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Review

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Renin-angiotensin-system and clear cell renal carcinoma: research advances and future perspectives

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Abstract

Hypertension is a known risk factor for clear cell renal cell carcinoma (ccRCC), yet the underlying mechanisms remain elusive. Studies have confirmed that the renin-angiotensin system (RAS) plays a role beyond regulating blood pressure, influencing various aspects of tumor development and metastasis. Generally, activation of the angiotensin-converting enzyme (ACE)/angiotensin II (Ang II)/angiotensin type 1 receptor (AT1R) axis elevates blood pressure and promotes tumor progression, while the activation of the angiotensin-converting enzyme 2 (ACE2)/[Ang-(1-7)]/Mas receptor (MasR) axis antagonizes these effects. Consequently, many cardiovascular drugs targeting the RAS may possess both hypotensive and antitumor properties. However, the role of RAS in ccRCC is controversial. To explore this, we reviewed the relevant literature. Surprisingly, apart from ACE2, the activation of RAS may facilitate the progression and metastasis of ccRCC. This unexpected finding suggests caution when using RAS inhibitors in ccRCC patients. This review provides an overview of the RAS, highlights research advances in RAS for ccRCC, elucidates the current status of RAS-targeted drugs in the treatment of ccRCC, and discusses the current challenges and future research directions in this field. In conclusion, the

upregulation of other effector peptides and the activation of receptors in the RAS, apart from ACE2, may expedite ccRCC progression. Therefore, careful consideration is needed when using relevant drugs in ccRCC patients with hypertension. This synthesis of available evidence is crucial for informing the clinical management of ccRCC and guiding the development of novel therapeutic strategies.

Keywords: Renin-angiotensin-system, ccRCC, hypertension, kidney, macrophage, cancer, tumor microenvironment

INTRODUCTION

Clear cell renal carcinoma (ccRCC) is the most common subtype of renal cell carcinoma, accounting for approximately 75%-85% of all cases[1]. The incidence of ccRCC has been increasing over the past few decades. The risk of developing ccRCC increases with age, with a significant increase in incidence in people over 40 years of age[2]. ccRCC is more prevalent in males than females, with a male-to-female ratio of approximately 2:1[2]. The prognosis for ccRCC patients depends on the stage and grade of the tumor at diagnosis. The 5-year overall survival rate for localized ccRCC is around 75%, while for metastatic disease, the 5-year survival rate is significantly lower, around 10%[3]. Risk factors such as smoking, obesity, and genetic predispositions contribute to a higher incidence of ccRCC. Additionally, the relative risk of ccRCC in individuals with hypertension is estimated to be 1.2 to 1.71 times higher compared to those without hypertension[4,5]. The elevated risk of ccRCC appears to be linked to long-term, chronic hypertension rather than short-term or recent-onset hypertension. Importantly, while the association between hypertension and ccRCC is well-established, the causal relationship remains unclear, necessitating further research to elucidate the underlying mechanisms.

The renin-angiotensin system (RAS) is a complex hormonal network crucial for regulating blood pressure, fluid and electrolyte balance, and other cardiovascular-related physiological and pathophysiological processes[6-9]. Two key axes of the RAS have been identified: the angiotensin-converting enzyme (ACE)/angiotensin (Ang) II/angiotensin type 1 receptor (AT1R) axis and the angiotensin-converting enzyme 2 (ACE2)/Ang-(1-7)/Mas receptor (MasR) axis. The former axis is often associated with the development of cardiovascular disease and hypertension, as it can upregulate inflammation and oxidative stress, while the latter axis is thought to counteract these effects. Given the established association between ccRCC and long-term hypertension and the central role of the RAS in blood pressure regulation, it has been hypothesized that the RAS may be implicated in the development and progression of ccRCC. Recent studies have confirmed that the RAS has been linked to the pathogenesis of various cancer types, including ccRCC. These findings present a promising avenue for investigating the potential anticancer effects of RAS inhibitors in the treatment of ccRCC. However, there remains a paucity of in-depth research elucidating the specific mechanisms by which the RAS contributes to the development and progression of ccRCC. Furthermore, there is a dearth of relevant drug testing to evaluate the efficacy of RAS-targeted therapies in the management of this malignancy. Additional research is necessary to fill these critical knowledge gaps.

To address the aforementioned questions, we conducted a search in the PubMed database for the most recent advancements in clinical, animal, and cell studies pertaining to RAS and ccRCC. This review aims to provide a concise introduction to the RAS, with a focus on the current research progress regarding its role in ccRCC, and explore the potential therapeutic implications of RAS-related drugs in the management of ccRCC. Figures and tables are included to facilitate comprehension. Additionally, the review discussed current challenges and future research directions in this field, and highlighted clinical implications of RAS for ccRCC treatment.

