Chapter 16
Renin-Angiotensin System and Cancer: From Laboratory to Clinics

Jinxuan Su, Qiuming Zou, Sijia Li, and Qi Qi

Abstract Renin-Angiotensin System (RAS) is a vital system regulating blood pressure and maintaining sodium homeostasis in the human body. It consists of Angiotensin I (Ang I), Angiotensin II (Ang II), Angiotensin-converting enzyme (ACE), Angiotensin II type 1 receptor (AT1R), and angiotensin II type 2 receptor (AT2R), which functions in both normal and pathological conditions including cancer. Besides, the effectors of RAS are also included, such as Angiotensin-(1-7). This review focuses on the pre-clinical studies and clinical trials assessing the roles of RAS in regulating tumor progression as well as the underlying mechanisms.

Keywords Renin-angiotensin system · Cancer progression · Proliferation · Angiogenesis · Metastasis

Abbreviations

ACE	Angiotensin-converting enzyme
Ang II	Angiotensin II
AT1R	Angiotensin II type 1 receptor
AT2R	Angiotensin II type 2 receptor
Ang (1-7)	Angiotensin 1-7
MASR	MAS Receptor
ACE-2	Angiotensin-converting enzyme 2
VEGF	Vascular endothelial growth factor
EMT	Epithelial mesenchymal transition
MMPs	Matrix metalloproteinases
ECM	Extracellular matrix

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ACE-Is	ACE inhibitors
ARBs	AT1R blockers
EC	Endometrial cancer
PC	Prostate cancer
PTK	Protein tyrosine kinase
ROS	Reactive oxygen species
AMPK	AMP-activated protein kinase
mTOR	Mammalian target of rapamycin
EGFR	Epidermal growth factor receptor
MAPK/STAT	Mitogen-activated protein kinase/signal transducer and activator of transcription
PI3K/AKT	Phosphoinositide 3-kinase/Akt
RCC	Renal cell carcinoma
HCC	Hepatocellular carcinoma
CRC	Colorectal cancer
NSCLC	Non-small cell lung cancer

Introduction

Renin-Angiotensin System (RAS) is a complex systemic hormonal cascade of interacting peptides and enzymes, which plays a vital role in regulating blood pressure and maintaining normal sodium homeostasis of the human body [1]. It contains Angiotensin I (Ang I), Ang II, Ang-(1-7), MAS Receptor (MASR), Angiotensin-converting enzyme (ACE), ACE-2, Angiotensin II type 1 receptor (AT1R), and angiotensin II type 2 receptor (AT2R) [2]. Angiotensinogen (AGT), a precursor peptide related to the family of serine protease inhibitors (serpins), is the unique substrate for the protease renin (EC 3.4.23.15). The hydrolysis of AGT by renin is rate-limiting for the whole system and results in the production of des(Ang I)-AGT and of the vasoinactive peptide Ang I, which is converted to the vasoactive peptides Ang II and Ang III by ACE (EC 3.4.15.1) and aminopeptidase A (EC 3.4.11.7), respectively [3]. Angiotensin-(1-7), converted from Ang II by ACE and ACE2, has been reported to counteract the function of Ang II in many aspects, serving as a biologically active intermediate of the vasodilatory arm of the renin-angiotensin system [4]. RAS plays a pivotal role in the maintenance of normal physiological state in the human body, whose dysregulation has been reported to lead to the onset of various diseases, such as hypertension [5], diabetes [5], stroke [6], chronic obstructive pulmonary disease (COPD) [7], cancer [8], etc.

Cancer is one of the leading causes of death in the world and acquires the malignancy depending on several abilities: constant proliferation signals, sustained angiogenesis, tissue invasion and metastases, and evasion of apoptosis [9]. It has been reported that upregulation of the components of RAS is in close relationship with some types of cancers, such as colorectal cancer [10], prostate cancer [11], renal

