation and enhance cell growth. mTOR, mechanistic target of rapamycin; mTORC, mTOR complex; PI3K, phosphatidylinositol 3-kinase; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol-3,4,5-triphosphate; TSC, tuberous sclerosis complex; Rheb, Ras homolog enriched in brain; PDK1, 3-phosphoinositol-dependent kinase-1; p70S6K, 70 kDa ribosomal protein S6 kinase; 4EBP, eukaryotic translation initiation factor 4E-binding protein 21.

and TNFR2 (51). TNFR1 is mainly expressed in endothelial cells in normal kidneys; it can activate apoptotic signal kinase 1 and NF-κB leading to cell death (52). TNFR2 is expressed primarily on damaged endothelial cells and tubular epithelial cells (TECs), which can activate endothelial/epithelial tyrosine kinase (Etk) and transactivate VEGF receptor 2 (VEGFR2) to promote cell proliferation (53). Aberrant expression of TNFR2 on tumor cells has been found in human RCC (54). The expression of TNFR2 in RCC is associated with grade of malignancy (55). Al-Lamki *et al* (56) showed that TNF is an autocrine growth factor that selectively promotes clear cell RCC (ccRCC) progression via the TNFR2/Etk/VEGFR2 pathway (56). It was earlier reported that TNF-α selectively activates the TNFR2 response, leading to activation of epithelial cells and Etk, and apparent transactivation of VEGR-2 phosphorylation at Tyr(P)-1054-1059. This pathway promotes the activation of NF-κB, which participates in tumor malignancy (55). The activation of NF-κB triggers transcription of anti-apoptotic proteins, including apoptosis inhibitors [cellular inhibitor of apoptosis proteins (c-IAPs)], cFLICE (procaspase-8) inhibitory protein (c-FLIP), mitogen-activated protein kinase (MAPK)-specific phosphatase and A20 (57). In addition, myeloid-derived suppressor cells (MDSCs) contribute to tumor immune evasion. Recent studies have shown that the generation, accumulation and function of MDSCs depend on TNF-TNFR2 signaling (58-60). Thus, the activation of TNFR2 can promote the progression of RCC.

STAT pathway. The STAT proteins are a family of cytoplasmic transcription factors comprising seven members, STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b and STAT6. Since cancer cells are more dependent on the activity of these proteins than their normal counterparts, STAT proteins are considered to be ideal targets for anticancer therapy (61). STAT3 is a potential transcription factor that mediates extracellular signals, such as cytokines and growth factors, by interacting with cell surface polypeptide receptors. Studies have shown that STAT3 promotes RCC occurrence and development (62-64). STAT3 responds to extracellular stimuli and is activated after tyrosine phosphorylation. Phosphorylated STAT3 dimerizes and translocates to the nucleus where it then binds the sequence-specific DNA elements, thereby activating transcription of the target gene (65). Cancer-associated inflammatory mediators, such as the interleukin (IL)-6 and IL-10 cytokine families, recruit Janus kinase (JAK) family members (JAK1, JAK2 and TYK2) to activate STAT3 phosphorylation after cross-phosphorylation. STAT3 forms homodimers in the cytoplasm, which migrate to the nucleus to regulate gene expression that leads to cancer (66). Numerous lines of evidence have reported that STAT3 regulates genes that play important roles in cell physiology, including the cell cycle, apoptosis, inflammatory immunity, metabolism and angiogenesis (67-69). Enhanced STAT3 activity can block the process of apoptosis and induce the upregulation of Cyclin D1, c-Myc and Survivin expression, resulting in abnormal cell proliferation (70). STAT has also been extensively studied in the field of RCC. Studies have shown that activated STAT3 is a potential regulator of HIF-1, which mediates VEGF expression in RCC (71,72). The aforementioned findings show that STAT affects not only gene expression through the JAK/STAT3 pathway, but also the expression of VEGF by regulating HIF-1. In this way, it affects the occurrence and progression of renal cancer.