RAS

The classical RAS pathway ACE/Ang II/AT1R

RAS is an endocrine system expressed at multiple sites throughout the body, consisting of various effector peptides [Figure 1]. However, the expression levels of individual components within this system vary across different regions. Angiotensinogen, the precursor protein, is predominantly of hepatic origin and is cleaved by renin, a protease secreted by the juxtaglomerular cells, to generate Ang I[10]. ACE, expressed by vascular endothelial cells, then converts Ang I into Ang II, the primary effector peptide of the RAS[11].

Ang II exerts its physiological effects by activating two distinct receptor subtypes, the AT1R and the angiotensin type 2 receptor (AT2R), which exhibit different affinities for Ang II and elicit opposing functional responses[12-14]. Activation of AT1R leads to vasoconstriction, elevated blood pressure, and the promotion of inflammation and oxidative stress. Conversely, stimulation of AT2R induces vasodilation, decreased blood pressure, and anti-inflammatory, as well as antioxidant responses. Furthermore, Ang III is produced through the cleavage of Ang II by the enzyme aminopeptidase A (APA), and its physiological effects are largely equivalent to those of Ang II[15]. Similarly, Ang III binds to and activates both the AT1R and the AT2R, though it exhibits a lower affinity for the AT1R compared to Ang II, and a higher affinity for the AT2R relative to Ang II. Among the various components of the RAS, the Ang II/AT1R axis represents the most central regulatory signal, and its overactivation is implicated in the pathogenesis of numerous cardiovascular and kidney diseases.

The alternative RAS pathway ACE2/Ang-(1-7)/MasR

The ACE2/Ang-(1-7)/MasR axis represents an alternative, counter-regulatory pathway within the RAS. ACE2 is a homolog of the ACE, primarily functions to convert Ang I to Ang-(1-9) or Ang II to Ang-(1-7)[16,17]. This enzymatic conversion serves to counteract the effects of the classical RAS pathway by decreasing the levels of Ang II while increasing the levels of the vasodilatory and anti-inflammatory peptide, Ang-(1-7)[18-20]. The discovery of ACE2 has opened up new avenues for potential therapeutic interventions targeting the RAS for the treatment of cardiovascular and related diseases.

Ang-(1-7) can be generated through the cleavage of Ang II and Ang I. Upon binding to the Mas receptor, Ang-(1-7) counteracts many of the deleterious effects associated with the ACE/Ang II/AT1R axis[21,22]. In addition, ACE is the major route for the metabolism of Ang-(1-7) to Ang-(1-5)[23]. Previous studies have shown that the genetic knockout of the Mas receptor significantly impairs the ability of Ang-(1-7) to improve vascular physiology and pathophysiology, suggesting that the Mas receptor is the primary receptor through which Ang-(1-7) exerts its protective effects[9,24].

RAS IN CANCER AND CCRCC

Generally, the upregulation of ACE/Ang II/AT1R has pro-tumorigenic effects, whereas the upregulation of ACE2/Ang-(1-7)/MasR antagonizes the former[25-27]. Furthermore, the downregulation of ACE2/Ang-(1-7)/MasR may also increase tumor risk. In other words, a balance between the two axes is crucial. However, current studies do not fully endorse this opinion. In fact, both the Ang II/AT1R and the Ang-(1-7)/MasR signaling pathways may contribute to the progression of ccRCC. This section will discuss the role and putative mechanisms of RAS in the pathogenesis and progression of ccRCC. Given the paucity of studies specifically targeting RAS in ccRCC, the discussion will predominantly utilize insights from existing research on RAS's involvement in other malignancies.

Mechanisms of RAS involvement in cancer development

The promotion of tumor growth by the Ang II/AT1R axis is associated with several key mechanisms. First,