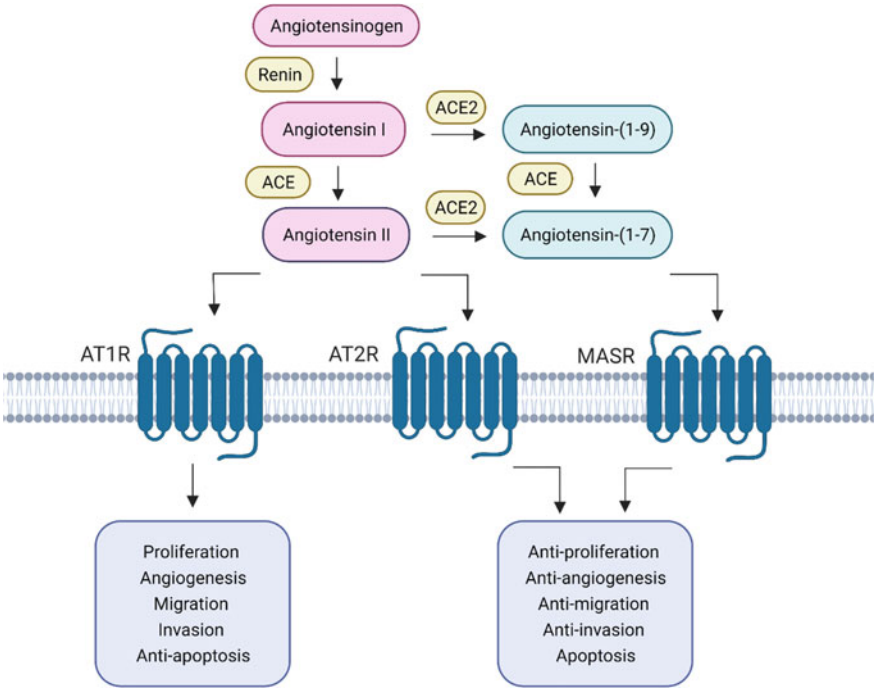

Fig. 16.1 The role of RAS in tumor progression. Main members of RAS include Ang I, Ang II, Ang-(1-7), MASR, ACE, ACE-2, AT1R, and AT2R. Binding of Ang II to AT1R increases angiogenesis, tumor proliferation, migration, invasion, and metastasis. On the contrary, binding of Ang II to AT2R inhibits angiogenesis, cell proliferation, migration, invasion, and metastasis. Binding of Ang-(1-7) with MASR exerts similar anti-tumor effects

clear cell carcinoma [12], and gliomas [13], etc. The importance of RAS and its components in cancer development merits attentions to cancer researchers. Here, this article reviews the role of RAS in tumor progression including cell proliferation, angiogenesis, metastasis, and the potential strategies for cancer treatment through modulation of RAS functions (Fig. 16.1).

RAS and Tumor Progression

RAS and Cell Proliferation

RAS has been first revealed as the regulator in proliferation of tumor cells. Among the members of RAS, Ang II and ACE have a close association with tumor cell proliferation, which are involved in multiple signaling pathways

including AT1R/PI3K/Akt/mTOR, AT1R/Raf/ERK1/2, and MAPK signaling pathways (Fig. 16.2). Insulin resistance induces the secretion of insulin-like growth factor (IGF)-1 in the liver, which promotes cell proliferation and inhibits cell apoptosis through Akt signaling pathway [14]. Besides, IGF-1 also triggers MAPK signaling and promotes mitosis in a variety of cancer cells [15, 16]. Ang II can activate the AT1R-mediated PI3K/Akt/mTOR pathway, promoting the occurrence, survival, and growth of cancer cells [17, 18], which can be blocked by antagonizing AT1R [19]. Ang II is able to upregulate CyclinD1, GSK3β, and downregulate p27 in hepatocellular carcinoma via AT1R-induced activation of PKC and MAPK signaling pathways [20].

The ACE inhibitor elicits outside-in signaling in endothelial cells, enhancing the activity of ACE-associated kinase CK2 and increasing the phosphorylation of the intracellular tail of ACE [21]. Researchers have found ACE activation might control the expression of diverse proteins besides ACE itself. Upon binding to ACE, Ang II internalizes with a faster onset compared to the binding of Ang II to its classical AT1 receptor [22]. Ang II and ACE can form a complex, which translocates to the nucleus through a clathrin-mediated process, and interacts with β3 isoform of PLC, triggering a nuclear Ca^{2+} signal resulting in induced cell proliferation [23, 24]. In melanoma TM-5 cells, Ang II induced cell proliferation through ACE activation, which was confirmed by ACE inhibitor (Lisinopril) or by the silencing of ACE [22].

Different RAS receptors either activate or inactivate various signaling pathways related to cancer development. AT1R activation through binding of Ang II leads to

