Clinical and Translational Oncology (2021) 23:682–696
https://doi.org/10.1007/s12094-020-02488-3

REVIEW ARTICLE

Renin-angiotensin system and cancer: epidemiology, cell signaling, genetics and epigenetics

B. Afsar[1] · R. E. Afsar[1] · L. A. Ertuglu[2] · M. Kuwabara[3] · A. Ortiz[4] · A. Covic[5] · M. Kanbay[6]

Received: 18 June 2020 / Accepted: 31 August 2020 / Published online: 15 September 2020

Abstract

Day by day, the health and economical burden of cancer increases globally. Indeed it can be considered that there is ''cancer pandemic''. Blocking the renin-angiotensin system (RAS) by angiotensin-converting enzyme (ACE) inhibitors (ACEI) or angiotensin-receptor blockers (ARB) are widely used measures to treat hypertension and heart failure. It has been recently suggested the activation and blocking of RAS has been associated with various types of cancer in epidemiological and experimental studies. Various studies have shown that RAS blockage is protective in some cancers. However, although fewer, contradictory data also showed that RAS blockage is either not related or adversely related to cancer. Although the reasons for these findings are not exactly known, different types of receptors and effectors in RAS may account for these findings. In the current review, we summarize the different RAS receptors and cancer development with regard to epidemiology, and pathogenesis including cell signaling pathways, apoptosis, genetic and epigenetic factors.

Keywords Angiotensin · Apoptosis · Cancer · Cell signaling · Genetic

Introduction

Recent evidence suggests that Renin–Angiotensin System (RAS) plays an important role in the development of cancer. Both preclinical and clinical studies show that RAS is active, especially in certain forms of cancer [1–3]. While proto-oncogenes, oncogenes, cell signaling, microRNAs and epigenetic factors were demonstrated to play important roles in the relationship between RAS and cancer development [4], there are also conflicting reports showing that RAS blockage may be associated with increased cancer incidence [5]. In this narrative review, we evaluate the relationship between RAS and cancer with respect to epidemiology, pathogenesis and future issues.

Epidemiology of RAS and cancer

In humans, almost every organ was shown to have a functional RAS with varying degrees [6]. Increased RAS activity has been demonstrated in various tumor types including kidney, prostate, bladder, stomach, cervix, brain, pancreas, colon, lung, liver, skin, and hematopoietic cancers [1–3]. Although controversial data exist, most experimental studies suggest that Angiotensin-receptor blockers (ARB) have anti-proliferative effects in breast cancer [7], induce cell death in pancreatic cancer [8, 9], ameliorate liver metastases in colon cancer [10], and improve the survival in non-small-cell lung cancer [11]. In addition, angiotensin-converting enzyme (ACE) inhibitors (ACEI) may decrease the risk of developing esophageal cancer [12]. Table 1 shows the summary of meta-analyses regarding the use of ACEI/ARB, various cancers and ACE polymorphisms.

✉ B. Afsar
afsarbrs@yahoo.com

1 Department of Internal Medicine, Division of Nephrology, Suleyman Demirel University, School of Medicine, 71100 Isparta, Turkey

2 Department of Internal Medicine, Koc University School of Medicine, Istanbul, Turkey

3 Department of Cardiology, Toranomon Hospital, Tokyo, Japan

4 Dialysis Unit, School of Medicine, IIS-Fundacion Jimenez Diaz, Universidad Autónoma de Madrid, Avd. Reyes Católicos 2, 28040 Madrid, Spain

5 Nephrology Department, "Grigore T. Popa" University of Medicine and Pharmacy Iasi, Iași, Romania

6 Division of Nephrology, Department of Internal Medicine, Koc University School of Medicine, Istanbul, Turkey

Table 1 The summary of meta-analyses regarding the ACEI/ARB Use and Cancer Risk

Study	Number of participants	Outcome measure	Main findings
Sipahi et al. (2010) [5]	New cancer data (61,590 patients-5 trials) Data on solid organ cancers 68,402 patients 5T rials)	Whether ARBs affect cancer occurrence	ARBs had a significantly increased risk of new cancer occurrence (7·2% vs 6·0%, risk ratio [RR] 1.08, 95% CI 1.01–1.15; $P=0.016$)
	Data on cancer deaths (93,515 patients-eight trials)		No statistically significant difference in cancer deaths (1.8% vs1.6%, RR 1.07, 0.97–1.18; $P=0.183$)
Bangalore et al. (2011) [103]	324,168 participants from 70 randomised controlled trials	Too assessed the association between antihypertensive drugs and cancer risk including ACEI/ARBs	No difference in the risk of cancer with ARBs odds ratio 1.01, 95% CI 0.93–1·09), and with ACEi (2·03%; 1.00, 0.92–1.09) There was an increased risk with the combination of ACEi plus ARBs (2·30%, 1.14, 1.02–1.28
Ruiter et al. (2011) [104]	20,817 from 24 studies	To Assess *ACE Insertion/Deletion* genotype and the risk of cancer	Overall no significance II genotype has a lower risk of prostate cancer and postmenopausal breast cancer compared to DD genotype
Sipahi et al. (2011) [105]	Data for cancer occurrence (10 trials—59,004 patients)	To determine the effect of ACE inhibitors on cancer occurrence and cancer death	No effect on occurrence of cancer 1.01, 95% confidence interval [CI] 0.95–1.07, $P=0.78$)
	Data for cancer death (7 trials of 37,515 patients)		No effect on cancer death RR 1.00, 95% CI 0.88–1.13, $P=0.95$)
	Data for GI cancer (5 trials 23,291 patients)		No effect on GI cancer (RR 1.09, 95% CI 0.88–1.35, $P=0.43$)
Xi et al. (2011) [106]	10 studies (1650 cases and 9283 controls) on ACE I/D polymorphism	To assess the association (ACE) I/D A240T, angiotensin II type 1 receptor (AGTR1) A1166C and angiotensinogen (AGT) M235T polymorphisms, and breast cancer risk	Overall, the meta-analysis showed no significant association between I/D or A240T polymorphism and breast cancer risk
	6 studies (1316 cases and 2632 controls) on ACE A240T polymorphism 3 studies (235 cases and 601 controls) on AGTR1 A1166C polymorphism		A marginally significant association was observed for AGTR1 A1166C polymorphism in Caucasians
	2 studies (273 cases and 3547 controls) on AGT M235T polymorphism		There was a significant association between AGT M235T polymorphism and breast cancer risk in Caucasians
Mc Menamin et al. (2012) [107]	4178 cancer patients from 10 studies	To investigate the association between ACEI/ ARBs use and disease progression and survival	Significant improvement in overall survival (OS) and progression-free survival in pancreas Ca Protective against breast cancer recurrence and colorectal cancer distant metastasis
Lin et al. (2015), [108]	(3639 cancer cases and 6684 controls from 8 studies)	To assess the association of AGT M235T variant with cancer risk	AGT M235T variant was marginally associated with cancer risk under dominant model This association was lost in sensitivity analysis
Dai et al. (2015) [109]	135,605 participants in the incidence studies and 13,031 in the mortality studies from 11 observational studies	To assess the association between ACEI/ ARB therapy and colorectal cancer	Decreased risk of CRC in ACEIs/ARBs users compared to non-users (95% CI 0.89–0.98). No difference regarding CRC mortality

Table 1 (continued)

Study	Number of participants	Outcome measure	Main findings
Yang et al. (2015) [110]	2903 digestive cancer cases and 10,833 controls from 16 studies	To assess of ACE I/D polymorphism with digestive cancer risk	ACE gene I allele might be a protective factor against gastric cancer
Mao et al. (2016) [111]	20,267 participants from 9 studies	To assess RAS the relationship system blockage and prostate cancer risk	RAS blockage is associated with reduced risk of prostate cancer (RR 0.92, 95% CI 0.87–0.98)
Shen et al. (2016) [112]	3,957,725 participants (350,329 ARB/ACEI users) from 14 randomised and 17 observational studies	To assess the association between ACEI/ARB use and risk of cancer and death	ACEI/ARB users had a lower incidence of cancer in the observational studies (RR 0.82, 95% CI 0.73–0.93) but not in the randomised controlled trials (RR 1.00, 95% CI 0.92–1.08) Mortality reduction with ARB/ACEI was marginally significant in the observational studies (RR 0.71, 95% CI 0.55–0.93) but not in the randomised controlled trials (RR 0.99, 95% CI 0.89–1.09
Sun et al. (2017) [113]	81,873 cancer cases from 55 studies	To evaluate the effect of RAS inhibitors on recurrence, metastasis, and survival in cancer patients	Significant improvements in overall survival ((HR = 0.82; 95% CI 0.77–0.88; $P < 0.001$), progression-free survival (HR = 0.74; 95% CI 0.66–0.84; $P < 0.001$), and disease-free survival (HR = 0.80; 95% CI 0.67–0.95; $P = 0.01$) with RAS inhibitors
Li et al. (2017) [114]	2436 cancer patients from 7 retrospective studies	To evaluate the effect of adjunctive therapy of RAS blockers combined with chemotherapeutic agents	A signifIcant reduction in overall mortality in a combination of chemotherapeutics with RAS blockers compared to chemotherapeutics alone
Datzmann et al. (2019) [43]	953,753 participants from 7 randomised, 4 case–control and one cohort study	To evaluate ARBs and carcinogenicity	There was no effect on carcinogenesis in randomised controlled trials for ARB usage. (OR 1.02, 95% CI 0.87–1.19; $P = 0.803$)
Abdeahad et al. (2019) [115]	3722 patients from 19 case–control studies	To evaluate the association between the ACE (I/D) polymorphism (DD vs II) and digestive system cancer susceptibility	No relationship between the ACE I/D polymorphism and digestive system cancer risk (odds ratio [OR], 0.93; 95% confidence interval [CI], 0.68–1.29; $P = 0.65$)
Cheng et al. (2019) [116]	928 cases from 8 studies for I/D polymorphism 1162 cases from 2 studies for M235T polymorphism	To evaluate the (I/D) and M235T polymorphisms with cancer risk	The ACE I/D polymorphism did not significantly correlate with colorectal cancer risk Angiotensinogen M235TM polymorphism was not associated with colorectal cancer risk
Xiao et al. (2019), [117]	Results: Eight case–control studies were identified from five articles	To assess A240T polymorphism in the (*ACE*) gene and cancer risk	ACE A240T polymorphism was related to cancer risk (AT vs AA: OR 2.14, 95% CI 1.51–3.04 T