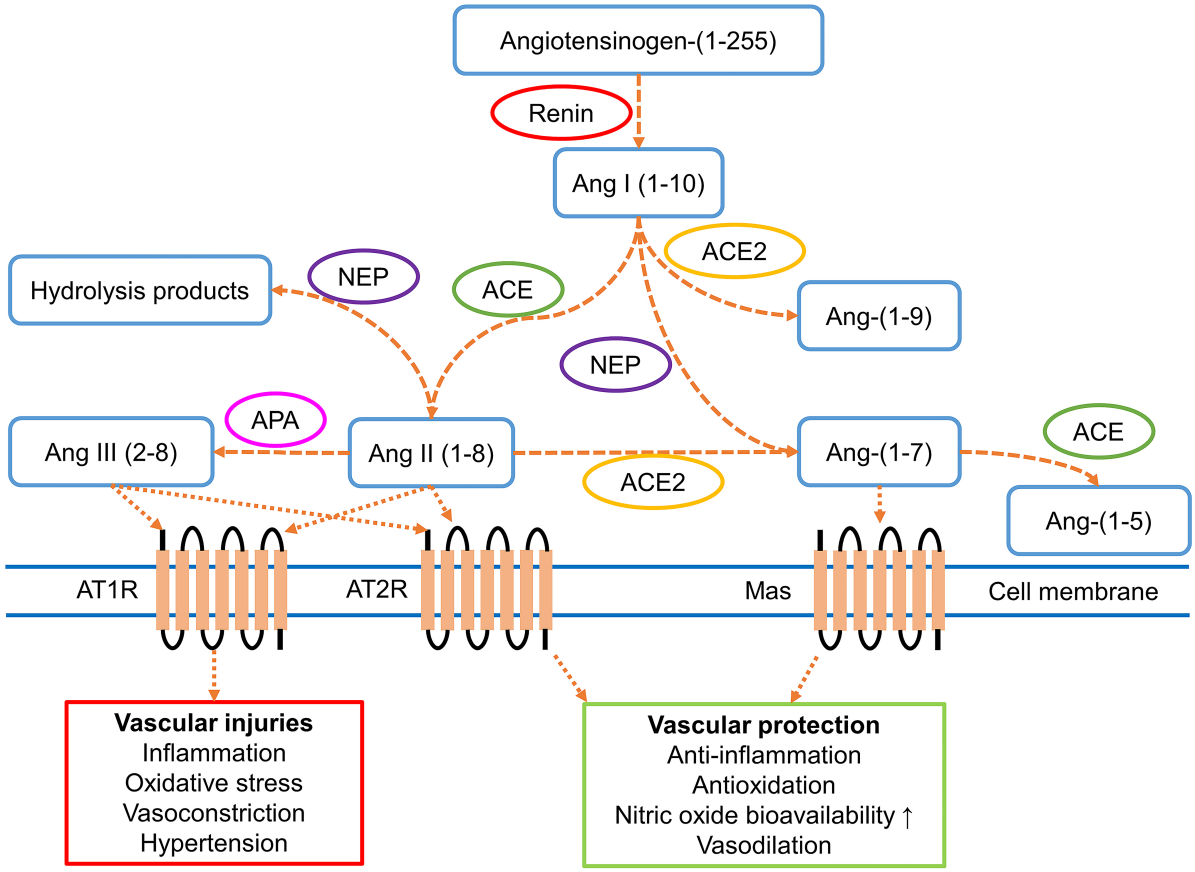

Figure 1. Illustration of the RAS. The ACE/Ang II/AT1R axis and the ACE2/Ang-(1-7)/MasR axis represent the two most prominent and physiologically relevant pathways within the RAS. The delicate balance between the two axes is a key determinant of cardiovascular function and the regulation of inflammation and oxidative stress. ↑: To increase; RAS: renin-angiotensin system; ACE: angiotensin converting enzyme; Ang II: angiotensin II; ACE2: angiotensin converting enzyme 2; Ang: angiotensin; MasR: Mas receptor; APA: aminopeptidase; NEP: neprilysin; AT1R: Ang II type 1 receptor; AT2R: Ang II type 2 receptor; Mas: Ang-(1–7) receptor. Picture adapted from ref. [8]. In addition, we have made modifications and additions to the picture. Therefore, this picture does not involve any copyright issues.

the activation of Ang II/AT1R signaling cascade upregulates the expression of pro-angiogenic factors, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (BFGF), and angiopoietins, thereby enhancing tumor angiogenesis and increasing blood supply to the tumor[28]. Second, Ang II/AT1R activation stimulates a variety of intracellular signaling cascades, including the mitogen-activated protein kinase (MAPK)/ extracellular signal-regulated kinase (ERK), phosphoinositide 3-kinase (PI3K)/ a serine/ threonine kinase (AKT), and Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathways, which collectively promote tumor cell proliferation. Third, Ang II/AT1R signaling can induce epithelial-mesenchymal transition (EMT), thereby enhancing tumor cell invasion and metastatic potential[29]. Fourth, Ang II/AT1R activation leads to the upregulation of pro-inflammatory cytokines, chemokines, and adhesion molecules, which not only creates a tumor-promoting inflammatory microenvironment but also suppresses antitumor immune responses, allowing the tumor to evade immune surveillance[30]. Finally, Ang II/AT1R signaling can promote oxidative stress within the tumor, which may contribute to genomic instability and the acquisition of additional oncogenic mutations, further driving tumor progression[31]. However, due to the limited studies specifically focused on the role of the Ang II/ AT1R axis in ccRCC, the applicability of these mechanisms in fully explaining the formation and

development of ccRCC may be constrained and requires further investigation.

The Ang-(1-7)/MasR axis acts oppositely to the Ang II/AT1R axis, significantly inhibiting tumor growth. In addition to the anti-angiogenic, anti-proliferative, anti-EMT, anti-inflammatory, and antioxidant effects described previously, Ang-(1-7)/MasR activation has also been shown to induce apoptosis in tumor cells. For instance, studies on hepatocellular carcinoma models have demonstrated that Ang-(1-7) inhibits tumor growth by suppressing tumor cell proliferation, promoting apoptosis, and inhibiting tumor angiogenesis[32]. These studies also revealed that Ang-(1-7) downregulates AT1R mRNA expression, upregulates AT2R and Mas mRNA levels, and inhibits p38-MAPK phosphorylation. Another study on tumor-induced cachexia has shown an antitumor effect of Mas receptor activation[33]. *In vitro* experiments revealed that overexpression or pharmacological activation of the Mas receptor ameliorated the muscle wasting induced by Colon-26 cancer cells. Moreover, *in vivo* studies demonstrated that Mas receptor activation inhibited tumor growth and alleviated muscle wasting.