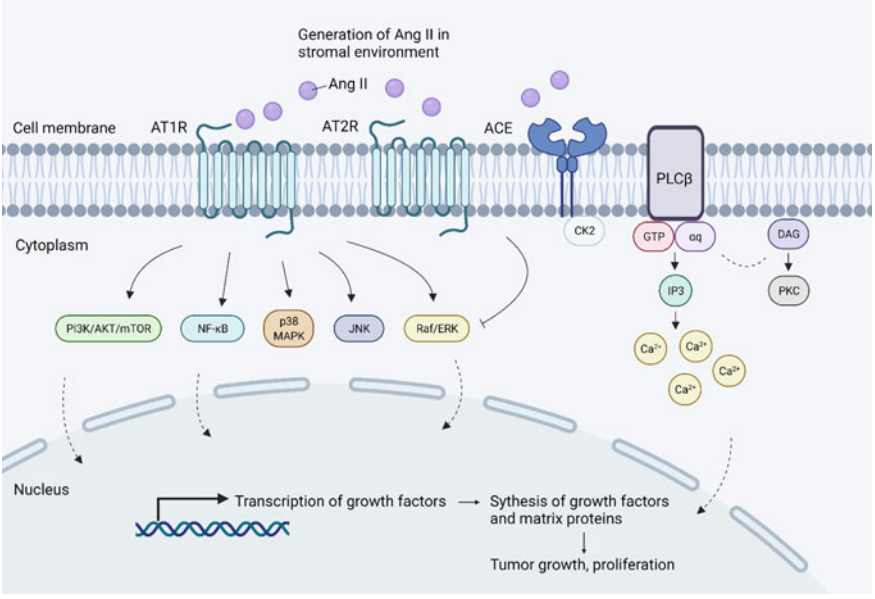

Fig. 16.2 The regulation of RAS in proliferation of tumor cells

activation of PI3K/AKT/mTOR, NF-κB, MAPK, JNK, Ras/ERK pathways. Transcription of growth factors and formation of matrix proteins are then triggered and lead to increased cell proliferation. Ang-(1-7) bind to MASR and is mediated through TGF-β, PAK1/NF-κB/Snail pathways.

RAS and Tumor Angiogenesis

Tumor angiogenesis produced by RAS is mainly induced by vascular endothelial growth factor (VEGF) and its related pathways. As opposed to the systemic RAS, recently, the concept of a localized RAS has been reported, such as in the central nervous system (CNS) [13] and female reproductive organs [25] (Fig. 16.3).

In CNS, the predominant cells expressing AGT are astrocytes [26], whereas renin, another key member of RAS system, is expressed in both astrocytes and neuron cells [27]. In glioblastoma, ACE activity cannot be detected in glioblastoma cells; however, ACE is highly expressed in the aberrant vasculature of human glioblastoma [28]. It was postulated that a complete angiotensin system existed in the brain, independent from the circulatory system and that its role in the regulation of vascular functions was crucial in tumors. In the vasculature, AGT, the unique and specific substrate of renin, is demonstrated to be antiangiogenic [29], while angiotensin peptides, in particular Ang II, have been shown to be proangiogenic and to be involved in vascular growth [3].

The mammalian VEGF family is comprised of five members: VEGFA, VEGFB, VEGFC, VEGFD, and placenta growth factor (PGF). VEGFA is the most functional

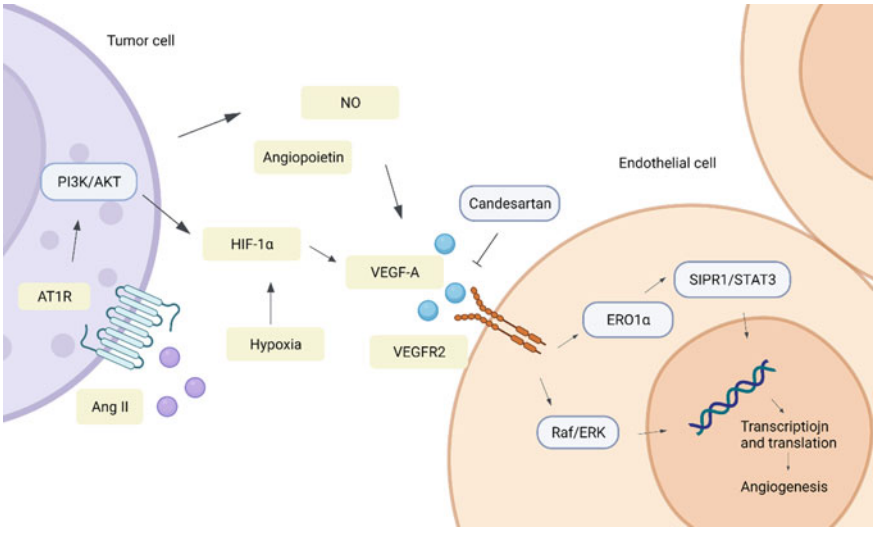

Fig. 16.3 The regulation of RAS in tumor angiogenesis

factor, which exerts angiogenic effects by activating VEGFR2 expressed in endothelial cells [30]. It has been revealed that ACE2 inhibits angiogenesis via suppressing the VEGFA/VEGFR2/ERK pathway in breast cancer [31]. Hypoxia leads to hypoxia-inducible factor 1α (HIF-1α) stabilization, increasing VEGF production in tumor cells. Besides, activation of the PI3K/AKT pathway also increases VEGF secretion in both HIF-1 dependent [32] and independent [33] manners. Moreover, the PI3K/AKT pathway also modulates the expression of other angiogenic factors such as nitric oxide [34] and angiopoietins [35, 36].