Table 1 (continued)

Study	Number of participants	Outcome measure	Main findings
Zhou et al. (2020), [118]	13 studies	To evaluate RAS inhibition in digestive system malignancies	ACEIs or ARBs showed improvement in overall survival (HR 0.79; 95% CI 0.70–0.89; $P<0.000$) Cancer-specific survival (HR 0.81; 95% CI 0.73–0.90; $P<0.000$) And recurrence-free survival (HR 0.68; 95% CI 0.54–0.85; $P=0.001$) No association between ACEI/ARB with progression-free survival (HR 0.88; 95% CI 0.73–1.07; $P=0.183$) and disease-free survival (HR 0.50; 95% CI 0.11–2.39; $P=0.103$)

The effect of ARBs on cancer development may depend on the type of ARB. In patients with diabetes mellitus Chang et al. [13]. did not demonstrate any association between ARB use and cancer incidence in general. (OR, 0.94; 95% CI 0.80–1.10). However, findings are heterogeneous among different ARBs. For instance, the risk was decreased with Losartan (OR, 0.78; 95% CI 0.63–0.97) but increased with Candesartan (OR, 1.79; 95% CI 1.05–3.06) and Telmisartan (OR, 1.54; 95% CI 0.97–2.43). The same study did not show any association between ACEI use and cancer incidence. In a population-based study including hypertensive patients, Huang et al. [14]. showed that ARB use was found to be independently associated with a decreased risk for cancer occurrence (HR: 0.66, 95% CI 0.63–0.68, $P<0.001$). Interestingly, all types of ARBs (Telmisartan, Candesartan, Irbesartan, Valsartan and Losartan) related to decreased risk of cancer. On the contrary, another nationwide study by Pasternak et al. [15]. did not demonstrate an association between ARB use and the risk of incident cancer development. In a cohort of more than 1 million patients, Rao et al. [16]. showed that ARBs use was protective against lung cancer, independent of the ARB subtype. Wang et al. [17]. followed 85,842 subjects (42,921 ARB users) for a mean duration of nearly 5 years and observed the cumulative incidence of cancer was reported as 4% for ARB users, and 6% for ARB non-users (HR: 0.58, 95% CI 0.55–0.62; *P*:0.001). All ARB subtypes were significantly correlated with lower cancer rates including liver, lung, colon, rectum, breast prostate and stomach cancers. ACEI/ARB use has been associated with survival outcome in metastatic renal cell carcinoma (MRCC). McKay et al. [18]. in 4736 MRCC patients of whom 783 were taking ACEI or ARB showed that ACEI/ARB regimens had improved overall survival compared to patients using other antihypertensive agents (HR, 0.838, *P*:0.0105, 26.68 vs. 18.07 months) and compared to patients not taking an antihypertensive drug (HR, 0.810, $P=0.0026$, 26.68 vs. 16.72 months).

In spite of the many studies reporting beneficial effects of RAS blockage in the incidence and prognosis of cancer, various others reported contradictory findings. Correspondingly, in an epidemiological study from Denmark did not confirm a protective effect of ACE inhibitors on the development of cancer [19]. Similarly, Connolly et al. [20]. did not report any significant association in the total or specific cancer risk with the use of ARBs (telmisartan, irbesartan, valsartan, candesartan, and losartan) according to the data from 15 trials enrolling nearly 140,000 individuals.

There are also reports of increased cancer risk with RAS blockage (Table 1). Hicks et al. [21]. compared the incidence of lung cancer in ACEI vs. ARB users and showed that, ACEIs were associated with an increased risk of lung cancer compared with ARBs (HR: 1.14, 95% CI 1.01–1.29). The hazard ratios increased gradually with longer durations

of use, and were higher after 5 years and even higher after 10 years.

Bearing all these issues in mind, a specific mention is needed regarding sartans and cancer. In July 2018, some sartan products were discovered to have been contaminated with N-nitrosodimethylamine (NDMA) which is "probably carcinogenic to human. Soon after another carcinogenic nitrosamine, N-nitrosodiethylamine (NDEA) was found in valsartan, irbesartan and losartan [22]. Thus, there is a concern of increased cancer risk with the use of these products, not due to the carcinogenic effects of RAS blockage but due to these contaminants. Pottegård et al. [23]. assessed the cancer risk associated with exposure to NDMA through contaminated valsartan products, using nationwide registries involving 6000 patients. Results showed no increased risk of cancer in patients using the contaminated tablets of valsartan. The principal weakness of the study was the limited median follow-up. On the other hand, there have been reports of a possible association of valsartan, with melanoma [24].

ACE polymorphism is needed to be considered in cancer epidemiology. Various meta-analyses with ACE polymorphisms is showed inconsistent results (Table 1). ACE polymorphisms, which change the expression level of ACE, have been associated with various cancers. The most studied ACE polymorphisms are the insertion/deletion (I/D) polymorphism. ACE levels of D/D carriers are higher than I/I carriers. D/D polymorphism is associated with the number of lymph node metastases in gastric cancer [25]. D/D polymorphism is also associated with worse prognosis in prostate cancer [26].

All these conflicting results of observational studies could be explained by study design, poor reporting and patient characteristics. It is obvious that more studies are needed with the use of specific ACEI/ARBs to assess the development of cancer.

Pathogenesis

As suggested above, RAS system is suggested to be involved in many types of cancer while the findings are not uniform and conflicting data exist among different studies. This may be due to the fact that RAS system is composed of various receptors, namely Angiotensin Type 1 and type 2 receptors (ATR1 and ATR2), pro-renin receptor (PRR) and Mas receptors and different kinds of effectors such as Angiotensin 2, Ang 1–9, Ang 1–7. Regarding cancer development these effectors and receptors have opposite actions with various aspects (Fig. 1). Classical data focuses on the processing of angiotensinogen to the active peptide angiotensin II (AngII) and the interactions of Ang II with its receptors

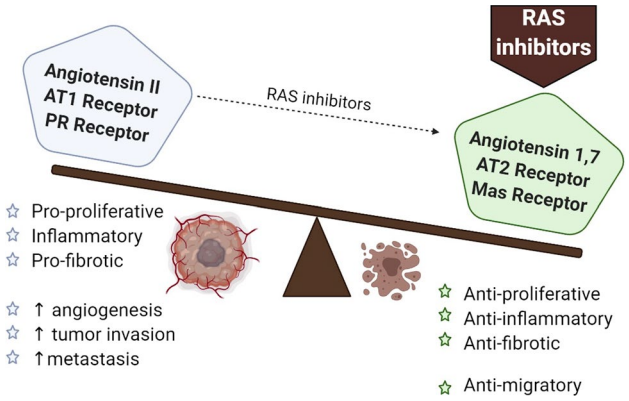

Fig. 1 The Contradictory Actions of Receptors and Effectors of Renin-Angiotensin System in Tumor Development. Renin-Angiotensin System has different receptors and effectors. Classic data focuses on the processing of angiotensinogen to the active peptide AngII and the interactions of Ang II with its receptors primarily ATR1. Binding of AngII to ATR1 increases inflammation, fibrosis angiogenesis, tumor invasion and metastasis. PRR has also similar action with AngII. On the other hand, when AngII binds to ATR2 the effects are opposite to ATR1 binding. Ang 1–7 when binds to its receptor Mas, causes anti-inflammatory, anti-fibrotic anti-proliferative and anti-migratory function. RAS inhibitors are mostly beneficial in cancer due to augmentation of ATR2 and Ang 1–7 mediated Mas signaling. *AngII* angiotensin 2, *ATR1* angiotensin type 1 receptor, *ATR2* angiotensin type 2 receptor, *PRR* pro-renin receptor, *Ang 1–7* angiotensin (1–7), *RAS* renin-angiotensin system

primarily ATR1. However, the homologue of ACE, known as ACE2, is more recently discovered and functions to cleave the carboxy-terminal amino acid from Ang II and generate angiotensin 1–7 (Ang 1–7). Ang 1–7 interacts with its Mas receptor (MASR) to antagonise the actions of Ang II [27]. ATR1 signaling appears to be the major component of RAS that is involved in tumor growth by inducing angiogenesis and tumor proliferation by promoting VEGF or epidermal growth factor receptor (EGFR) expression [6, 28–30]. Angiotensin II can also promote cell growth and proliferation via transforming growth factor-beta [31], tyrosine kinase [32] and activating mammalian target of rapamycin (mTOR) pathways [33] (Fig. 2). In addition, activation of AT1R in LNCaP, DU145, and PrSC cells resulted in increased mitogen-activated protein kinase (MAPK) activation, janus kinase signal transducers and activators of transcription (JAK-STAT) signaling, and cell proliferation [34, 35], ARBs, including candesartan and telmisartan, have been reported to inhibit AT1R expression, suppress cell proliferation, and augment apoptosis in prostate cancer [36–38]. Indeed, in many cancer types including breast, pancreas and lung cancer, ATR1 is upregulated [28] and studies have shown that ACEI/ARB blockage results in amelioration of cancer by a variety of mechanisms [28].