Collectively, these studies have illustrated that the activated Ang II/AT1R axis promotes tumor growth, whereas the activated Ang-(1-7)/MasR axis inhibits it. Furthermore, the effects of ACE and ACE2 are realized by regulating the balance between Ang II and Ang-(1-7).

ACE and ACE2 in ccRCC

A 2010 clinical study found that ACE and ACE2 were generally downregulated in ccRCC, chromophobe renal cell carcinoma, and renal oncocytoma[34]. While this finding suggests a potential association between altered ACE and ACE2 expression and renal tumor pathogenesis, no specific correlation between ACE/ACE2 dysregulation and ccRCC was identified. This may be attributable to the lack of subgroup analysis in the study design. In contrast, another clinical investigation demonstrated that ACE, ACE2, and neprilysin (NEP) were highly expressed in ccRCC tissues and positively correlated with tumor invasiveness[35]. Moreover, NEP expression was associated with improved 15-year overall survival rates. Additionally, APA expression was inversely correlated with tumor grade in ccRCC, with the absence of APA linked to favorable 15-year survival outcomes. Subsequent blood-based assays revealed increased serum activities of ACE2, NEP, and APA in patients with renal tumors compared to healthy controls, while serum ACE activity was lower in individuals with high-grade and metastatic ccRCC. Recently, two bioinformatics analyses have implicated ACE inhibitors as potential therapeutic options for ccRCC[36,37]. Similarly, a recent pan-cancer bioinformatics study further found that high ACE2 expression was associated with improved prognosis specifically in ccRCC, suggesting a potential role for antihypertensive medications in the management of this malignancy[38]. Furthermore, a clinical study also demonstrated that higher ACE2 expression levels correlated with better overall survival in ccRCC patients[39]. Subsequent *in vitro* and animal studies have further indicated that ACE2 may inhibit tumor growth by upregulating Ang-(1-7) levels[39]. Collectively, these findings have suggested that ACE upregulation is associated with ccRCC development and invasiveness, whereas ACE2 upregulation is linked to antitumor effects and improved survival outcomes.

In addition, transmembrane protein 27 (TMEM27/collectrin), a homolog of ACE2 and potentially protective in the context of hypertension, has also been found to be associated with ccRCC[40,41]. Clinical studies have demonstrated that TMEM27 deficiency is linked to more aggressive ccRCC and poorer overall survival and disease-free survival in patients[42]. This may be one of the significant factors contributing to the promotion of ccRCC progression by hypertension.

Ang II/AT1R in ccRCC

The Ang II/AT1R axis has been extensively implicated in tumor development and metastasis across various cancer types, including ccRCC. However, the evidence specifically linking this pathway to ccRCC pathogenesis remains relatively limited, with only a few studies providing more indirect support. For instance, clinical investigations have shown that high expression of AT1R and AT2R in ccRCC specimens is associated with high-grade tumors and poorer progression-free survival[43]. Furthermore, in a mouse model of ccRCC, the AT1R antagonist telmisartan significantly reduced tumor growth by inducing tumor necrosis, decreasing VEGF levels, and inhibiting angiogenesis[44]. Additionally, studies utilizing the Ang II infusion model have explored the role of hypertension-associated mechanisms in ccRCC. In one such study, Wang *et al*. demonstrated that Ang II promoted tumor cell proliferation and migration in a mouse ccRCC model, an effect mediated by the downregulation of tissue inhibitor of metalloproteinase 3 (TIMP3)[5].

Ang-(1-7)/MasR in ccRCC

The role of the Ang-(1-7)/MasR axis has been studied less extensively in ccRCC compared to other cancer types. Only a limited number of studies have suggested that Ang-(1-7) may have potential therapeutic effects in ccRCC[39]. Interestingly, more evidence has indicated that activation of the Ang-(1-7)/MasR axis may promote the development and metastasis of ccRCC, which contradicts findings reported in other cancer models. For instance, a cellular study revealed that Ang-(1-7) enhanced the migration and invasion of 786-O and Caki-1 ccRCC cell lines, whereas antagonizing or silencing the Mas receptor abrogated the stimulatory effects of Ang-(1-7)[45]. Furthermore, the pro-migratory and pro-invasive effects of Ang-(1-7) in 786-O cells were found to be mediated through the AKT signaling pathway. Consistent with these *in vitro* findings, an animal study demonstrated that Ang-(1-7) dose-dependently promoted the growth and migration of Caki-1 and Caki-2 cells, and that the Mas receptor antagonist A779 did not block these pro-tumorigenic effects[46]. Notably, Ang-(1-7) did not affect cell proliferation or intratumoral vascular density in this model. Additionally, the NHERF4 has been shown to inhibit phospholipase C (PLC)/AKT signaling by directly binding to the Mas receptor, thereby suppressing the invasive potential of ccRCC[47]. Furthermore, a recent clinical study reported that the expression level of the Mas-related G protein-coupled receptor D (MrgD) in both the tumor center and the invasive front of ccRCC specimens was positively correlated with histological grade, tumor diameter, local invasion, regional lymph node involvement, and distant metastasis[48]. Collectively, these findings have suggested that, in contrast to the antitumor effects observed in other cancer types, the Ang-(1-7)/MasR axis may have pro-tumorigenic and pro-metastatic roles in the context of ccRCC.