In the female reproductive system, activated RAS exists in the uterine endometrium, ovary, and placenta under both physiologic and pathological conditions [25, 37–39]. In ovarian carcinoma, VEGF is induced by Angiotensin II via AT1R, which is significantly correlated with poor prognosis [40]. AT1R upregulation in different cancers performs the function of promoting angiogenesis, contributing to cancer progression [25]. Angiotensin II also stimulated cell proliferation, invasion, and VEGF secretion via AT1R in cervical cancer [41, 42], endometrial cancer [43], choriocarcinoma [20], and ovarian cancer [44]. Besides, the host AT1R pathway supports tumor-associated macrophage infiltration, which results in enhanced VEGF levels [45]. Under neoplastic conditions, ACE inhibitors could inhibit the function of Ang II in angiogenesis. Serving as the most important cytokine affecting angiogenesis, VEGF is in a positive relationship with ERO1α, which promotes angiogenesis through the S1PR1/STAT3/VEGF pathway [46, 47]. Candesartan, an AT1R antagonist, has been reported to inhibit angiogenesis by downregulating AT1R/VEGF pathway [17, 48].

Angiogenesis generated by RAS system is mainly due to the binding of Ang II and AT1R. Activation of the PI3K/AKT pathway increases VEGF secretion in both HIF-1 dependent and independent manners. VEGFA exerts angiogenic effects by activating VEGFR2 expressed in endothelial cells through SIPR1/STAT3 and Raf/ERK pathways.

RAS and Tumor Metastasis

Metastasis is a multi-step process that accelerates tumor spread in the whole body, which starts with proliferation and acquires the escape capability from the primary tumor, then enters into the body circulation system, seeds into adjacent tissue cavities [49]. Growing evidence indicates that components of RAS are involved in tumor metastasis, especially Ang II [49]. Clinical research has also found that the use of renin-angiotensin system inhibitors (RASIs) can reduce cancer metastasis in several different cancer types, including hepatocellular carcinoma (HCC) [50] and bladder cancer [51].

Preliminary research in one murine renal cancer model has found that the blockade of Ang II with ACEI or ARB alone or in combination reduced tumor growth and the number of lung metastases [52]. NF-κB, a multi-regulatory transcription factor,

can upregulate the expression of VEGF and matrix metalloproteinase-9 (MMP-9) genes, and accelerate the occurrence, invasion, and metastasis of liver tumors [53]. RAS inhibitors, such as perindopril, fosinopril, and losartan, could inhibit the activation of NF-κB and further downregulate the levels of VEGF and MMP, thereby inhibiting metastasis [17, 54]. ACE2/Ang-(1-7)/MAS axis is silenced in human breast cancer; its downregulated expression critically promotes breast cancer metastasis to the lungs through activating PAK1/NF-κB/Snail signaling pathway by increasing SOCE-mediated Ca^{2+} influx, leading to decreased E-cadherin expression [55]. MAS receptor antagonist A-779 blocks the ACE2/Ang-(1-7)/Mas axis, leading to anti-metastatic effects [55].

Epithelial-mesenchymal transition (EMT) is one major process in metastasis, which can be indicated by downregulation of E-cadherin and upregulation of Vimentin. In A549 lung cancer cells, overexpression of ACE suppressed metastasis in vivo with increased level of E-cadherin and decreased level of Vimentin both in vitro and in vivo [56]. Dysregulation of TGF-β may contribute to the metastasis and invasiveness of cancerous pancreatic cells in advanced cancers [57]. ACE2 attenuated TGF-β1-mediated EMT in A549 cells. DX600, an inhibitor of ACE2, could reverse the sensitivity to TGF-β1 [56]. Ang II-treatment exacerbated hematogenous cancer metastasis by promoting E-selectin-mediated adhesion of cancer cells to vascular endothelial cells [58]. 20(S)-protopanaxadiol (PPD), the final metabolite of protopanaxadiol-type ginsenosides, effectively prevented Ang II-induced EMT via upregulation of the class III deacetylase sirtuin 1 (SIRT1). Downregulation of SIRT1 was involved in the suppression of Ang II-induced EMT by PPD [59].

Inhibition of the AT1R via angiotensin-converting enzyme inhibitors (ACE-Is) has demonstrated a decrease in solid tumor development and metastasis. In colorectal cancer (CRC) liver metastases, decreased Ang II and increased Ang-(1-7) were detected [60]. Captopril not only inhibits ACE, but also reduces the level of AGT in the host liver, leading to a distinct anti-metastatic effect [60, 61]. A study demonstrated an inverse relationship between the history of hypertension with the prescription of ACE-Is and the risk of distant metastasis in stage 2 CRC patients, implicating ACE-Is as a potential chemo-preventative option [61] (Fig. 16.4).