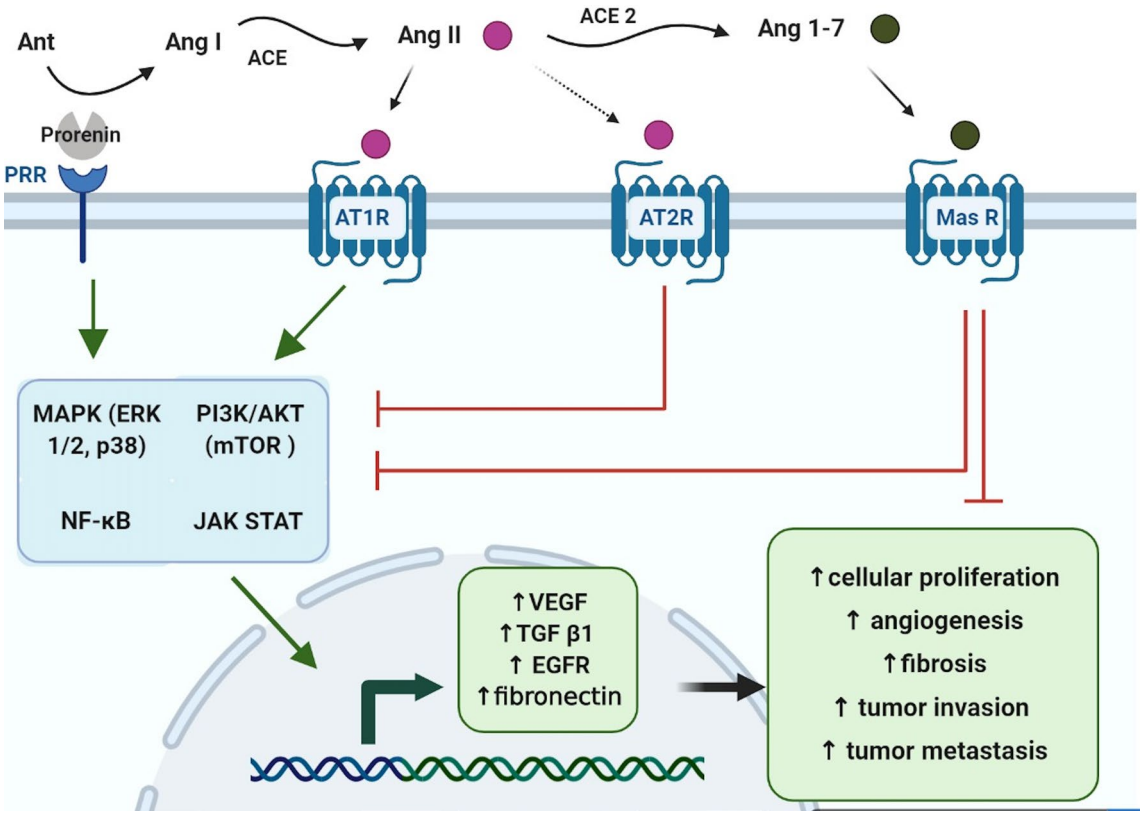

Fig. 2 RAS Receptor Signaling Pathways Related with Cancer Biology. Different RAS receptors either activate or inactivate various signaling pathways related to cancer development. ATR1 and PRR receptor signaling activate MAPK, PI3K/AKT/mtor, NF-κB and JAK/STAT pathways and increase in VEGF, TGFβ1, EGFR and fibronectin which ultimately lead to increased cellular proliferation, angiogenesis, fibrosis, tumor invasion and metastasis. These pathways are inhibited by ATR2 and Ang 1–7 mediated Mas signaling. *RAS* renin-angiotensin system, *ATR1* angiotensin type 1 receptor, *PRR* pro-renin receptor, *MAPK* mitogen-activated protein kinase, *PI3K* phosphatidylinositol 3-kinase, *Akt* a serine/threonine kinase, *mTOR* mammalian target of rapamycin, *NF-κB* nuclear factor kappa-light-chain-enhancer of activated B cells, *JAK* Janus kinase, *STAT* signal transducer and activator of transcription, *VEGF* vascular endothelial growth factor, *TGF-β1* transforming growth factor-beta 1, *EGFR* epidermal growth factor receptor

Pro-renin receptor (PRR) is another receptor that plays an important role as a regulator of the RAS. The major role of PRR is Ang II formation. In addition, the PRR is involved in Wnt signalling, function of the vacuolar H^+adenosinetriphosphatase (V-ATPase), the Par3 system, and tyrosine-phosphorylation-dependent signalling pathways [39]. In general, PRR has been upregulated in prostate cancer [40], leukemia [41], and in pancreas cancer [42], thus both ATR1 and pro-renin receptors are suggested to have meaningful roles in oncogenesis (Fig. 1). As mentioned above, ATR2 and other RAS related peptides, such as Ang 1–7, should also be considered. During ARB blockage, AngII levels cannot bind to ATR1 thus limiting proliferation capacity. In contrast to the proliferative effects of ATR1, ATR2 and MASR have anti-proliferative effects [43, 44]. Unlike AngII, Ang (1–7) inhibits both angiogenesis and cell proliferation [45, 46]. The dominance of Ang (1–7) and ATR2 over AngII and ATR1 may provide an explanation to the beneficial effects of ARB on cancer development. Indeed, it was shown that downregulation of ACE2/Ang-(1–7)/Mas axis [47], as well as decreased Ang (1–7) levels were found in breast cancer [48]. Moreover, Ang (1–7) inhibits the growth of tumors cells in several types of cancer including lung cancer [49], prostate cancer [50], nasopharyngeal carcinoma [51] and esophageal squamous cell carcinoma [52].

Many studies have now shown that Ang (1–7) exerts inhibitory effects on inflammation and on vascular and cellular growth mechanisms via Mas receptor [53]. In general, Ang1-7/ Mas axis has been reported to be protective in various cancer by a variety of mechanisms including inhibition of cell proliferation, invasion and metastasis and inhibiting epithelial to mesenchymal transition [54]. In contrast, it was also suggested that MASR was significantly up-regulated in colon cancer [55] and was associated with colorectal cancer metastasis [56].

To sum up, various components of RAS seem to play different roles in oncogenesis. The contradicting findings in the

literature may be related to different patterns of activation of distinct RAS components, in addition to different levels of tissue expressions and the low selectivity and sensitivity of the antibodies assays used, which poses a limitation for precise measurement of the protein expression levels.

RAS and cell signaling

RAS has interactions with various intracellular signaling pathways that also play substantial roles in carcinogenesis (Fig. 2). Although an extensive review of RAS signaling is beyond the scope of this review, we should remember that RAS system can couple with cell signaling pathways including MAPKs (extracellular-regulated kinases, extracellular signal-regulated kinase (ERK) 1 and ERK2, p38 MAPK and Jun N-terminal kinase and the Jak-STAT pathway which may have a role in tumor development [27].

One of these pathways is adenosine monophosphate (AMP)-activated protein kinase (AMPK) signaling pathway which is involved in oncogenesis. AMPK has a tumor suppressor function via cell cycle arrest with stabilization of p53 and the cyclin-dependent kinase inhibitors p21WAF1 and p27CIP1. This pathway also inhibits the synthesis mTOR-1 and hypoxia-inducible factor-1α (HIF-1α) along with fatty acids, triglycerides, cholesterol, glycogen, ribosomal RNA and proteins, resulting inhibition of cell growth [57].

Yang et al. [58]. investigated the relationship between RAS and AMPK signaling pathway in carcinogenesis using the uninephrectomized (UNX) rat model. 96 rats were equally randomized into four groups: sham operation, left uninephrectomy, left uninephrectomy plus treatment with lisinopril or left uninephrectomy with losartan. After 10 months, UNX rats had decreased expression of AMPK compared to sham. There were atypical proliferation and carcinoma of tubular epithelia in UNX rats along with glomerulosclerosis and casts. Treatment with ACEI and ARB increased the AMPK expression by 41.7% and 50.0%, respectively. Moreover, a decrease in AMPK expression was associated with over-expressions of Ki-67. and mutant p53 and morphologic transformations of malignancy in the UNX rat model. These alterations were significantly decreased by RAS blockage, highlighting the interaction of RAS and AMPK signaling pathway in the carcinogenesis of UNX rats.

As mentioned above, Ang II acts on various types of receptors including AT2R. It is accepted that AT2R antagonizes the effects of the AT1R and generates anti-inflammatory, anti-proliferative and anti-migratory responses [59]. AT2R receptor-interacting proteins (ATIP) are important proteins for these responses and ATIP1 was the first reported ATIP member which constitutively interacts with AT2R at the cell membrane. ATIP1 plays a dominant role fort he inhibitory action of AT2R on cell proliferation, receptor tyrosine kinase activation and ERK phosphorylation [60]. ATIP-1 also contributes to AT2R receptor transport and signaling. ATIP-3 is another protein interacting with AT2R with tumor suppressor action. In invasive breast cancer, decreased levels of ATIP-3 are observed and restoration of ATIP3 expression in breast cancer cells reduces tumor cell proliferation [61]. Under those circumstances, AT2R may possibly have beneficial effects in cancer pathogenesis. Indeed, some experimental studies have shown that AT2R expression and activation ameliorate tumor growth, vascularization and/or metastasis progression in different models of cancer [62, 63].

PRR also plays important roles in various pathways, such as the Wnt/β-catenin, MAPK/ERK and PI3K/AKT/mTOR pathways that are involved in a wide range of physiological and pathological processes including tumorigenesis. It is shown that PRR activates transforming growth factor β (TGFβ), activates MAPK/ERK signaling and PI3K/AKT/mTOR signaling pathways [64] while silencing of these pathways down regulates the expression of ERK1/2, AKT and NF-κB (32) in pancreatic cancer cells [42]. Furthermore, Lin et al. [51]. found that Ang (1–7) downregulated PI3K/Akt/mTOR signaling in human nasopharyngeal carcinoma xenografts and inhibited tumor growth via autophagy. Similar findings were also observed in breast cancer, as Ang (1–7) decreased PI3K/AKT pathway activation as well as VEGF expression, epithelial-mesenchymal transition, matrix metalloproteinase MMP-9 activity [65].

The AT1R, the major receptor of Ang II, has extensively modulates many cellular signaling pathways. Du et al. [66]. investigated the downstream effects of the activation and silencing of AT1R using RNA interference in breast cancer. The cancer cells had significantly upregulated levels of AT1R expression. Angiotensin II significantly increased the expression of p-Ras, p-Erk, NF-κB-P65, p-CREB, PCNA, and cyclin D1 and decreased p53 expression in AT1R (+) cell lines, while AT1R(−) cell line created by RNA interference was not affected by AngII. Irbesartan, an ARB, blocked the effects of AngII on cell growth, cell cycle, and downstream signaling events, including the stimulation of MAPK pathway and NF-Kb. These findings implied that the pro-proliferative effects of AngII may be dependent on its interaction with AT1R in certain cancer types.

NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) is a protein complex that controls transcription of DNA and plays an active role in oncogenesis by promoting proliferation, transformation, angiogenesis, invasion, metastasis, chemo and radio resistance [67]. Angiotensin II plays a synergistic role with NF-κB in cancer development. Zahaoet et al. showed that AngII affected cell migration in breast cancer. In addition, AngII induced phosphorylation ofPI3K/Akt and resulted in increased NF-κB activity. Thus AngII activates the AT1R/

PI3K/Akt pathway, which further activates IKKα/β and NF-κB, resulting in enhanced expression of matrix metalloproteinase (MMP)-2, MMP-9 and in increased cell migration in human breast cancer cells [68]. Bakhtiari et al. [69]. assessed the effect of angiotensin II and NF-κB blockage in breast cancer cell line. Both angiotensin II and NF-κB blockage resulted in decreased cell viability and increase apoptosis separately, while, these affects were more pronounced when angiotensin II and NF-κB blockage were combined. Saber et al. [70]. studied the effects of RAS inhibitors, using losartan (10 mg/kg), perindopril (1 mg/kg) or fosinopril (2 mg/kg) in hepatocellular carcinoma. RAS inhibitors improved liver function and histology and reduced Alpha-Fetoprotein levels, by the inactivation of NFκB pathway through the inhibition of NFκB p65 phosphorylation at the Ser536 residue and phosphorylation-induced degradation of NFκBia. Additionally, NFκB-induced tumor necrosis factor alpha (TNF-α) and TGF-β1 levels were reduced, leading to lower levels of MMP-2 and VEGF.

Another signaling pathway involving both RAS and oncogenesis is mitogen-activated protein kinase (MAPK) pathway. Indeed, Ang (1–7), decreased the proliferation of human lung cancer cells via a reduction in MAPK signaling [71]. Major on–off switches of MAPK signaling are MAPK kinases and MAPK phosphatases, which activate and inactivate MAPK via phosphorylation and dephosphorylation, respectively. It was also shown that Ang (1–7) reduces MAPK activity by upregulating MAPK phosphatase named dual-specificity phosphatase 1 (DUSP1). This, in turn, inactivates ERKs1 and 2, potent mitogenic signaling proteins implicated in cell viability, growth, and proliferation in breast tumors. Furthermore, the upregulation of DUSP1 was blocked by Ang (1–7) receptor antagonist, indicating that DUSP1 induction by Ang (1–7) was a receptor-mediated process. Ang (1–7) also prevented the production of TGF-β1, an ERK1/2 activator, and fibronectin synthesis, thus reducing fibrosis in the tumor environment [72].

Correspondingly, AngII has been shown to stimulate ERK1/2 with a resultant increase in monocyte chemoattractant protein (MCP)-1 in pancreatic ductal adenocarcinoma (PDA). In addition, AngII induced MCP-1 transcription was inhibited by AT1R blocker but was unchanged by an AT2R blocker. Inhibition of ERK1/2 activation also reduced the AngII induced MCP-1 synthesis [73, 74].

Overall, evidence suggests that various signaling pathways including protein kinases, NF-κB, ERK1/ERK2, and molecules including VEGF, MCP1, inhibitors of metalloproteinases and HIF1α are involved in RAS activation and tumor behaviour.

Apoptosis, cell proliferation and RAS

The relationship of RAS with apoptosis also deserves special attention. Ang II stimulated ATR1 signaling effects p53 and influences Bcl-2/Bax ratio and decrease apoptosis (Fig. 3). In a study of non-small cell lung cancer (NSCLC), telmisartan, an AT2R receptor antagonist, was found to significantly inhibit cellular invasion and migration, while also increasing pro-apoptotic proteins caspase-3 and Bcl-associated expression. Additionally, levels of phosphorylated RAC serine/threonine-protein kinase (p-AKT), p-mechanistic target of rapamycin, p70-S6 kinase and cyclin D1 were decreased in the telmisartan-treated group. The findings of this study imply that telmisartan-induced apoptosis may be regulated via the phosphoinositide 3-kinase/AKT signaling pathway [75]. On the contrary, RAS inhibitors have been reported to have anti-apoptotic effects as well. It was shown that proapoptotic changes were associated with upregulation of cardiac RAS activity and ACEI treatment was effective in counteracting apoptotic tendency in ovariectomized spontaneously hypertensive rats (SHRs). In response to ovariectomy, Bcl-2/Bax ratio was decreased, leading to a proapoptotic microenvironment in the cardiomyocytes. At the same time, ACE and ATR1 genes were upregulated. Treatment with ramipril effectively reduced apoptosis by downregulation of ACE and ATR1. Similarly, other studies found that AngII could induce apoptosis via inhibition of PI3K/Akt [76] and activation of Janus kinase and signal transducers and activators of transcription (STAT) [77].

These findings provided insight into the proapoptotic effects of RAS while suggesting the possibility of an undesirable

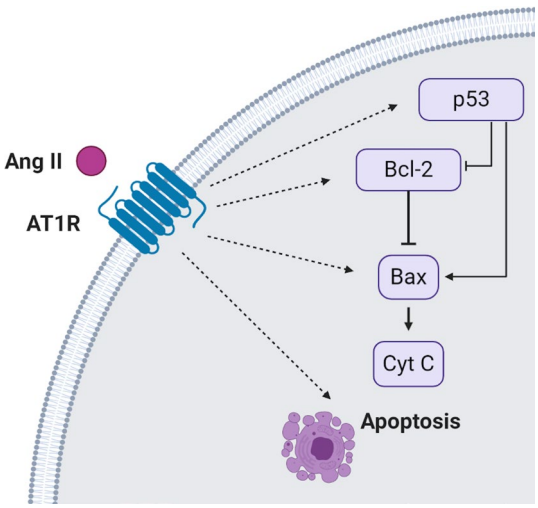

Fig. 3 The impact of ATR1 signaling on apoptosis. RAS system influences apoptosis. AngII. by binding to ATR1 receptor suppress p53 which in turn changes the Bax/Bcl ratio leading to decreased apoptosis

anti-apoptotic milieu after RAS inhibition which should be investigated in cancer tissue. P53, the major regulator of apoptosis and one of the major defense mechanisms against abnormal cellular proliferation, is a key element in the relationship between RAS and apoptosis. It is well appreciated that the ratio of Bcl-2 to Baxplays a major role in determining the apoptotic fate of the cell [78] and is decreased by p53 signaling, leading to apoptosis [79]. It was shown that p53 and resultant RAS activation increases apoptosis during ischemia reperfusion in heart tissue [80]. Indeed it was shown that ACEI enarapril decreased the p53 expression and cardiac hypertrophy after aortic stenosis [81]. However, there is also conflicting data regarding the relationship of RAS and p53.

For example, in one study the effect of RAS blockage on p53 was investigated in UNX rats. After 10 months, mutant p53 were markedly increased. Treatment with ACEI or ARB attenuated the inhibition of AMPK signaling pathway as well as carcinogenesis, signifying an interaction between RAS p53 in carcinogenesis. These alterations were significantly decreased by RAS blockage, highlighting the interaction of RAS and AMPK signaling pathway in the carcinogenesis of UNX rats [58].

In dysplastic Barrett's esophagus (BE), ACE inhibitor enalapril increased the levels of p53 and possibly apoptosis, suggesting that AngII inhibits p53 expression in dysplastic BE [82]. Currently, consistent evidence is lacking on whether the primary effect of RAS blockage is pro-or anti-apoptotic and whether such an effect is dependent on the tissue type.

RAS activity is shown to modulate cell growth by interacting with protooncogenes and oncogenes as well as apoptosis (explained above). Gopi et al. [4]. reported that cardiac myofibroblast cells exposed to angiotensin II showed increased expression of proto-oncogenes c-fos, (seven-fold), c-myc (five-fold), and c-jun (three-fold), compared with control cells. Correspondingly, losartan reduced the expression of these proto-oncogenes. Inigo et al. [83]. Compared the effects of ACEI/ARB in leukemic myeloid cell lines positive and negative for renin expression. The authors showed that captopril and trandolapril inhibit cell growth in these cell lines independent of their renin expression, while growth arrest was reversed when the agents were removed from the medium. Furthermore, ACEI treatment also decreased the c-myc expression. Losartan had similar anti-proliferative effects, which seemed to be associated with AngII induced Smad activation. Therefore, ACEI/ARB treatment seems to decrease cell growth and c-myc, an important proto-oncogene in hematologic malignancies.

While these studies primarily focused on Ang II and its associated receptor ATR1, PRR may also be responsible for stimulating the downstream factors that contribute to oncogenesis during RAS activation [84].