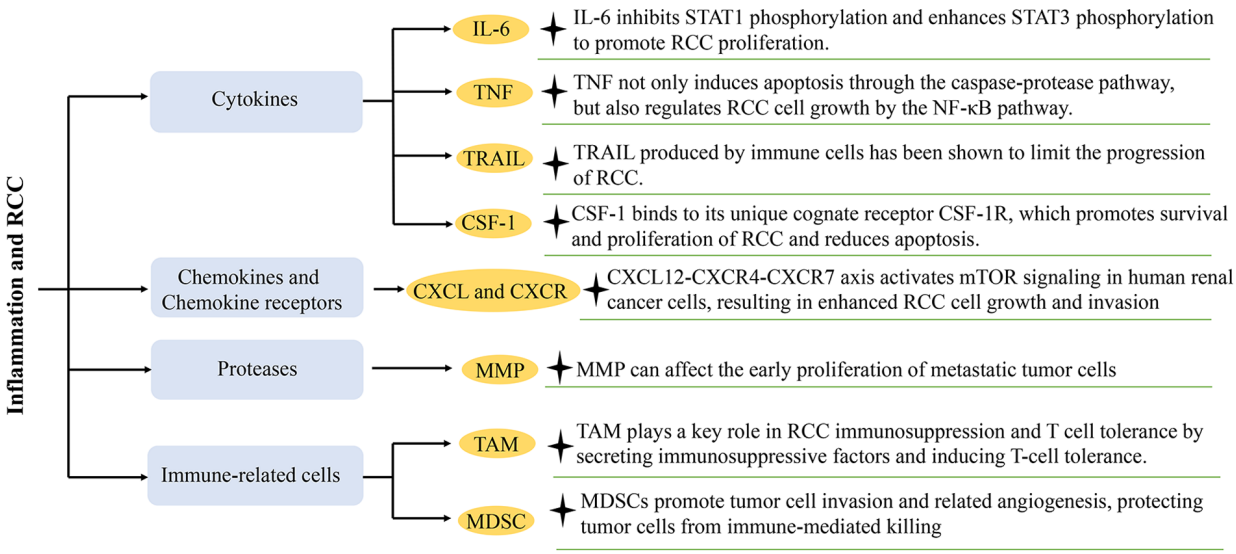

Figure 2. Inflammatory molecules associated with RCC. The role of different inflammatory factors and immune cells in RCC-promoting inflammation and RCC tumor immunity. RCC, renal cell carcinoma; IL, interleukin; STAT, signal transducer and activator of transcription; TNF, tumor necrosis factor; NF-κB, nuclear factor-κB; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; CSF-1, colony-stimulating factor 1; CSF-1R, CSF-1 receptor; CXCL, chemokine (C-X-C motif) ligand; CXCR, CXC chemokine receptor; MMP, matrix metalloproteinase; TAM, tumor-associated macrophage; MDSC, myeloid-derived suppressor cell.

5. Role of inflammation factors and immune-related cells in the occurrence and progression of RCC

A variety of inflammatory factors and immune-related cells are involved in the interactions between inflammation and RCC, where they play an important role. Cytokines, chemokines and other small inflammatory proteins from host cells coordinate intracellular communication in the TME. Continuous crosstalk between cells is critical for tumor growth, invasion, angiogenesis and metastatic spread (9). The present review focuses on the major contributors to tumor-associated inflammation and local immune responses, including cytokines and chemokine receptors, transcription factors and immune-related cells (Fig. 2).

Cytokines

IL-6. IL-6 is an inflammatory cytokine with multiple biological effects; it is composed of 184 amino acids, with a molecular weight of 21-28 kDa. IL-6 has a 4-helix bundle structure consisting of 4 long α-helices (73-75). It has been reported that enhancing the production of IL-6 stimulates the expression of proinflammatory factors, such as IL-1, TNF-α, interferons, bacterial endotoxin and lipopolysaccharide or viral infection (76,77). Numerous studies have explored the role of IL-6 in kidney functions. Renal cortical tissue and kidney cancer tissue can produce IL-6 (78). IL-6 is expressed in most RCC cell lines and in patient tissues, and it plays an important role in the proliferation of RCC cells (78). Mechanistic studies showed that IL-6 activates IL-6 receptor (IL-6R) and glycoprotein 130 (gp130), causing phosphorylation of the tyrosine kinases JAK1, JAK2 and TYK2. This results in phosphorylation of STAT3 (79). Pathophysiological conditions play an important role in the regulation of IL-6. The transcriptional signal of IL-6 appears to be activated only during immune stress, and the IL-6/soluble IL-6R complex is usually upregulated in pathophysiological conditions (80). Matsumoto *et al* (81) indicated that tumor endothelial cells upregulate the expression of gp130 and downregulate the expression of membrane-bound IL-6R through the IL-6/IL-6sR complex, leading to cell proliferation, inhibition of apoptosis and enhancement of tumor development. IL-6 inhibits STAT1 phosphorylation, enhances STAT3 phosphorylation, promotes RCC proliferation and blunts the antitumor effect of IFN (82). Meanwhile, studies have shown that IL-6-activated plasma membrane-associated sialidase (NEU3) may also contribute to the expression of malignant phenotypes in RCC (83) (Fig. 3).