Angiotensin-(1-7), converted from Ang II by ACE2, binds to MasR and activates TGF-β and PAK1/NF-κB/Snail pathways. Dysregulation of these signalling pathways contributes to the transcription of targeted genes, including E-cadherin, Vimentin, and SIRT1, etc., which regulates tumor metastasis. RAS inhibitors, such as perindopril, fosinopril, and losartan, inhibit the activation of NF-κB. A-779 blocks the ACE2/Ang-(1-7)/Mas axis.

RAS and Cell Apoptosis

Research investigating the relationship between RAS and apoptosis has been focused on the AT2R which plays an opposite role of AT1R, protecting the normal function of RAS. It is reported that AT2R could stimulate apoptosis in various cancer cell

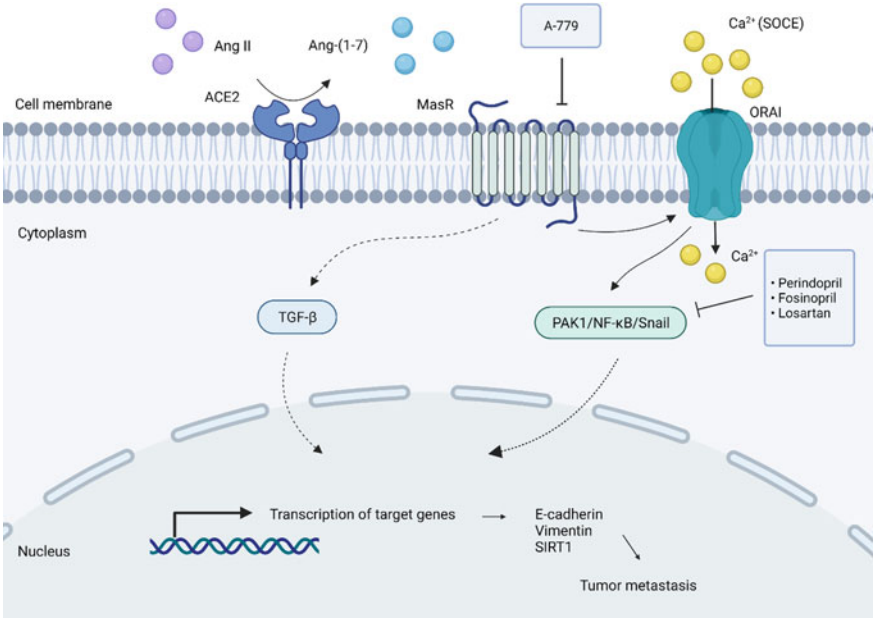

Fig. 16.4 The regulation of RAS in tumor metastasis

lines, including vascular smooth muscle cells, such as cardiomyocytes, endothelial cells, prostate cancer cells, and lung cancer cells [62–67]. Depending on the cell type, AT2R-mediated apoptosis involves distinct biological processes. In INS-1O rat insulinoma cells, overexpression of AT2R induced cleavage of caspase-8, caspase-9, and caspase-3, and decreased Bcl-2, p-AKT, and p-ERK levels [68]. In intestinal epithelial cells, Ang II signals upregulate GATA-6 expression through AT2R, which in turn upregulates the expression of Bax and eventually leads to apoptosis in these cells [63]. Increased apoptosis appears to be caused by INOs upregulation following enhanced AT2R expression in HL-1 cardiomyocytes [64]. Moreover, AT2R signaling stimulates the MAPK tyrosine phosphatase, which inhibits MAPK activation and consequently inactivates Bcl-2 and induces apoptosis in proximal tubular cells [69]. AT2R-mediated apoptosis was mediated by p38 MAPK and downregulation of Gadd45a, TRAIL-R2, and harakiri Bcl-2-interacting protein (HRK) in prostate cancer cells [65, 70]. In HCC cells, researchers found that apoptosis caused by AT2R overexpression is due to the activation of p38 MAPK, phosphorylated c-Jun N-terminal kinase (p-JNK), caspase-8, and caspase-3, and inactivation of pp42/44 MAPK (ERK1/2) [66]. Similarly, AT2R overexpression-induced apoptosis in BCA cells is mediated via an extrinsic cell death signaling pathway that is dependent on activation of p38 MAPK, caspase-8, and caspase-3 and downregulation of ERK/MAPK [71]. AT2R overexpression also leads to upregulation of 2 apoptosis-related genes (BCL2A1, TNFSF25) and downregulation of 8 apoptosis-related genes