Micro RNA, RAS And cancer

A microRNA (miRNA) denotes for a small non-coding RNA molecule that functions in RNA silencing and post-transcriptional regulation of gene expression [85]. miRNAs are involved in cell proliferation, cell death, and apoptosis and are known to be up or down regulated in different types of cancer [86, 87]. There is accumulating evidence that miRNAs are involved in the regulation of RAS [88]. For instance, miR-155 is shown to dysregulate the expression of AT1 gene mRNA, which was strongly associated with the malignant transformation of B cells [89]. A miRNA that deserves specific attention is miRNA21, a major player in lung cancer. Previously, a positive correlation between EGF receptor (EGFR) and miRNA-21 was demonstrated in lung carcinoma celllines. In addition, EGFR-tyrosine kinase inhibitors (EGFR-TKI) suppressed miRNA-21, suggesting that the EGFR positively regulates miRNA-21expression [90]. Indeed, the higher miRNA-21 expression is associated with the acquired resistance to EGFR-TKIs in non-small cell lung cancer (NSCLC) [91]. It was suggested that angiotensin II-induced micro RNA-21 can be the culprit for non-small-cell lung adenocarcinoma [6]. Different from the proto-oncogenic miRNA, miRNA 205 is a tumor-suppressing miRNA [92]. Yue et al. [93]. investigated the effect of olmesartan, a AT1R antagonist, on the expression of miRNA-205 and VEGF-A. Olmesertan caused overexpression of miRNA-205 and decreased VEGF-A, which contributed to olmesartan-induced anti-tumor effect on cervical cancer cells. The effects of miRNA-155 on AngII induced vascular smooth muscle cell (VSMC) proliferation were also explored in mice. Cultured cells from the aorta were incubated with AngII and miR-155. While angiotensin II enhanced the viability of VSMCs in a dose-dependent fashion, miRNA-155 prevented this effect of AngII on VSMC and further decreased the expression of ATR1 gene and protein [94]. The anti-proliferative effects of miRNA-155 have been also shown in human extravillous trophoblast-derived HTR-8/SVneo cells via reducing cyclin D1 pathway [95] and by inducing apoptosis [96]. Other miRNAs such as miRNA-221 and miRNA-222 are involved in cell proliferation by the inhibition of the cell cycle regulator, p27kip1 [97]. Enhanced expression of miR-141 and miR-200a mimic p38α deficiency and increases tumor growth in mouse models, but it also improves chemotherapeutic response. Higher miR-200a was found in high grade human ovarian adenocarcinomas along with low concentrations of p38α and an increased oxidative stress [98]. As miRNA biology is evolving, more studies are needed reveal the role of specific miRNAs in a variety of cancers and its corresponding interaction with RAS, keeping in mind that RAS blockage may be a therapeutic option under certain circumstances.

Table 2 The knowns, Unknowns and Recommendations Regarding RAS System and Cancer Biology

What is known
Various studies have suggested that ACEI/ARBs have anti-proliferative effects, improve survival or decrease the risk of many types of cancers
There are also reports of increased cancer risk in ACEI/ARB users
NDMA, a possibly carcinogenic contaminant was found in ARB tablets
Ang II has pro-proliferative and inflammatory effects via its interaction with ATR1
Ang 1–7 has anti-proliferative and anti-inflammatory effects via its interaction with MASR
In the presence of ARBs, Ang II binds to ATR2 and MASR instead and has anti-proliferative effects
AT1R exerts its effects via MAPK, JAK STAT and mTOR pathways
Certain microRNA that are involved in oncogenesis may regulate RAS
What is unknown
The exact relationship between RAS blockage and development cancer (meta-analysis contradicting) and cancer subtypes
The role of RAS inhibition in cancer treatment
The effects of Ang II and RAS blockage on apoptosis
The possible co-founding effect of NDMA in the cancer incidence of ARB users
Recommendations
More studies are needed to demonstrate the effects of RAS blockage in apoptosis and cancer cell lines
Longitudinal prospective cohort studies are needed to assess the long-term effects of RAS blockage on cancer risk
Clinical trials are needed to investigate the effects of RAS blockage in cancer patients

RAS renin-angiotensin system, *ACEI* angiotensin-converting enzyme Inhibitors, *ARB* angiotensin receptor blockers, *NDMA N*-nitrosodimethylamine, *AngII* angiotensin 2, *ATR1* ATR1: angiotensin type 1 receptor, *Ang 1–7* angiotensin 1–7, *MASR* Mas receptor, *MAPK* mitogen-activated protein kinase, *JAK* Janus kinase, *STAT* signal transducer and activator of transcription, *mTOR* mammalian target of rapamycin

Future Perspectives

The RAS is complex with regard to cancer biology and their knowns, unknowns and future issues are of concern (Table 2). RAS has various receptors and effectors that have contrasting effects in cancer development. Although most studies have shown that RAS activation is associated with cancer, minor studies showed contrasting findings. Currently, we do not know fully whether RAS is activated or inhibited in tumors of different origins. There is also no data regarding the role of the other components of RAS such as angiotensin IV and its receptor, the insulin-regulated amino peptidase (IRAP). Equally important, there is much to investigate the relationship of RAS with intracellular signaling pathways, oncogenes and tumor suppressor genes. Another area of uncertainty is the role of epigenetic regulation of cancer [99]. Although the epigenetic reorganization of the expression of RAS components is a relatively new and little studied area in oncology, epigenetic alterations RAS components in cancer pathogenesis has been suggested [100]. Some data suggest that the renin gene expression in normal and malignant hematopoiesis can be controlled by epigenetic mechanisms [101]. Besides, Ang (1–7) has important epigenetic effects via limiting the mobility of cancer cells and their ability to metastasize [102]. However the research regarding epigenetics RAS and cancer is at its infancy and further research is necessary regarding epigenetics, RAS system and cancer development.

Conclusion

It is now clear that RAS is related to cancer. Mostly, RAS blockage is protective in cancer but fewer studies have also shown contradictory data. These discordant findings may be due to opposite actions of different types of receptors and effectors which are found in RAS. These actions may impact various cell signaling pathways, oncogenes, tumor suppressor genes and epigenetic mechanisms differently. Future research will show the exact cellular mechanisms and their association with different RAS elements with regard to cancer development and pathogenesis.

Acknowledgements MK gratefully acknowledge the use of the services and facilities of the Koc University Research Center for Translational Medicine (KUTTAM), funded by the Presidency of Turkey, Presidency of Strategy and Budget. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Presidency of Strategy and Budget.

Funding This study was not funded by any grant.

Compliance with Ethical Standards

Conflict of Interest All authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent As this is review, no informed consent is needed.

References

1. Ager EI, Neo J, Christophi C. The renin-angiotensin system and malignancy. Carcinogenesis. 2008;29(9):1675–84. https://doi.org/10.1093/carcin/bgn171.
2. Hanif K, Bid HK, Konwar R. Reinventing the ACE inhibitors: some old and new implications of ACE inhibition. Hypertens Res. 2010;33(1):11–21. https://doi.org/10.1038/hr.2009.184.
3. Haznedaroglu IC, Malkan UY. Local bone marrow renin-angiotensin system in the genesis of leukemia and other malignancies. Eur Rev Med Pharmacol Sci. 2016;20(19):4089–111.
4. Gopi V, Subramanian V, Manivasagam S, Vellaichamy E. Angiotensin II down-regulates natriuretic peptide receptor-A expression and guanylyl cyclase activity in H9c2 (2–1) cardiac myoblast cells: Role of ROS and NF-kappaB. Mol Cell Biochem. 2015;409(1–2):67–79. https://doi.org/10.1007/s11010-015-2513-0.
5. Sipahi I, Debanne SM, Rowland DY, Simon DI, Fang JC. Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials. Lancet Oncol. 2010;11(7):627–36. https://doi.org/10.1016/s1470-2045(10)70106-6.
6. Luan Z, Liu B, Shi L. Angiotensin II-induced micro RNA-21 culprit for non-small-cell lung adenocarcinoma. Drug Dev Res. 2019;80(8):1031–9. https://doi.org/10.1002/ddr.21597.
7. Rhodes DR, Ateeq B, Cao Q, Tomlins SA, Mehra R, Laxman B, Kalyana-Sundaram S, Lonigro RJ, Helgeson BE, Bhojani MS, Rehemtulla A, Kleer CG, Hayes DF, Lucas PC, Varambally S, Chinnaiyan AM. AGTR1 overexpression defines a subset of breast cancer and confers sensitivity to losartan, an AGTR1 antagonist. Proc Natl Acad Sci USA. 2009;106(25):10284–9. https://doi.org/10.1073/pnas.0900351106.
8. Fujimoto Y, Sasaki T, Tsuchida A, Chayama K. Angiotensin II type 1 receptor expression in human pancreatic cancer and growth inhibition by angiotensin II type 1 receptor antagonist. FEBS Lett. 2001;495(3):197–200. https://doi.org/10.1016/s0014-5793(01)02377-8.
9. Gong Q, Davis M, Chipitsyna G, Yeo CJ, Arafat HA. Blocking angiotensin II Type 1 receptor triggers apoptotic cell death in human pancreatic cancer cells. Pancreas. 2010;39(5):581–94. https://doi.org/10.1097/MPA.0b013e3181c314cd.
10. Neo JH, Malcontenti-Wilson C, Muralidharan V, Christophi C. Effect of ACE inhibitors and angiotensin II receptor antagonists in a mouse model of colorectal cancer liver metastases. J Gastroenterol Hepatol. 2007;22(4):577–84. https://doi.org/10.1111/j.1440-1746.2006.04797.x.
11. Wilop S, von Hobe S, Crysandt M, Esser A, Osieka R, Jost E. Impact of angiotensin I converting enzyme inhibitors and angiotensin II type 1 receptor blockers on survival in patients with advanced non-small-cell lung cancer undergoing first-line platinum-based chemotherapy. J Cancer Res Clin Oncol. 2009;135(10):1429–35. https://doi.org/10.1007/s00432-009-0587-3.
12. Sjoberg T, Garcia Rodriguez LA, Lindblad M. Angiotensin-converting enzyme inhibitors and risk of esophageal and gastric cancer: a nested case-control study. Clin Gastroenterol Hepatol. 2007;5(10):1160–1166.e1161. https://doi.org/10.1016/j.cgh.2007.08.005.
13. Chang CH, Lin JW, Wu LC, Lai MS. Angiotensin receptor blockade and risk of cancer in type 2 diabetes mellitus: a nationwide case-control study. J Clin Oncol. 2011;29(22):3001–7. https://doi.org/10.1200/jco.2011.35.1908.
14. Huang CC, Chan WL, Chen YC, Chen TJ, Lin SJ, Chen JW, Leu HB. Angiotensin II receptor blockers and risk of cancer in patients with systemic hypertension. Am J Cardiol. 2011;107(7):1028–33. https://doi.org/10.1016/j.amjcard.2010.11.026.
15. Pasternak B, Svanstrom H, Callreus T, Melbye M, Hviid A. Use of angiotensin receptor blockers and the risk of cancer. Circulation. 2011;123(16):1729–36. https://doi.org/10.1161/circulationaha.110.007336.
16. Rao GA, Mann JR, Shoaibi A, Pai SG, Bottai M, Sutton SS, Haddock KS, Bennett CL, Hebert JR. Angiotensin receptor blockers: are they related to lung cancer? J Hypertens. 2013;31(8):1669–755. https://doi.org/10.1097/HJH.0b013e3283621ea3.
17. Wang KL, Liu CJ, Chao TF, Huang CM, Wu CH, Chen TJ, Chiang CE. Long-term use of angiotensin II receptor blockers and risk of cancer: a population-based cohort analysis. Int J Cardiol. 2013;167(5):2162–6. https://doi.org/10.1016/j.ijcard.2012.05.096.
18. McKay RR, Rodriguez GE, Lin X, Kaymakcalan MD, Hamnvik OP, Sabbisetti VS, Bhatt RS, Simantov R, Choueiri TK. Angiotensin system inhibitors and survival outcomes in patients with metastatic renal cell carcinoma. Clin Cancer Res. 2015;21(11):2471–9. https://doi.org/10.1158/1078-0432.Ccr-14-2332.
19. Friis S, Sorensen HT, Mellemkjaer L, McLaughlin JK, Nielsen GL, Blot WJ, Olsen JH. Angiotensin-converting enzyme inhibitors and the risk of cancer: a population-based cohort study in Denmark. Cancer. 2001;92(9):2462–70. https://doi.org/10.1002/1097-0142(20011101)92:9<2462:aid-cncr1596>3.0.co;2-l.
20. ARB Trialists Collaboration. Effects of telmisartan, irbesartan, valsartan, candesartan, and losartan on cancers in 15 trials enrolling 138,769 individuals. J Hypertens. 2011;29(4):623–35. https://doi.org/10.1097/HJH.0b013e328344a7de.
21. Hicks BM, Filion KB, Yin H, Sakr L, Udell JA, Azoulay L. Angiotensin converting enzyme inhibitors and risk of lung cancer: population based cohort study. BMJ (Clin Res Ed). 2018;363:k4209. https://doi.org/10.1136/bmj.k4209.
22. Sorgel F, Kinzig M, Abdel-Tawab M, Bidmon C, Schreiber A, Ermel S, Wohlfart J, Besa A, Scherf-Clavel O, Holzgrabe U. The contamination of valsartan and other sartans, part 1: New findings. J Pharm Biomed Anal. 2019;172:395–405. https://doi.org/10.1016/j.jpba.2019.05.022.
23. Pottegard A, Kristensen KB, Ernst MT, Johansen NB, Quartarolo P, Hallas J. Use of N-nitrosodimethylamine (NDMA) contaminated valsartan products and risk of cancer: Danish nationwide cohort study. BMJ (Clin Res Ed). 2018;362:k3851. https://doi.org/10.1136/bmj.k3851.
24. Tchernev G, Temelkova I. Additional 4 cases of valsartan/irbesartan-induced melanomas? J Biol Regul Homeost Agents. 2019;33(3):911–2.
25. Rocken C, Lendeckel U, Dierkes J, Westphal S, Carl-McGrath S, Peters B, Kruger S, Malfertheiner P, Roessner A, Ebert MP. The number of lymph node metastases in gastric cancer correlates with the angiotensin I-converting enzyme gene insertion/deletion polymorphism. Clin Cancer Res. 2005;11(7):2526–30. https://doi.org/10.1158/1078-0432.Ccr-04-1922.
26. Medeiros R, Vasconcelos A, Costa S, Pinto D, Lobo F, Morais A, Oliveira J, Lopes C. Linkage of angiotensin I-converting enzyme gene insertion/deletion polymorphism to the progression of human prostate cancer. J Pathol. 2004;202(3):330–5. https://doi.org/10.1002/path.1529.
27. George AJ, Thomas WG, Hannan RD. The renin-angiotensin system and cancer: old dog, new tricks. Nat Rev Cancer. 2010;10(11):745–59. https://doi.org/10.1038/nrc2945.
28. Deshayes F, Nahmias C. Angiotensin receptors: a new role in cancer? Trends Endocrinol Metab TEM. 2005;16(7):293–9. https://doi.org/10.1016/j.tem.2005.07.009.