Other effectors and metabolite

Beyond the primary bioactive peptides, the RAS encompasses a variety of effectors and metabolites, the functions of which in ccRCC remain largely unknown. A case in point is the vasoactive peptide bradykinin (BK), which serves as the optimal substrate for ACE and is quickly metabolized into its fragments, BK-(1-7) and subsequently BK-(1-5). To date, a single study has suggested a potential link between the BK receptor B2 and the prognosis of ccRCC[49]. Likewise, the (pro)renin receptor (PRR) emerges as an innovative receptor within the RAS. Ubiquitous expression of PRR is observed across kidney tumor subtypes, with particularly heightened staining intensities noted in chromophobe renal cell carcinomas (ChRCCs) and renal oncocytomas (ROs)[50]. The heightened expression of PRR at the core of the tumor and the advancing edge of the infiltrating ccRCC is significantly correlated with elevated tumor grade, increased diameter, localized invasion, and advanced staging[50]. Moreover, this elevated expression is markedly linked to an escalated risk of mortality. However, this association is not yet supported by substantial direct evidence or detailed mechanistic studies. Consequently, the involvement of RAS in ccRCC deserves further investigation to elucidate its underlying mechanisms and potential therapeutic implications.

Section summary

It has been shown that the level of Mas receptor expression in mouse arteries decreases with age, which may lead to a diminished vascular response to Ang-(1-7)[51,52]. Similarly, ACE2 and AT2R expression levels were simultaneously reduced[51]. Conversely, age is associated with increased expression of ACE, Ang II, and AT1R[51]. This suggests that the antitumor effect of ACE2 may be more closely related to the reduction of Ang II/AT1R signaling. Furthermore, the pathomechanisms and therapeutic outcomes of ccRCC may differ between younger and older patients.

Taken together, the available evidence suggests that only ACE2 has an antitumor effect and is associated with improved prognostic survival, while the remaining peptides and receptors in the RAS appear to promote tumor growth and metastasis [Figure 2 and Table 1]. This implies that ACE2 may be a critical target for the treatment of hypertension-associated ccRCC.

RAS-RELATED DRUGS IN CANCER AND CCRCC

ACE inhibitors and angiotensin receptor blockers (ARBs) are the two main RAS inhibitors, both of which are commonly used in the management of kidney and cardiovascular disease[25]. ACE inhibitors inhibit Ang II production, whereas ARBs specifically block Ang II binding to downstream receptors. Recent studies have found that ACE inhibitors and ARBs present anticancer efficacy related to inhibition of tumor metastasis, growth, and angiogenesis in some cancers. For instance, the common ARB losartan has been shown to reduce tumor growth rates in human xenograft models of pancreatic, breast, and prostate cancer[53-55]. Additionally, a study in prostate cancer demonstrated that ARBs such as telmisartan and candesartan were able to inhibit AT1R expression, induce apoptosis in tumor cells, and suppress their proliferation[56-58]. Similarly, studies on hepatocellular carcinoma have revealed that the ACE inhibitor captopril inhibits tumor angiogenesis and metastasis[59]. Furthermore, studies involving patients with rectal cancer have indicated a better response to neoadjuvant therapy when combined with ARBs or ACE inhibitors[60]. Collectively, clinical trials have generally shown that the use of RAS inhibitors significantly improves overall survival and patient outcomes across various cancer types[61,62]. Therefore, ACE inhibitors and ARBs have been proposed as potential therapeutic options for cancer.

However, the existing literature also presents divergent insights. A meta-analysis encompassing 8,818 publications found no significant effect of ARB use on cancer incidence in randomized controlled trials (OR 1.02, 95%CI 0.87-1.19; P = 0.803)[63]. Similarly, another meta-analysis based on 14 randomized controlled trials and 17 observational studies made a comparable observation[64]. Specifically, cancer incidence was lower among ARB/ACE inhibitor users in observational studies (RR = 0.82, 95%CI = 0.73-0.93); however, this association was not observed in randomized controlled trials (RR = 1.00, 95%CI = 0.92-1.08). Furthermore, the beneficial effects of ARBs/ACE inhibitors were only evident in lung cancer (RR 0.85, 95%CI 0.75-0.97). Interestingly, the relative risk of cancers associated with RAS blockade decreased with a longer duration of follow-up, and the reduction in mortality was of marginal significance with ARB/ACE inhibitor use in observational studies but not in randomized controlled trials. These findings suggest that the potential antitumor effects of RAS inhibitors may vary depending on the specific tumor type, research methodology, and duration of treatment.