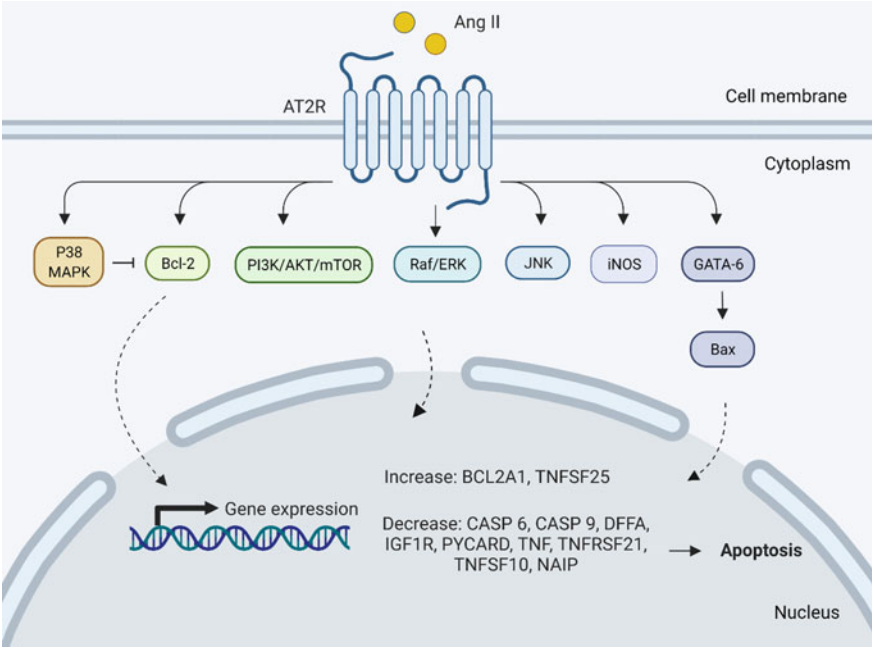

Fig. 16.5 The regulation of RAS in cell apoptosis

(CASP 6, CASP 9, DFFA, IGF1R, PYCARD, TNF, TNFRSF21, TNFSF10, NAIP) in transduced EJ cells [71] (Fig. 16.5).

Ang II binds to the AT2R, which activates P38 MAPK, GATA-6, INOS, PI3K/AKT/mTOR, and Ras/ERK pathways. Signals in the cytoplasm are then transported into the nucleus to upregulate anti-apoptotic genes and downregulate pro-apoptotic genes, leading to apoptosis.

Angiotensin-(1-7) and Tumor Progression

In addition to RAS system itself, the main effector peptide of RAS, Ang-(1-7), has been identified as a biologically active mediator of the RAS [72]. Ang-(1-7), converted from Ang II by ACE and ACE2, has been reported to counteract the function of Ang II in many aspects, which has attracted a lot of attention in recent years. Ang-(1-7), acting mainly through the MAS receptor, abolishes Ang II-induced migration, invasion, VEGF expression, and MMP-9 activity in breast cancer cells [72]. Moreover, Ang-(1-7) has been reported to completely block Ang II-induced EMT in breast cancer [72].

The angiotensin II receptor family members include AGTR1 and AGTR2, which belong to the G-protein-coupled receptor superfamily. AGTR1, overexpressed in

many primary and metastatic tumors [73, 74], enhances tumor growth and angiogenesis in breast cancer cells, as evidenced by upregulation of nuclear accumulation of phospho-Smad3, Snail, increased Smad4 and N-cadherin levels [75]. By enhancing adhesion of epithelial to the extracellular matrix, Ang-(1-7) can partially prevent the EMT process [72]. Besides, Ang II promotes survival and proliferation in breast cancer cells through activating PI3K/Akt pathway [72]. Ang II induces AKT phosphorylation in mammary epithelial cells at a very early time point (1 min). In contrast, Ang-(1-7) can blunt the AKT phosphorylation by the Ang II at a later time point (15 min) [72]. Recent studies have reported that AT1 stimulation by Ang II induces EMT via the Smad signaling pathway in renal epithelial cells and vascular smooth muscle cells in vitro [76, 77]. Ang-(1-7) reduced the cell migratory and invasive abilities by reducing the expression and activity of MMP-2 and MMP-9 mediated through inactivation of the PI3K/Akt, P38, and JNK signal pathways [78, 79].

Ang-(1-7) hampers the angiogenesis caused by the activation of Ang II [80]. In MDA-MB-231 cells, knockdown of MMP-2 and MMP-9 by siRNA significantly suppressed Ang II-induced cell migration [80, 81]. Enhanced expression and enzymatic activity of MMP-9 by Ang II are significantly abolished by Ang-(1-7). Besides, Ang-(1-7) suppresses Ang II-induced VEGF expression in breast cancer cells, which is consistent with prior research showing considerable VEGF reduction in nasopharyngeal carcinoma cells overexpressing Ang-(1-7) [82]. It has been discovered that Ang-(1-7) inhibits cancer cell invasion. Induced activation of ACE2/Ang-(1-7)/Mas axis attenuates breast cancer cell invasion by upregulating E-cadherin expression through downregulating SOCE-induced NF-κB and PAK signal pathways [55].