29. Chua CC, Hamdy RC, Chua BH. Upregulation of vascular endothelial growth factor by angiotensin II in rat heart endothelial cells. Biochem Biophys Acta. 1998;1401(2):187–94. https://doi.org/10.1016/s0167-4889(97)00129-8.
30. Yang X, Zhu MJ, Sreejayan N, Ren J, Du M. Angiotensin II promotes smooth muscle cell proliferation and migration through release of heparin-binding epidermal growth factor and activation of EGF-receptor pathway. Mol Cells. 2005;20(2):263–70.
31. Daemen MJ, Lombardi DM, Bosman FT, Schwartz SM. Angiotensin II induces smooth muscle cell proliferation in the normal and injured rat arterial wall. Circ Res. 1991;68(2):450–6. https://doi.org/10.1161/01.res.68.2.450.
32. Buharalioglu CK, Song CY, Yaghini FA, Ghafoor HU, Motiwala M, Adris T, Estes AM, Malik KU. Angiotensin II-induced process of angiogenesis is mediated by spleen tyrosine kinase via VEGF receptor-1 phosphorylation. Am J Physiol Heart Circ Physiol. 2011;301(3):H1043–1055. https://doi.org/10.1152/ajpheart.01018.2010.
33. Li SH, Lu HI, Chang AY, Huang WT, Lin WC, Lee CC, Tien WY, Lan YC, Tsai HT, Chen CH. Angiotensin II type I receptor (AT1R) is an independent prognosticator of esophageal squamous cell carcinoma and promotes cells proliferation via mTOR activation. Oncotarget. 2016;7(41):67150–65. https://doi.org/10.18632/oncotarget.11567.
34. Uemura H, Ishiguro H, Nagashima Y, Sasaki T, Nakaigawa N, Hasumi H, Kato S, Kubota Y. Antiproliferative activity of angiotensin II receptor blocker through cross-talk between stromal and epithelial prostate cancer cells. Mol Cancer Ther. 2005;4(11):1699–709. https://doi.org/10.1158/1535-7163.Mct-04-0295.
35. Uemura H, Ishiguro H, Nakaigawa N, Nagashima Y, Miyoshi Y, Fujinami K, Sakaguchi A, Kubota Y. Angiotensin II receptor blocker shows antiproliferative activity in prostate cancer cells: a possibility of tyrosine kinase inhibitor of growth factor. Mol Cancer Ther. 2003;2(11):1139–47.
36. Alhusban A, Al-Azayzih A, Goc A, Gao F, Fagan SC, Somanath PR. Clinically relevant doses of candesartan inhibit growth of prostate tumor xenografts in vivo through modulation of tumor angiogenesis. J Pharmacol Exp Ther. 2014;350(3):635–45. https://doi.org/10.1124/jpet.114.216382.
37. Ishiguro H, Ishiguro Y, Kubota Y, Uemura H. Regulation of prostate cancer cell growth and PSA expression by angiotensin II receptor blocker with peroxisome proliferator-activated receptor gamma ligand like action. Prostate. 2007;67(9):924–32. https://doi.org/10.1002/pros.20571.
38. Takahashi S, Uemura H, Seeni A, Tang M, Komiya M, Long N, Ishiguro H, Kubota Y, Shirai T. Therapeutic targeting of angiotensin II receptor type 1 to regulate androgen receptor in prostate cancer. Prostate. 2012;72(14):1559–722. https://doi.org/10.1002/pros.22505.
39. Ichihara A, Yatabe MS. The (pro)renin receptor in health and disease. Nat Rev Nephrol. 2019;15(11):693–712. https://doi.org/10.1038/s41581-019-0160-5.
40. Mohammad AH, Assadian S, Couture F, Lefebvre KJ, El-Assaad W, Barres V, Ouellet V, Boulay PL, Yang J, Latour M, Furic L, Muller W, Sonenberg N, Mes-Masson AM, Saad F, Day R, Teodoro JG. V-ATPase-associated prorenin receptor is upregulated in prostate cancer after PTEN loss. Oncotarget. 2019;10(48):4923–36. https://doi.org/10.18632/oncotarget.27075.
41. Kaneko K, Ohba K, Hirose T, Totsune K, Furuyama K, Takahashi K. Expression of (Pro)renin receptor during rapamycin-induced erythropoiesis in K562 erythroleukemia cells and its possible dual actions on erythropoiesis. Tohoku J Exp Med. 2017;241(1):35–433. https://doi.org/10.1620/tjem.241.35.
42. Arundhathi A, Chuang WH, Chen JK, Wang SE, Shyr YM, Chen JY, Liao WN, Chen HW, Teng YM, Pai CC, Wang CH. Prorenin receptor acts as a potential molecular target for pancreatic ductal adenocarcinoma diagnosis. Oncotarget. 2016;7(34):55437–48. https://doi.org/10.18632/oncotarget.10583.
43. Datzmann T, Fuchs S, Andree D, Hohenstein B, Schmitt J, Schindler C. Systematic review and meta-analysis of randomised controlled clinical trial evidence refutes relationship between pharmacotherapy with angiotensin-receptor blockers and an increased risk of cancer. Eur J Intern Med. 2019;64:1–9. https://doi.org/10.1016/j.ejim.2019.04.019.
44. Pei N, Mao Y, Wan P, Chen X, Li A, Chen H, Li J, Wan R, Zhang Y, Du H, Chen B, Jiang G, Xia M, Sumners C, Hu G, Gu D, Li H. Angiotensin II type 2 receptor promotes apoptosis and inhibits angiogenesis in bladder cancer. J Exp Clin Cancer Res CR. 2017;36(1):77. https://doi.org/10.1186/s13046-017-0542-0.
45. Machado RD, Santos RA, Andrade SP. Opposing actions of angiotensins on angiogenesis. Life Sci. 2000;66(1):67–766. https://doi.org/10.1016/s0024-3205(99)00562-7.
46. Benndorf R, Boger RH, Ergun S, Steenpass A, Wieland T. Angiotensin II type 2 receptor inhibits vascular endothelial growth factor-induced migration and in vitro tube formation of human endothelial cells. Circ Res. 2003;93(5):438–47. https://doi.org/10.1161/01.Res.0000088358.99466.04.
47. Yu C, Tang W, Wang Y, Shen Q, Wang B, Cai C, Meng X, Zou F. Downregulation of ACE2/Ang-(1–7)/Mas axis promotes breast cancer metastasis by enhancing store-operated calcium entry. Cancer Lett. 2016;376(2):268–77. https://doi.org/10.1016/j.canlet.2016.04.006.
48. Luo Y, Tanabe E, Kitayoshi M, Nishiguchi Y, Fujiwara R, Matsushima S, Sasaki T, Sasahira T, Chihara Y, Nakae D, Fujii K, Ohmori H, Kuniyasu H. Expression of MAS1 in breast cancer. Cancer Sci. 2015;106(9):1240–8. https://doi.org/10.1111/cas.12719.
49. Ma X, Pang Z, Zhou J, He L, Hao Q, Li W, Zhang K, Wang S, Zhang W, Xue X, Zhang W, Zhang Y, Zhang C, Li M. Acetylation and amination protect angiotensin 1–7 from physiological hydrolyzation and therefore increases its antitumor effects on lung cancer. Mol Pharm. 2018;15(6):2338–477. https://doi.org/10.1021/acs.molpharmaceut.8b00181.
50. Dominska K, Okla P, Kowalska K, Habrowska-Gorczynska DE, Urbanek KA, Ochedalski T, Piastowska-Ciesielska AW. Angiotensin 1–7 modulates molecular and cellular processes central to the pathogenesis of prostate cancer. Sci Rep. 2018;8(1):15772. https://doi.org/10.1038/s41598-018-34049-8.
51. Lin YT, Wang HC, Chuang HC, Hsu YC, Yang MY, Chien CY. Pre-treatment with angiotensin-(1–7) inhibits tumor growth via autophagy by downregulating PI3K/Akt/mTOR signaling in human nasopharyngeal carcinoma xenografts. J Mol Med (Berlin, Germany). 2018;96(12):1407–18. https://doi.org/10.1007/s00109-018-1704-z.
52. Chen YH, Lu HI, Lo CM, Huang CC, Hsiao CC, Li SH. The clinical impact of angiotensin-(1–7)/mitochondrial assembly receptor axis in esophageal squamous cell carcinoma patients receiving curative esophagectomy. J Formosan Med Assoc Taiwan yi zhi. 2020;119(1 Pt 2):310–8. https://doi.org/10.1016/j.jfma.2019.05.022.
53. Simoes e Silva AC, Silveira KD, Ferreira AJ, Teixeira MM, ACE2, angiotensin-(1–7) and Mas receptor axis in inflammation and fibrosis. Br J Pharmacol. 2013;169(3):477–92. https://doi.org/10.1111/bph.12159.
54. Xu J, Fan J, Wu F, Huang Q, Guo M, Lv Z, Han J, Duan L, Hu G, Chen L, Liao T, Ma W, Tao X, Jin Y. The ACE2/Angiotensin-(1–7)/Mas receptor axis: pleiotropic roles in cancer. Front Physiol. 2017;8:276. https://doi.org/10.3389/fphys.2017.00276.
55. Bernardi S, Zennaro C, Palmisano S, Velkoska E, Sabato N, Toffoli B, Giacomel G, Buri L, Zanconati F, Bellini G, Burrell LM, De Manzini N, Fabris B. Characterization and