TNF. TNF is a potent pro-inflammatory cytokine that mediates complex biological responses, including inflammation, antiviral response, septic shock and apoptotic cell death (84). TNF can trigger apoptosis through the caspase-protease pathway and the NF-κB pathway. In the NF-κB pathway, TNF binds to TNFR to activate atypical protein kinase C and phosphorylates inhibitor of nuclear factor-κB kinase subunit β (IKKβ). Subsequently, the activated IKKβ phosphorylates inhibitor of NF-κB (IκB), resulting in ubiquitin-mediated degradation of IκB. NF-κB is released after IκB degradation and translocated into the nucleus where it activates the transcription of a number of anti-apoptotic genes, including the c-FLIP and c-IAP families (85,86). It has been shown that TNF-α regulates RCC cells growth by modulating the NF-κB-mediated anti-apoptotic pathway (55). Harrison *et al* (87) used an anti-TNF monoclonal antibody, infliximab, in two phase II clinical trials in patients with locally advanced and metastatic RCC. It was found that targeting TNF may be a beneficial therapeutic approach for cancer management. A previous study has reported that patients with high serum inflammatory cytokine levels in RCC have a poor prognosis, thus, TNF-α can be used as an independent prognostic indicator. Normal TNF-α plasma levels are high predictors of good prognosis in untreated patients (88).