However, in contrast to the anti-cancer properties, there are also reports showing Ang-(1-7) exerted a growth-stimulatory effect on glioma cells [83]. Ang-(1-7)/Mas axis has also been shown to mediate Ang II-stimulated epithelial-to-mesenchymal transformation (EMT) in tubule cells [84]. Ang-(1-7) is also reported to promote the migration and invasion of human renal cell carcinoma cells via MAS-mediated AKT signaling pathway [85]. The reasons for the different functions of Ang-(1-7) in different cancer types are unknown, which are possibly due to experimental conditions or cell-specific signaling.

Regulation of RAS in Clinical Utilization

Currently, two types of regulators of RAS are being studied for clinical utilization. One is ACEIs that suppress signaling of Ang II receptors by reducing Ang II synthesis; the other is ARB, blockers of AT1R signaling, which have been tested in clinical studies (Table 16.1).

Table 16.1 The effect of ACEIs and ARBs in clinical cancer treatments

Types of cancer	Study characteristics			Treatment outcomes	Year	References
	Types of studies	Types of drugs	Number of patients			
Gastric cancer	Clinical study	ACEIs and ARB	63 patients	Disease control rate:77.8% Response rate:25.4% Patient characteristic: no different MPFS and OS: elevation of survival in user groups compared to non-user group	2001–2009	[102]
Pancreatic cancer	Clinical study	Enalapril, lisinopril, temocapril, candesartan, losartan, Olmesartan, valsartan	155 patients	PFS and OS: elevation of survival in user groups compared to non-user group Patient characteristic: no different except age and HT medication	2003–2011	[103]
Nonmetastatic Pancreatic Ductal Adenocarcinoma	Cohort study	Angiotensin system inhibitors (ASI)	794 patients	OS: chronic ASI use is associated with longer OS	2006–2010	[100]

(continued)

Table 16.1 (continued)

Types of cancer	Study characteristics			Treatment outcomes	Year	References
	Types of studies	Types of drugs	Number of patients			
Renal cancer	Cohort study	ACEIs and ARBs	127 patients	Objective response:86% Progressive disease:14% MPFS and OS: elevation of survival in user groups compared to non-user group	1995–2002	[104]
	Clinical study	ACEIs and ARBs	4736 patients	OS: elevation of survival in RASIs groups compared to other hypertensive drug and non-user groups Reduction of cell viability	2004–2010	[105]
	Clinical study	ACEIs and ARBs	213 patients	PFS and OS: elevation of survival in hypertensive patients compared to non-hypertensive elevation of survival in user groups compared to non-user group	2003–2013	[106]

(continued)

Table 16.1 (continued)

Types of cancer	Study characteristics			Treatment outcomes	Year	References
	Types of studies	Types of drugs	Number of patients			
Lung cancer	Observational study	Angiotensin system inhibitors (ASI)	117 patients	OS: elevation of survival in user groups compared to non-user group Follow-up period: it was longer in user groups	2004–2013	[107]
Lung cancer	Retrospective analysis	Long-term medication with ACEIs and ARBs	287 patients	MPFS: patients receiving either ACEI or ARB had a 3.1 month longer MPFS	1996–2007	[108]
Lung cancer (NSCLC)	Retrospective analysis	Chemotherapy or Erlotinib with ACEIs and ARBs	37 patients	OS: The use of ARBs during erlotinib treatment may prolong OS of patients with metastatic NSCLC	2003–2011	[103]

(continued)

Table 16.1 (continued)

Types of cancer	Study characteristics			Treatment outcomes	Year	References
	Types of studies	Types of drugs	Number of patients			
Lung cancer NSCLC (stage IIIb or IV) or early-stage disease (stage I-IIIa)	Retrospective analysis	Platinum-based chemotherapy ACEIs and ARBs	228 advanced NSCLC patients 73 early-stage disease patients	PFS: elevation in the ACEI/ARB group than the non-ACEI/ARB group OS: in combination with standard chemotherapy or TKIs, elevation in the ACEI/ARB group than the non-ACEI/ARB group both in the early or advanced stage	2000–2014	[109]
Lung cancer	Retrospective analysis	RAS-Is combined with paclitaxel (CP) or bevacizumab (CPB)	1813 patients 273 of 1,465 CP + ACEI/ARB 78 of 348 had CPB + ACEI/ARB	OS: elevation in the ACEI/ARB group than the non-ACEI/ARB group combined with CP No significant difference combined with CPB	2005–2011	[110]