significance of ACE2 and Mas receptor in human colon adenocarcinoma. J Renin Angiotensin Aldosterone Sys JRAAS. 2012;13(1):202–9. https://doi.org/10.1177/1470320311426023.
56. Neo JH, Ager EI, Angus PW, Zhu J, Herath CB, Christophi C. Changes in the renin angiotensin system during the development of colorectal cancer liver metastases. BMC Cancer. 2010;10:134. https://doi.org/10.1186/1471-2407-10-134.
57. Hardie DG, Alessi DR. LKB1 and AMPK and the cancer-metabolism link - ten years after. BMC Biol. 2013;11:36. https://doi.org/10.1186/1741-7007-11-36.
58. Yang KK, Sui Y, Zhou HR, Zhao HL. Interaction of renin-angiotensin system and adenosine monophosphate-activated protein kinase signaling pathway in renal carcinogenesis of uninephrectomized rats. Tumour Biol. 2017;39(5):1010428317699116. https://doi.org/10.1177/1010428317699116.
59. Rodrigues-Ferreira S, Nahmias C. An ATIPical family of angiotensin II AT2 receptor-interacting proteins. Trends Endocrinol Metab TEM. 2010;21(11):684–90. https://doi.org/10.1016/j.tem.2010.08.009.
60. Nouet S, Amzallag N, Li JM, Louis S, Seitz I, Cui TX, Alleaume AM, Di Benedetto M, Boden C, Masson M, Strosberg AD, Horiuchi M, Couraud PO, Nahmias C. Trans-inactivation of receptor tyrosine kinases by novel angiotensin II AT2 receptor-interacting protein. ATIP J Biol Chem. 2004;279(28):28989–977. https://doi.org/10.1074/jbc.M403880200.
61. Rodrigues-Ferreira S, Di Tommaso A, Dimitrov A, Cazaubon S, Gruel N, Colasson H, Nicolas A, Chaverot N, Molinie V, Reyal F, Sigal-Zafrani B, Terris B, Delattre O, Radvanyi F, Perez F, Vincent-Salomon A, Nahmias C. 8p22 MTUS1 gene product ATIP3 is a novel anti-mitotic protein under expressed in invasive breast carcinoma of poor prognosis. PLoS ONE. 2009;4(10):e7239. https://doi.org/10.1371/journal.pone.0007239.
62. Doi C, Egashira N, Kawabata A, Maurya DK, Ohta N, Uppalapati D, Ayuzawa R, Pickel L, Isayama Y, Troyer D, Takekoshi S, Tamura M. Angiotensin II type 2 receptor signaling significantly attenuates growth of murine pancreatic carcinoma grafts in syngeneic mice. BMC cancer. 2010;10:67. https://doi.org/10.1186/1471-2407-10-67.
63. Pickel L, Matsuzuka T, Doi C, Ayuzawa R, Maurya DK, Xie SX, Berkland C, Tamura M. Over-expression of angiotensin II type 2 receptor gene induces cell death in lung adenocarcinoma cells. Cancer Biol Therapy. 2010;9(4):277–85. https://doi.org/10.4161/cbt.9.4.10643.
64. Wang J, Nishiyama A, Matsuyama M, Wang Z, Yuan Y. The (pro)renin receptor: a novel biomarker and potential therapeutic target for various cancers. Cell Commun Signal CCS. 2020;18(1):39. https://doi.org/10.1186/s12964-020-0531-3.
65. Cambados N, Walther T, Nahmod K, Tocci JM, Rubinstein N, Bohme I, Simian M, Sampayo R, Del Valle SM, Kordon EC, Schere-Levy C. Angiotensin-(1–7) counteracts the transforming effects triggered by angiotensin II in breast cancer cells. Oncotarget. 2017;8(51):88475–87. https://doi.org/10.18632/oncotarget.19290.
66. Du N, Feng J, Hu LJ, Sun X, Sun HB, Zhao Y, Yang YP, Ren H. Angiotensin II receptor type 1 blockers suppress the cell proliferation effects of angiotensin II in breast cancer cells by inhibiting AT1R signaling. Oncol Rep. 2012;27(6):1893–903. https://doi.org/10.3892/or.2012.1720.
67. Chaturvedi MM, Sung B, Yadav VR, Kannappan R, Aggarwal BB. NF-kappaB addiction and its role in cancer: 'one size does not fit all'. Oncogene. 2011;30(14):1615–30. https://doi.org/10.1038/onc.2010.566.
68. Zhao Y, Wang H, Li X, Cao M, Lu H, Meng Q, Pang H, Li H, Nadolny C, Dong X, Cai L. Ang II-AT1R increases cell migration through PI3K/AKT and NF-kappaB pathways in breast cancer. J Cell Physiol. 2014;229(11):1855–62. https://doi.org/10.1002/jcp.24639.
69. Bakhtiari E, Hosseini A, Boroushaki MT, Mousavi SH. Angiotensin II receptor antagonist olmesartan and NF-kappaB inhibitor as cytotoxic and apoptotic agents in MCF-7 human cell line. J Chemother (Florence, Italy). 2016;28(4):314–20. https://doi.org/10.1179/1973947815y.0000000055.
70. Saber S, Mahmoud AAA, Goda R, Helal NS, El-Ahwany E, Abdelghany RH. Perindopril, fosinopril and losartan inhibited the progression of diethylnitrosamine-induced hepatocellular carcinoma in mice via the inactivation of nuclear transcription factor kappa-B. Toxicol Lett. 2018;295:32–40. https://doi.org/10.1016/j.toxlet.2018.05.036.
71. Gallagher PE, Tallant EA. Inhibition of human lung cancer cell growth by angiotensin-(1–7). Carcinogenesis. 2004;25(11):2045–52. https://doi.org/10.1093/carcin/bgh236.
72. Cook KL, Metheny-Barlow LJ, Tallant EA, Gallagher PE. Angiotensin-(1–7) reduces fibrosis in orthotopic breast tumors. Can Res. 2010;70(21):8319–28. https://doi.org/10.1158/0008-5472.Can-10-1136.
73. Chehl N, Gong Q, Chipitsyna G, Aziz T, Yeo CJ, Arafat HA. Angiotensin II regulates the expression of monocyte chemoattractant protein-1 in pancreatic cancer cells. J Gastrointest Surg. 2009;13(12):2189–200. https://doi.org/10.1007/s11605-009-1055-8.
74. Ino K, Uehara C, Kikkawa F, Kajiyama H, Shibata K, Suzuki T, Khin EE, Ito M, Takeuchi M, Itakura A, Mizutani S. Enhancement of aminopeptidase A expression during angiotensin II-induced choriocarcinoma cell proliferation through AT1 receptor involving protein kinase C- and mitogen-activated protein kinase-dependent signaling pathway. J Clin Endocrinol Metab. 2003;88(8):3973–82. https://doi.org/10.1210/jc.2002-021582.
75. Zhang S, Wang Y. Telmisartan inhibits NSCLC A549 cell proliferation and migration by regulating the PI3K/AKT signaling pathway. Oncol Lett. 2018;15(4):5859–64. https://doi.org/10.3892/ol.2018.8002.
76. Kou B, Vatish M, Singer DR. Effects of angiotensin II on human endothelial cells survival signalling pathways and its angiogenic response. Vascul Pharmacol. 2007;47(4):199–208. https://doi.org/10.1016/j.vph.2007.06.011.
77. Mehta PK, Griendling KK. Angiotensin II cell signaling: physiological and pathological effects in the cardiovascular system. Am J Physiol Cell Physiol. 2007;292(1):C82–97. https://doi.org/10.1152/ajpcell.00287.2006.
78. Misao J, Hayakawa Y, Ohno M, Kato S, Fujiwara T, Fujiwara H. Expression of bcl-2 protein, an inhibitor of apoptosis, and Bax, an accelerator of apoptosis, in ventricular myocytes of human hearts with myocardial infarction. Circulation. 1996;94(7):1506–12. https://doi.org/10.1161/01.cir.94.7.1506.
79. Pierzchalski P, Reiss K, Cheng W, Cirielli C, Kajstura J, Nitahara JA, Rizk M, Capogrossi MC, Anversa P. p53 Induces myocyte apoptosis via the activation of the renin-angiotensin system. Exp Cell Res. 1997;234(1):57–655. https://doi.org/10.1006/excr.1997.3604.
80. Kossmehl P, Kurth E, Faramarzi S, Habighorst B, Shakibaei M, Wehland M, Kreutz R, Infanger M, Danser AHJ, Grosse J, Paul M, Grimm D. Mechanisms of apoptosis after ischemia and reperfusion: role of the renin-angiotensin system. Apoptosis. 2006;11(3):347–58. https://doi.org/10.1007/s10495-006-4350-9.
81. Ziori H, Kyriakidis M, Zioris H, Gorgoulis V, Kostomitsopoulos N, Kittas C, Karayannakos P. The effects of enalapril on p53 expression in left ventricular cardiomyocytes after aortic stenosis. In Vivo (Athens, Greece). 2006;20(4):459–65.
82. Bratlie SO, Casselbrant A, Edebo A, Fändriks LJSJOG. Support for involvement of the renin–angiotensin system in dysplastic Barrett's esophagus. Scand J Gastroenterol. 2017;52(3):338–43.