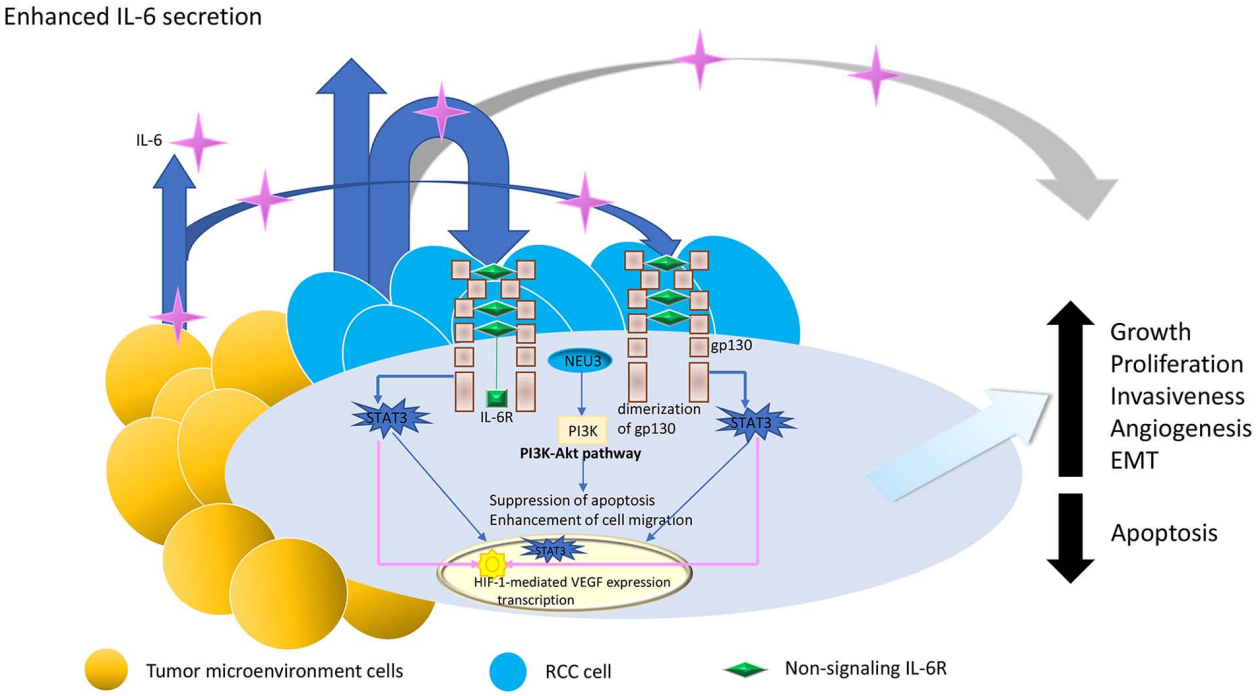

Figure 3. IL-6 pathway promotes RCC development. IL-6 (pink stars) binds first to the membrane-bound non-signaling IL-6R (green diamonds). Non-signaling IL-6R is activated as IL-6R (green square), which can be signal transduced. After recruitment of 2 gp130 (brown-colored rectangular squares) molecules, the signaling complex is formed and signal transduction is induced (brown-colored squares represent 'dimerization of gp130'). Signaling via membrane-bound IL-6R can promote the development of RCC by activating STAT3, a potential regulator of HIF-1-mediated VEGF expression transcription. This may be associated with the proliferation of RCC. Human NEU3 plays an important role in cell differentiation and transmembrane signal transduction, and its expression is associated with IL-6. NEU3 is sensitive to IL-6 signaling via the PI3K pathway. Overexpression of NEU3 can enhance the action of IL-6, inhibit apoptosis and promote cell migration. IL-6, interleukin-6; IL-6R, IL-6 receptor; RCC, renal cell carcinoma; gp130, glycoprotein 130; STAT3, signal transducer and activator of transcription 3; HIF-1, hypoxia-inducible factor 1; VEGF, vascular endothelial growth factor; NEU3, plasma membrane-associated sialidase; PI3K, phosphatidylinositol 3-kinase; EMT, epithelial-mesenchymal transition.

TNF-related apoptosis-inducing ligand (TRAIL). TRAIL is a molecule belonging to the TNF superfamily; it is an effective anticancer agent as it specifically targets cancer cells while retaining normal cells, thereby inducing apoptosis (89). TRAIL can bind to death receptor DR4 and DR5, and assembles a death-inducing signaling complex by recruiting FAS-associated protein associated with death domain and caspase-8. Autocatalytic activation of caspase-8 leads to caspase cascade activation, ultimately leading to cell death (90). In cancer treatment, normal cells highly express decoy receptors DcR1 and DcR2, while cancer cells highly express death receptors DR4 and DR5 (89). TRAIL can bind to DR4 and DR5 and ultimately target cancer cell death (91). The complex formed by the binding of TRAIL to the DcR does not activate the apoptotic signaling pathway. Therefore, there is a weaker influence of TRAIL on the apoptosis of normal cells than cancer cells. Furthermore, TRAIL produced by immune cells has been shown to limit the progression of RCC (92).

Colony-stimulating factor 1 (CSF-1). CSF-1 is an important regulator of macrophage homeostasis (93). Co-expression of CSF-1 and CSF-1 receptor (CSF-1R) promotes proliferation and anti-apoptosis during regeneration of renal TECs. The CSF-1-dependent autocrine pathway is an important pathway for RCC growth. High levels of CSF-1 and tumor-associated macrophages (TAMs) are associated with a poor cancer prognosis. Co-expression of CSF-1 and CSF-1R on RCCs and adjacent TECs promotes tumor proliferation and tumor metastasis (94). The paracrine interaction between tumor cells and TAMs promotes tumor cell migration, invasion and metastasis, accelerating the spread of tumors in the host (95,96). Tumor-derived CSF-1 regulates TAMs, while CSF-1 and CSF-1R co-expression-regulated macrophages affect the TME of the host (97,98). A study by Dosquet *et al* (88) indicated that the autocrine CSF-1-dependent RCC mechanism is the core of RCC growth, and that the binding of CSF-1 to its unique cognate receptor CSF-1R promotes the survival and proliferation of RCC, and reduces apoptosis. Moreover, EGF induces CSF-1 and CSF-1R on RCC, thereby promoting tumor cell proliferation and inhibiting tumor cell apoptosis (99). This indicates that CSF-1R signaling promotes the growth of RCC.

Chemokines and chemokine receptor

Chemokine (C-X-C motif) ligand (CXCL) and CXC chemokine receptor (CXCR). Chemokines are a subfamily of cytokines that contain ~50 different signaling proteins. Similar to other cytokines, chemokines affect cell behavior through both autocrine and paracrine modes (100). Chemokines and their receptors are involved in the regulation of growth, angiogenesis and metastasis of RCC (101). It has been shown that CXCR4 is an ideal target for tumor diagnosis and treatment (102). The expression of CXCR4 in most cases is associated with tumor-specific survival in ccRCC with VHL mutations. A close association between VHL and CXCR4 has been observed. The VHL disease tumor suppressor (pVHL) is a protein that negatively regulates CXCR4. pVHL can target