(continued)

Table 16.1 (continued)

Types of cancer	Study characteristics			Treatment outcomes	Year	References
	Types of studies	Types of drugs	Number of patients			
Lung cancer	Retrospective cohort study	ACEIs and ARBs	678 patients	PFS: elevation in the ACEI/ARB group than the non-ACEI/ARB group OS: no significant difference between ACEI/ARB group than the non-ACEI/ARB group	2016–2018	[111]
Glioblastoma	Clinical study	Propranolol, aliskiren, cilazapril, celecoxib, curcumin with piperine, aspirin, and metformin	17 patients	Increased survival by 5.3 months but not statistically significant	2022	[112]
Infantile hemangioma (IH)	Randomized controlled trial	Captopril, propranolol	30 patients	Clinical improvement was significantly better and faster in the patients treated with propranolol	2016	[113]

(continued)

Table 16.1 (continued)

Types of cancer	Study characteristics			Treatment outcomes	Year	References
	Types of studies	Types of drugs	Number of patients			
Colorectal cancer	Nested case–control study	ACEIs and ARBs	2847 patients	Long-term/high dose exposure to ACE-Is/ARBs may be associated with a decreased incidence of CRC	1987–2002	[114]

Angiotensin-Converting Enzyme Inhibitors (ACEIs)

ACEIs have been shown to block solid tumor development and metastasis. Captopril, a classic ACEI, not only inhibits ACE, but also lowers ACE levels and angiotensinogen expression in the host liver, leading to inhibition of metastasis and further inhibitory mechanisms [60]. In lung cancer, Captopril also exerted anti-metastatic and growth inhibitive effects [86]. However, in renal carcinoma, the effects of Captopril are controversial. One group reported that Captopril inhibited tumor growth [87], while another group showed the induction of tumor by Captopril [88]. Independently of VEGF expression, ACE inhibition promoted neovascularization through activation of bradykinin B2 receptor signaling, whereas it reduced blood vessel growth through inhibition of the Ang II pathway [89, 90]. Besides, Perindopril was tested targeting breast cancer and found that Perindopril reduced tumor volume and downregulated the level of VEGF [91], leading to blockage of angiogenesis and metastasis in hepatocellular carcinoma [92].

AT1R Blockers (ARB)

ARBs are drugs that target the AT1R receptor. The effects of ARBs on cancer are not consistent currently. ARBs may suppress the promotional effect on proliferation by antagonizing AT1R caused by Ang II [19]. The blockade of Ang II with ACEI and ARB alone or in combination reduced tumor proliferation and metastatic capacity of RCC [52]. Losartan, the most commonly used ARB, was found to inhibit tumor growth and promote apoptosis in glioma [68]. However, Losartan was revealed to induce cancer progression and angiogenesis in lung cancer [93, 94]. Besides, it was also found to promote cell proliferation in human melanoma [95]. One research found that Losartan slowed pancreatic tumor progression by abrogating aberrant TGF-β activation [96].

Clinical Study of ACEI/ARB

In clinical studies, the efficacy of ACEI/ARB in the treatment of cancer patients is also controversial currently. It has been revealed that in 13 projects with breast cancer, only two studies showed beneficial effects of ACEI/ARB, whereas three studies reported poor outcomes [57]. Evaluating the tumor subtype information may be helpful to understand the different responsiveness of patients to the ACEI/ARB treatment [74]. Similarly, population-based studies failed to show any association or risk reduction, in patients receiving ACEI/ARB treatment [97–99]. However, a retrospective study in stage I-II colorectal cancer (CRC) patients showed that ACEI/ARB treatment reduced tumor recurrence in left-sided CRC and early-stage CRC [99]. Improved survival

was also observed in non-metastatic pancreatic ductal adenocarcinoma (PDAC) in a large-scale study [100]. Hence, multiple strategies and strict criteria should be applied to identify and include the studies to reveal the factors that may influence the association between RAS inhibitors and cancer progression [101]. Response to ACEI/ARB treatment may not only vary with tumor types but also depend on certain tumor characteristics, cancer treatment, and RASI type and dosing [50].

Conclusion

RAS participates in tumor progression in many cancer types and its dysregulation leads to increased malignancy of cancer. Although the role of RAS and the underlying mechanisms have been well studied, there are also controversies in its functions in cancer due to different environments and tissue conditions. ACE inhibitors and ARB have been investigated in preclinical research, and their roles in restricting the development of cancer is promising. However, limitations of the in vivo experiments with animal models indicate that there is still a possibility that the mechanism will be different in the human body. How to accelerate the transformation from experimental animals to clinics still needs further exploration.

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