Currently, there is a paucity of studies investigating the effects of RAS inhibitors in ccRCC. Drawing upon the existing findings regarding the impact of RAS inhibitors in other tumor types, it can be hypothesized that ARBs/ACE inhibitors may potentially exert inhibitory effects on ccRCC. However, further research is still warranted to substantiate this hypothesis.

Table 1. The main references on the relationship between RAS and ccRCC

No.	Main research contents	Level of evidence	Ref.
1	ACE and ACE2 were downregulated in ccRCC.	Clinical observation	[34]
2	ACE, ACE2, and NEP were highly expressed in ccRCC tissues and positively correlated with tumor invasiveness. NEP expression was associated with improved 15-year overall survival rates. APA expression was inversely correlated with tumor grade in ccRCC. Increased serum activities of ACE2, NEP, and APA in patients with renal tumors compared to healthy controls, while serum ACE activity was lower in individuals with high-grade and metastatic ccRCC.	Clinical observation	[35]
3	Pan-cancer studies indicate that high ACE2 expression is only associated with improved prognosis in ccRCC.	Clinical observation	[38]
4	Higher levels of ACE2/Ang-(1-7) inhibit the proliferation of ccRCC.	Clinical observation and animal studies	[39]
5	TMEM27 deficiency is linked to more aggressive ccRCC and poorer overall survival and disease-free survival.	Clinical observation	[41] [42]
6	High expression of AT1R and AT2R in ccRCC specimens is associated with high-grade tumors and poorer progression-free survival.	Clinical observation	[43]
7	Telmisartan reduced tumor growth by inducing tumor necrosis, decreasing VEGF levels, and inhibiting angiogenesis.	Animal studies	[44]
8	Ang II promoted tumor cell proliferation and migration via downregulation of TIMP3.	Animal studies	[5]
9	Ang-(1-7) enhanced 786-O and Caki-1 ccRCC cell lines' migration and invasion via mediating the AKT signaling pathway. Antagonizing or silencing Mas receptor abrogated its stimulatory effects.	Cellular studies	[45]
10	Ang-(1-7) dose-dependently promoted the growth and migration of Caki-1 and Caki-2 cells, and the Mas receptor antagonist A779 did not block these pro-tumorigenic effects. Ang-(1-7) did not affect cell proliferation or intratumoral vascular density.	Animal and cellular studies	[46]
11	The NHERF4 inhibits PLC/AKT signaling by directly binding to the Mas receptor, suppressing the invasive potential of ccRCC.	Cellular studies	[47]
12	The expression level of the MrgD in both the tumor center and the invasive front of ccRCC specimens was positively correlated with histological grade, tumor diameter, local invasion, regional lymph node involvement, and distant metastasis.	Clinical observation	[48]

RAS: Renin-angiotensin system; ccRCC: clear cell renal cell carcinoma; ACE: angiotensin converting enzyme; ACE2: angiotensin converting enzyme 2; NEP: neprilysin; APA: aminopeptidase; TMEM27: transmembrane protein 27; AT1R: Ang II type 1 receptorplc; AT2R: Ang II type 2 receptor; VEGF: vascular endothelial growth factor; TIMP3: tissue inhibitor of metalloproteinase 3; AKT: a serine/threonine kinase; Ang: angiotensin; PLC: phospholipase C; MrgD: Mas-related G protein-coupled receptor D. This table is arranged by ourselves and there is no copyright issue involved.

CHALLENGES AND FUTURE PERSPECTIVES

Distal organ regulation and targeted drug delivery

Tumors commonly induce physiological dysfunction within the affected tissues. For instance, an imbalance in the intrarenal RAS significantly impacts patient prognosis and response to first-line immunotherapy[48]. However, the RAS is a ubiquitously expressed system across multiple organs, and locally produced RAS peptides may exert effects on distal organs through the circulatory system[65,66]. Recent studies have uncovered an intriguing phenomenon wherein overactivation of the RAS in the brain can influence chronic kidney disease (CKD)[67-69]. Furthermore, direct administration of trace amounts of RAS inhibitors into the brain can substantially ameliorate the progression of CKD[70-72]. These findings suggest that the development of hypertension-associated ccRCC may be related not only to local RAS imbalance but also to dysregulation of the RAS in distal organs. While non-targeted drug therapy can be beneficial in controlling hypertension, there is a potential risk of nonspecific side effects associated with long-term use. Therefore, precise diagnosis and targeted treatment of hypertension-associated ccRCC may help to mitigate this risk, and focused therapies could further reduce adverse effects by lowering the required drug doses.