the degradation of HIF under normoxic conditions to prevent CXCR4 expression. This process is inhibited under hypoxic conditions (103-105). A study by Ieranò *et al* (106) indicated that the CXCL12-CXCR4-CXCR7 axis activates mTOR signaling in human renal cancer cells, resulting in enhanced RCC cell growth and invasion (106). Other studies have shown that the CXCR4-CXCL12-CXCR7 axis also plays a key role in RCC. The activity of CXCR4 is mainly γ-mediated; however, CXCR7 is considered to be an atypical G protein-coupled receptor, as it does not cause intracellular Ca^{2+} release when bound to a ligand (107). Some studies have shown that CXCR7 is a DcR that isolates extracellular CXCL12 or regulates the CXCR4 signaling pathway by forming a CXCR7-CXCR4 heterodimer (108,109). High expression of CXCR7 in human cancer types such as bladder cancer, glioma, colorectal cancer, ovarian cancer and breast cancer, and in tumor-associated blood vessels, may be critical for tumor cell survival, adhesion and growth (110-115). Overall, CXCR4 and CXCR7 are potential molecules affecting the prognosis of RCC (116).

Proteases

Matrix metalloproteinases (MMPs). MMPs are members of the zinc-dependent endopeptidase family; they regulate signaling pathways that control cell growth, inflammation or angiogenesis. Hence, MMPs participate in molecular communication between tumors and stroma, mediating microenvironmental changes during tumor progression (117,118). Compelling evidence from knockout mouse experiments has shown that MMPs play an important role in acute and chronic inflammation (119). Numerous studies have demonstrated that MMPs can aggregate leukocytes to cause tumor-related inflammation (120,121). Studies have confirmed that MMPs affect the early proliferation of metastatic tumor cells, while tissue inhibitors of MMP (TIMPs) inhibit MMP activity to indirectly regulate tumor cell proliferation (122,123). Among these MMPs, MMP-9 has the most important function in tumors. MMP-9 exhibit higher expression in malignant tumors than in benign or non-invasive tumors, and it also exhibits high expression in RCC; it can denature type I, II and IV collagen, enabling tumor cells to penetrate the basement membrane (124,125). Additionally, membrane type 1 MMP (MT1-MMP/MMP-14) is involved in tumor invasion; it is widely expressed in most malignant tumors, and its overexpression enhances cell invasion ability (126). MT1-MMP not only degrades extracellular matrix molecules such as type I, II and III collagen, vitronectin, laminin-1 and -5, fibronectin and aggrecan (127), but it also recruits pro-MMP-2 to the cell surface and causes the activation of MMP-2 by cleaving the propeptide sequence (128). A study by Petrella and Brinckerhoff (129) showed that MT1-MMP is the main trigger of type I collagen degradation and the invasiveness of VHL RCC cells expressing MT1-MMP or HIF-2α. In addition, in the absence of VHL, the protein and gene levels of MT1-MMP are significantly upregulated in RCC (130).

Immune-related cells

TAMs. TAMs are derived from peripheral blood mononuclear cells. Macrophages usually undergo M1 or M2 activation under inflammatory stimuli (131). In RCC, M1 cells produce inflammatory cytokines such as TNF-α, IL-6, IL-12 and IL-23, while M2 cells produce anti-inflammatory cytokines such as IL-10, thereby promoting RCC-related immune dysfunction (132). Santoni *et al* (133) showed that high TAM infiltration in the RCC microenvironment promotes tumor progression and metastasis by stimulating angiogenesis, tumor growth and cell migration. RCC is a typical hemangioma in which VEGF is significantly upregulated. VEGF, considered to be a chemokine of TAM, supports tumor proliferation. TAM can self-produce VEGF, which increases the accumulation of TAM in tumor sites (134). TAM plays a key role in RCC immunosuppression and T-cell tolerance by secreting immunosuppressive factors and inducing T-cell immunity without response (135).

MDSC. MDSCs are a group of heterogeneous cells derived from the bone marrow, which are preferentially expanded in cancer and have a significant ability to suppress immune cell responses; they primarily inhibit T-cell proliferation and NK-cell activation, and induce differentiation and proliferation of regulatory T cells (136). MDSCs have the ability to inhibit T-cell activation through upregulation of arginase-1 (Arg1) and inducible nitric oxide synthase in monocytic MDSCs, and Arg1 and reactive oxygen species in granulocytic MDSCs (137). The TME affects the progression and metastasis of solid tumors, which consist of tumor cells and other primitive stromal cells (138,139). MDSCs are the main components of the TME, and the increase in blood volume is associated with a shorter patient survival time. Mechanistic studies have shown that MDSCs promote tumor cell survival, associated angiogenesis, invasion and metastasis (140,141). MDSCs also protect tumor cells from immune-mediated killing, establish a TME and interact with tumor cells to promote epithelial-mesenchymal transition to support tumor growth and metastasis (142). A close association between MDSCs and clinical outcomes of cancer patients has been established. MDSCs hold great promise as novel biomarkers for tumor prognosis (143).