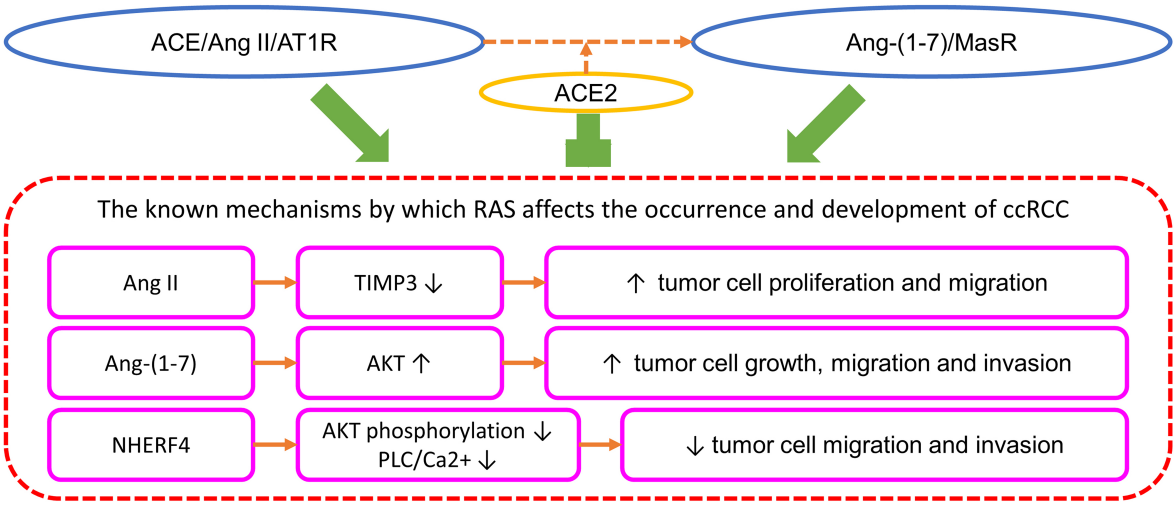

Figure 2. Of the components of the RAS, only ACE2 has been demonstrated to inhibit the development and metastasis of ccRCC. In contrast, activation of the remaining RAS signaling pathways is believed to promote tumor progression and metastasis. However, the underlying mechanisms driving these effects remain incompletely understood. ↑: To increase; ↓: to decrease; RAS: renin-angiotensin system; ACE2: angiotensin converting enzyme 2; ccRCC: clear cell renal cell carcinoma; ACE: angiotensin converting enzyme; Ang II: angiotensin II; AT1R: Ang II type 1 receptorplc; Ang: angiotensin; MasR: Mas receptor; TIMP3: tissue inhibitor of metalloproteinase 3; AKT: a serine/threonine kinase; PLC: phospholipase C. This picture is drawn by ourselves and there is no copyright issue involved.

Blood-brain barrier and engineered exosomes

When considering the role of the brain's RAS in regulating the kidneys, a key issue that must be addressed is the blood-brain barrier (BBB)[73]. The BBB refers to the specialized barriers formed by the walls of the brain's capillaries and the surrounding neuroglia, selectively preventing the entry of certain substances from the bloodstream into the brain tissue without interfering with the normal transport of essential nutrients. While the BBB is crucial for maintaining central nervous system (CNS) homeostasis, it also impedes the penetration of many drugs into the brain tissue, thereby limiting their therapeutic efficacy.

Exosomes are extracellular vesicles secreted by cells that serve as a means of intercellular communication by delivering their cargo of various biomolecular substrates[74]. The utilization of exosomes as drug delivery vehicles has emerged as a promising therapeutic strategy due to their inherently low immunogenicity and ability to penetrate tissue barriers. Notably, exosomes derived from macrophages, neutrophils, and natural killer (NK) cells possess membrane proteins with chemotactic properties, enabling them to localize at sites of injury and to cross the BBB[75-78]. Furthermore, biotechnological modification of exosomal membrane proteins can further enhance their brain-targeting capabilities. It has been demonstrated that incorporating specific peptides and ligands, such as c(RGDyK), AS1411 aptamer, neuropilin-1-targeting peptide, angiopep-2 peptide, T7 chimeric antigen receptor, transferrin receptor, and ANG-TRP-PK1, can significantly improve the BBB-penetrating ability of exosomes, thereby enhancing their utility as drug delivery systems targeting the CNS[78-84].

Challenges of clinical application of RAS drugs

While numerous RAS-targeted pharmacological agents have demonstrated promising results in preclinical studies for managing hypertension, their efficacy and safety profiles in the clinical control of hypertension-associated ccRCC remain uncertain. Furthermore, the sequential relationship between hypertension and the development of ccRCC is not well understood. It is plausible that the presence of tumors may lead to dysregulation of the kidney RAS, or RAS dysfunction may accelerate tumor growth. Consequently,

strategically utilizing these pharmacological agents to optimize therapeutic benefits while minimizing adverse effects represents a valuable research direction for future investigation.