6. Inflammation-associated molecules and clinical prognosis in patients with RCC

A number of inflammation-related factors, including Th1-related factors (IFN-γ), Th1-related chemokines (monokine induced by IFN-γ [MIG], IFN-γ inducible protein 10 [IP-10] and IFN-γ-inducible T-cell A chemoattractant [I-TAC]), Th2-related factors (IL-4) and Th2-associated chemokines (eotaxin and macrophage-derived chemokine [MDC]) are elevated in tumor tissues (138). A variety of inflammatory factors are associated with recurrence in patients, for example, MIG and IFNγ-mediated mononuclear factors (144).

Inflammation-related factors TNF-α, CXCR4 and C-C chemokine receptor type 3 (CCR3) are associated with the prognosis and staging of patients with RCC. For instance, TNF-α is an independent prognostic indicator, and normal levels in plasma can highly predict the good prognosis of untreated RCC patients (88,145). In addition, CXCR4 has significant prognostic value in univariate analysis, and its low expression indicates a good prognosis (146). The high expression of CCR3 in immunohistochemical analysis is associated with the degree of malignancy of the tumor. Upregulation of CCR3 and its ligands may promote tumor cell proliferation (147). In another study, Kallakury *et al* (148) showed that

Table I. Main anti-inflammatory agents in RCC.

Agent	Target/associated pathway	Therapeutic effects
Simvastatin	AKT, mTOR and ERK pathway; IL -6-induced phosphorylation of JAK2 and STAT3 pathway	Inhibit the proliferation and migration of RCC cells
ATRA	RAR/RXR pathway; PI3K/AKT pathway	Regulate the cell cycle
Nivolumab	PD-1 pathway	Antitumor activity in metastatic RCC
LY294002	PI3K/AKT pathway	Influences tumor cell growth and apoptosis
Antibodies against 15-LOX2	15-LOX2/15(S)-HETE pathway	Influences the RCC tumor microenvironment

RCC, renal cell carcinoma; ATRA, all-trans retinoic acid; mTOR, mechanistic target of rapamycin; ERK, extracellular signal-regulated kinase; IL-6, interleukin-6; JAK2, Janus kinase 2; STAT3, signal transducer and activator of transcription 3; RAR, retinoic acid receptor; RXR, retinoid X receptor; PI3K, phosphatidylinositol 3-kinase; PD-1, programmed death 1; 15-LOX2/15(S)-HETE, 15-lipoxygenase 2/15(S)-hydroxyeicosatetraenoic acid.

increased expression of MMP2, MMP9, TIMP1 and TIMP2 in RCC correlated with a poor prognosis. In summary, inflammation-related factors may be predictive indicators of RCC clinical prognosis and have a huge potential role in RCC therapy.

7. Anti-inflammatory immunotherapy in RCC

With in-depth basic research and a better understanding of the mechanism of inflammation in RCC, new anti-inflammation-related therapeutics and immunotherapy-related agents may be developed. In recent years, simvastatin, all-trans retinoic acid (ATRA), nivolumab and other immunotherapeutic agents have played a role in the treatment of RCC (Table I).

Anti-inflammation-related agents

Simvastatin. Simvastatin is a cholesterol-lowering drug for the prevention of cardiovascular disease, and is involved in tumor growth, spread and endothelial function (149). A previous study has reported that the extracellular signal-regulated kinase (ERK)1/2 signaling pathway is a statin-dependent pro-apoptotic mediator (150). Knockdown of ERK can make RCC cells sensitive to simvastatin-induced anticancer effects. Simvastatin can inhibit the proliferation and migration of RCC cells by inhibiting the phosphorylation of AKT, mTOR and ERK; it also exhibits antitumor effects by inhibiting the IL-6-induced phosphorylation of JAK2 and STAT3 (151).

ATRA. ATRA is the active metabolite of vitamin A, involved in cell proliferation, differentiation and apoptosis; its role is mediated by nuclear flavonoid receptors, MAPK and cAMP/cAMP-dependent protein kinase signaling pathways (152). ATRA reduces cell proliferation and alters gene expression through nuclear receptor- and non-receptor-mediated pathways, thereby accelerating cell differentiation and apoptosis. In genomic action, the function of ATRA is mediated by nuclear receptors, particularly retinoic acid receptors (RARs) (α, β and γ). Nuclear RAR acts as a retinoid-inducible transcription factor, and regulates cell cycle arrest, cell differentiation and cell regulation through heterodimer formation with retinoid X receptor (153). Among the RARs, RARβ is a tumor suppressor that is expressed at low levels in a number of cancer types, such as breast and prostate cancer, and whose expression is regulated by ATRA (154). In the non-genomic pathway, ATRA independently activates the transcription of genes involved in the PI3K/AKT pathway in cells, reversing the dysregulation of the PI3K/AKT pathway in most human cancer types. In more detail, this process entails the activation of PI3K by ATRA through G-protein coupled receptors and multiple receptor tyrosine kinases. Activated PI3K catalyzes the production of phosphatidylinositol-3,4,5-triphosphate to promote aggregation and activation of AKT on the membrane (155).

Nivolumab. Nivolumab is a programmed death 1 (PD-1) checkpoint inhibitor that selectively blocks the interaction between PD-1 and PD ligand (PD-L)1/PD-L2 expressed on activated T cells, thereby preventing T-cell inactivation (156). Expression of PD-L1 as a remote immunomodulator occurs in 20-50% of human cancer types. A variety of cancer immunotherapies targeting the interaction between PD-L1 and PD-1 have been developed (157,158). PD-L1 effectively inhibits the tumor-killing ability of T cells. Once the PD-L1:PD-1 interaction is blocked, T cells can quickly restore their effector function. PD-L1 expressed on tumor cells binds to PD-1 on activated effector T cells, and phosphatase SHP-2 is recruited, resulting in inactivation of the PI3K signaling cascade (159). It has been found that PD-L1 or PD-1 inhibitors have a positive effect on the treatment of cancer. Nivolumab exerts antitumor activity in metastatic RCC (160). The immunotherapeutic agent ipilimumab is a human cytotoxic T-lymphocyte antigen-4 (CTLA-4) immune checkpoint inhibitor antibody, which can prevent CD80 and CD86 ligands on antigen-presenting cells from binding to the CTLA-4 receptor on activated T cells, thereby preventing the downregulation of antitumor T cell activity (161). CTLA-4 plays a significant role in early immune response, primarily occurring in lymphoid tissues, while PD-1, whose expression is upregulated after T-cell activation in peripheral tissues, is more involved in late immune response (162). The combined application of CTLA-4 and PD-1 blockers can synergistically activate the antitumor immune response and increase the response rate of patients (163). Thus,

a combination of nivolumab and ipilimumab will effectively control tumor development with a good safety profile (164).

Immunotherapy for RCC. Emerging clinical data reveals that immunotherapy has great potential in the treatment of cancer. Associated studies have shown that a series of gradual and repeated immune response events, defined as the cancer-immune cycle, can effectively kill cancer cells. In the first step of this process, tumor antigens are captured by dendritic cells (DCs) for processing (165). Proinflammatory cytokines and factors released by dying tumor cells can be used as a designated immune signal to avoid induction of tumor tolerance antigens (step 1) (166,167). DCs then present the captured antigen on the major histocompatibility complex I (MHCI) and MHCII molecules to the T cells (step 2) (168). This initiates and activates the effector T-cell response (step 3) (169). This is followed by the entry (step 4) and invasion (step 5) of the tumor bed by the activated effector T cells (170), which then recognize and bind to specific cancer cells (step 6) and kill them (step 7) (171). Subsequently, the tumor-associated antigens released from the dying cells amplify the cycle of immune response and make it more widespread and repetitive (172).