Tumor microenvironment

Tumor development and metastasis, including ccRCC, are closely intertwined with the tumor microenvironment and tumor-associated macrophages[85]. RAS has been shown to regulate the tumor microenvironment and modulate macrophage phenotypes through immunomodulatory mechanisms[86]. This suggests that the RAS may influence tumor progression by mediating alterations within the tumor microenvironment. While previous studies have primarily focused on the relationship between individual genes and ccRCC, investigating whether changes in the tumor microenvironment induced by the RAS can impact the trajectory of tumor progression remains a worthwhile endeavor.

Vasculogenic mimicry

Vasculogenic mimicry (VM) refers to the ability of aggressive cancer cells to form vascular-like channels that can transport blood, without the involvement of endothelial cells[87,88]. This process enables the tumor to obtain nutrients and oxygen, thereby promoting its growth and metastasis. Recent studies have explored the role of VM in ccRCC and found that its presence is often associated with poor prognosis[89-91]. Therefore, targeting VM may be a promising therapeutic approach for ccRCC.

Furthermore, 48 genes have been implicated in the formation of VM in osteosarcoma[92]. Several of these genes, such as matrix metalloproteinases (MMPs) and inflammatory factors, are also associated with RAS activation. A recent study on non-small cell lung cancer demonstrated that local RAS fluctuations can affect VM formation[88]. ACE2 and ACE inhibitors can promote VM formation through the Nodal/Notch4 signaling pathway and enhance VM structure by inhibiting VE-cadherin internalization. However, the study of the role of RAS in ccRCC-related VM is still lacking. Elucidating this relationship represents an important area for future research.

Stress and exercise

A long-term high-stress state frequently induces the body to secrete more stress hormones. This might trigger the activation of the RAS, subsequently increasing the generation of Ang II[93]. Additionally, recent studies propose that such long-term psychological stress can enhance the occurrence and development of cancer[94]. For instance, one study noticed that the levels of Ang II in serum and breast cancer genes (BRCA) tissues rose under chronic stress, resulting in accelerated BRCA growth in mouse models[95]. The AT1R inhibitor candesartan mitigated Ang II-induced cell proliferation and metastasis by suppressing the focal adhesion pathway PARP1/FN1. Subsequent clinical studies presented analogous outcomes[95]. Compared to patients in the control group, the levels of Ang II in tumor tissues and serum of stressed patients were higher, and the serum Ang II levels positively correlated with chronic stress indicators. Nevertheless, currently, there is no evidence indicating the relationship between stress and ccRCC, nor the role of RAS within it.

Conversely, moderate physical activity typically exerts a salutary regulatory influence on the RAS. It is widely acknowledged that exercise can ameliorate cardiovascular function, and enhance the elasticity and dilation capacity of blood vessels, all of which contribute to reducing the generation of Ang II and the activation of AT1R[96,97]. Furthermore, recent studies have also indicated that regular physical activities can retard the progression of cancer, including highly invasive malignant tumors[98-100]. Although the potential mechanisms related to the antitumor effect of exercise remain elusive, it is generally believed to be associated with exercise-stimulated infiltration of diverse immune cell subtypes into tumors[98]. There is also evidence suggesting that immune cells collected from the blood following exercise can be employed as

adoptive cell therapy for cancer[100]. However, the role of exercise and exercise-mediated RAS in ccRCC remains indistinct.

LIMITATIONS

This study has several limitations. Firstly, the impact of RAS on ccRCC was only discovered in recent years, and the effect of RAS on ccRCC is not entirely consistent with that on other tumors. Thus, the mechanism by which RAS affects ccRCC remains uncertain. Secondly, although hypertension may accelerate the progression of ccRCC, the relationship between this mechanism and RAS is still undefined. Thirdly, it is also undetermined whether ccRCC can activate RAS. Fourthly, there are numerous drugs currently available for treating hypertension, but the efficacy of these drugs in treating ccRCC and its related hypertension is unclear. Fifthly, it remains unclear whether the current treatment plans for ccRCC will bring about blood pressure changes and RAS activation. Finally, current studies mainly focus on the influences of the two axes, namely ACE/Ang II/AT1R and ACE2/Ang-(1-7)/MasR, on ccRCC. The impacts of other effectors and metabolites in RAS on ccRCC remain under-researched. Many issues still await future resolution.

CONCLUSION

In conclusion, apart from ACE2 showing a protective effect, both the ACE/Ang II/AT1R and Ang-(1-7)/MasR axes may contribute to the progression and metastasis of ccRCC, underscoring the complex and multifaceted nature of the RAS in this malignancy. This also suggests caution in the use of hypertension medication in patients with hypertension-related ccRCC. Further research is warranted to fully elucidate the relative contributions and underlying mechanisms of these pathways in the context of ccRCC.

DECLARATIONS

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Authors' contributions

Writing and discussion of the article: Yang G, Wang Y, Lai ZW, Zhang H, Zhang Y, Song F
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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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