The entire immune cycle is enhanced through the positive regulatory signal or suppressed via the negative regulatory signal in the aforementioned steps during therapeutic treatments. The first phase of treatment corresponds to chemotherapy, radiotherapy and targeted therapy. These treatments induce immune cell death by activating the immune system (173). The second phase corresponds to use of cancer vaccines, which rely on tumor cell-associated antigens to awaken the immune system against cancer (174). The third phase is mainly associated with CTLA-4 inhibitors. CTLA-4 is a receptor found on the surface of activated T-cells, which predominantly acts by competing with CD28 receptors for binding to B7 ligands on antigen presenting cells (APCs). In the process of T cell activation, CD28 receptors on the T-cells bind to the B7 ligands on APCs and provide the essential second activation signal for T-cell. However, CTLA-4 receptors can competitively bind to B7 ligands with higher affinity, resulting in the lack of second activation signal. Lack of the second activation signal in the presence of CTLA-4 receptors would lead to anergy in T-cells (163,175). The fourth phase involves the transport of T lymphocytes, and no intervention is available at this stage. The fifth stage is predominantly through anti-VEGF treatment to enhance T cell transport and tumor bed infiltration. The transfer of activated T cells from the lymph nodes into circulation and then to the tumor requires a series of steps. VEGF promotes the formation of abnormal tumor blood vessels, which can negatively affect the transmigration of T-cells from lymph nodes to the tumor bed (176). In addition, the blockade of VEGF can increase the expression of E-selectin on tumor vascular endothelium and down-regulate the Fas ligand on vascular endothelial cells, ultimately promoting the increased of T-cell tumor infiltration (177). The sixth phase involves CAR-T-cell therapy, which is to generate a powerful immune-mediated anti-tumor response through the *in vitro* manipulation of T-cells (178). This treatment is achieved through the selection and expansion of tumor-infiltrating lymphocytes (TILs), or through gene transfer of a synthetic TCR (sTCR) or a chimeric antigen receptor (CAR) into T-cells (179). The seventh stage corresponds to PD-1/PD-L1 inhibitor treatment (180). Immunotherapy has successfully been applied to RCC in recent years (172).

In addition, it has been found that inhibiting the inflammatory pathway is an effective approach to suppress the progression of RCC. Thus agents, such as LY294002, that inhibit the PI3K/AKT signaling cascade may benefit patients with RCC (181). Activation of the 15-lipoxygenase 2/15(S)-hydroxyeicosatetraenoic acid pathway increases the metabolism of arachidonic acid in the RCC TME, compromising the function of the recruited immune cells, thereby promoting local immunosuppression and tumor escape (182).

8. Conclusions and prospects

Inflammation influences all aspects of tumor occurrence and progression, as well as the tumor response to treatment. In the early stages of tumor formation, inflammatory cells play a pro-tumor development role, creating favorable conditions for tumor growth (183). Chemokines and cytokines provided by inflammatory cells affect the entire tumor organ and regulate the growth, migration and differentiation of cells in the TME. In the later stages of tumorigenesis, tumor cells also switch inflammatory mechanisms, such as the production of chemokines and MMP, favoring tumor proliferation and metastasis (119,184). However, aggregation of inflammatory cells may suppress tumor growth (7).

Accumulating evidence indicates that the TME harbors multiple inflammatory cells that regulate tumor cell growth, proliferation, survival and migration (185). The aforementioned inflammation-related pathways (the VHL, mTOR, TNF and STAT pathways) can promote the occurrence and progression of RCC by activating the inflammatory response. Pro-inflammatory cytokines (IL-6, TNF and CSF-1) and chemokines (CXCL and CXCR) are involved in tumor-related pathways and promote the proliferation of RCC cells. When highly expressed, they confer a poor prognosis for RCC. TRAIL expression has been recorded as a prognostic factor for improved RCC-specific survival (186). As a key participant in the molecular communication between tumors and stroma, MMP overexpression enhances RCC cell invasion ability (187). TAM cells and MDSCs support the growth and metastasis of RCC by suppressing the ability of immune cell responses. In terms of the therapy, agents targeting inflammation (simvastatin, ATRA, nivolumab, PI3K/AKT pathway inhibitor and cancer immune cycle inhibitors) have shown great promise in prolonging the survival time of RCC patients. Understanding the nature of inflammation and RCC will reveal important targets for developing treatments of RCC (9,188).

On the basis of recent technological advances and in-depth research on the pathology and mechanism of RCC, new findings and breakthroughs have been reported. The association between inflammation and RCC phenotypes has become the new hotspot of current cancer research (9,189,190). Numerous studies have demonstrated that the expression of most inflammation-related factors is associated with the poor prognosis of RCC and that immune-infiltrating cell profiles can also predict the prognosis of patients (72,92,191). Research on

immune-targeted treatments has become one of the hotspots in basic and clinical research, providing hope for tumor treatment. In the past 12 years, the medical treatment of RCC has transitioned from non-specific immune methods to targeted therapy for VEGF to new immunotherapeutic agents (192). The interaction between tumor immune status and cancer-related systemic inflammation is essential for the treatment of RCC. Therapies targeted at inflammatory pathways are likely to be a new direction for RCC treatment.

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Authors' contributions

JS, KC and XZ conceived the present study. JS, KW and ZX drafted the manuscript. CY, CW, QC, HYu, XM and ZC made substantial contributions to the interpretation and analysis of the data, drafting the study and revising it critically for important intellectual content. KX and HYa were major contributors in the revision of the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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