83. De la Iglesia IS, Lopez-Jorge CE, Gomez-Casares MT, Lemes Castellano A, Martin Cabrera P, Lopez Brito J, Suarez Cabrera A, Molero Labarta T. Induction of apoptosis in leukemic cell lines treated with captopril, trandolapril and losartan: a new role in the treatment of leukaemia for these agents. Leuk Res. 2009;33(6):810–6. https://doi.org/10.1016/j.leukres.2008.09.029.
84. Delforce SJ, Lumbers ER, Corbisier de Meaultsart C, Wang Y, Proietto A, Otton G, Scurry J, Verrills NM, Scott RJ, Pringle KG. Expression of renin-angiotensin system (RAS) components in endometrial cancer. Endocr Connect. 2017;6(1):9–19. https://doi.org/10.1530/ec-16-0082.
85. Ambros V. MicroRNAs and developmental timing. Curr Opin Genet Dev. 2011;21(4):511–7. https://doi.org/10.1016/j.gde.2011.04.003.
86. Dvinge H, Git A, Graf S, Salmon-Divon M, Curtis C, Sottoriva A, Zhao Y, Hirst M, Armisen J, Miska EA, Chin SF, Provenzano E, Turashvili G, Green A, Ellis I, Aparicio S, Caldas C. The shaping and functional consequences of the microRNA landscape in breast cancer. Nature. 2013;497(7449):378–82. https://doi.org/10.1038/nature12108.
87. Lu J, Getz G, Miska EA, Alvarez-Saavedra E, Lamb J, Peck D, Sweet-Cordero A, Ebert BL, Mak RH, Ferrando AA, Downing JR, Jacks T, Horvitz HR, Golub TR. MicroRNA expression profiles classify human cancers. Nature. 2005;435(7043):834–8. https://doi.org/10.1038/nature03702.
88. Sethupathy P, Borel C, Gagnebin M, Grant GR, Deutsch S, Elton TS, Hatzigeorgiou AG, Antonarakis SE. Human microRNA-155 on chromosome 21 differentially interacts with its polymorphic target in the AGTR1 3' untranslated region: a mechanism for functional single-nucleotide polymorphisms related to phenotypes. Am J Hum Genet. 2007;81(2):405–13. https://doi.org/10.1086/519979.
89. Costinean S, Zanesi N, Pekarsky Y, Tili E, Volinia S, Heerema N, Croce CM. Pre-B cell proliferation and lymphoblastic leukemia/high-grade lymphoma in E(mu)-miR155 transgenic mice. Proc Natl Acad Sci USA. 2006;103(18):7024–9. https://doi.org/10.1073/pnas.0602266103.
90. Seike M, Goto A, Okano T, Bowman ED, Schetter AJ, Horikawa I, Mathe EA, Jen J, Yang P, Sugimura H, Gemma A, Kudoh S, Croce CM, Harris CC. MiR-21 is an EGFR-regulated anti-apoptotic factor in lung cancer in never-smokers. Proc Natl Acad Sci USA. 2009;106(29):12085–90. https://doi.org/10.1073/pnas.0905234106.
91. Li B, Ren S, Li X, Wang Y, Garfield D, Zhou S, Chen X, Su C, Chen M, Kuang P, Gao G, He Y, Fan L, Fei K, Zhou C, Schmit-Bindert G. MiR-21 overexpression is associated with acquired resistance of EGFR-TKI in non-small cell lung cancer. Lung Cancer (Amsterdam, Netherlands). 2014;83(2):146–53. https://doi.org/10.1016/j.lungcan.2013.11.003.
92. Gandellini P, Folini M, Longoni N, Pennati M, Binda M, Colecchia M, Salvioni R, Supino R, Moretti R, Limonta P, Valdagni R, Daidone MG, Zaffaroni N. miR-205 Exerts tumor-suppressive functions in human prostate through down-regulation of protein kinase Cepsilon. Can Res. 2009;69(6):2287–95. https://doi.org/10.1158/0008-5472.Can-08-2894.
93. Yue Z, Yun-Shan Z, Feng-Xia X. miR-205 mediates the inhibition of cervical cancer cell proliferation using olmesartan. J Renin Angiotensin Aldosterone Syst JRAAS. 2016;17(3):1470320316663327. https://doi.org/10.1177/1470320316663327.
94. Yang LX, Liu G, Zhu GF, Liu H, Guo RW, Qi F, Zou JH. MicroRNA-155 inhibits angiotensin II-induced vascular smooth muscle cell proliferation. J Renin Angiotensin Aldosterone Syst JRAAS. 2014;15(2):109–16. https://doi.org/10.1177/1470320313503693.
95. Dai Y, Qiu Z, Diao Z, Shen L, Xue P, Sun H, Hu Y. MicroRNA-155 inhibits proliferation and migration of human extravillous trophoblast derived HTR-8/SVneo cells via down-regulating cyclin D1. Placenta. 2012;33(10):824–9. https://doi.org/10.1016/j.placenta.2012.07.012.
96. Lu C, Huang X, Zhang X, Roensch K, Cao Q, Nakayama KI, Blazar BR, Zeng Y, Zhou X. miR-221 and miR-155 regulate human dendritic cell development, apoptosis, and IL-12 production through targeting of p27kip1, KPC1, and SOCS-1. Blood. 2011;117(16):4293–303. https://doi.org/10.1182/blood-2010-12-322503.
97. Liu X, Cheng Y, Zhang S, Lin Y, Yang J, Zhang C. A necessary role of miR-221 and miR-222 in vascular smooth muscle cell proliferation and neointimal hyperplasia. Circ Res. 2009;104(4):476–87. https://doi.org/10.1161/circresaha.108.185363.
98. Mateescu B, Batista L, Cardon M, Gruosso T, de Feraudy Y, Mariani O, Nicolas A, Meyniel JP, Cottu P, Sastre-Garau X, Mechta-Grigoriou F. miR-141 and miR-200a act on ovarian tumorigenesis by controlling oxidative stress response. Nat Med. 2011;17(12):1627–35. https://doi.org/10.1038/nm.2512.
99. Zheng YG, Wu J, Chen Z, Goodman M. Chemical regulation of epigenetic modifications: opportunities for new cancer therapy. Med Res Rev. 2008;28(5):645–87. https://doi.org/10.1002/med.20120.
100. Dolomatov S, Zuko W, Novikov N, Markaryan A, Eremeeva E. Expressıon of the renin-angiotensin system components in oncologic diseases. Acta clinica Croata. 2019;58(2):354–64. https://doi.org/10.20471/acc.2019.58.02.21.
101. Belyea BC, Xu F, Pentz ES, Medrano S, Li M, Hu Y, Turner S, Legallo R, Jones CA, Tario JD, Liang P, Gross KW, Sequeira-Lopez ML, Gomez RA. Identification of renin progenitors in the mouse bone marrow that give rise to B-cell leukaemia. Nat Commun. 2014;5:3273. https://doi.org/10.1038/ncomms4273.
102. Silva Bde O, Lima KF, Goncalves LR, Silveira MB, Moraes KC. MicroRNA profiling of the effect of the heptapeptide angiotensin-(1–7) in A549 lung tumor cells reveals a role for miRNA149-3p in cellular migration processes. PLoS ONE. 2016;11(9):e0162094. https://doi.org/10.1371/journal.pone.0162094.
103. Bangalore S, Kumar S, Kjeldsen SE, Makani H, Grossman E, Wetterslev J, Gupta AK, Sever PS, Gluud C, Messerli FH. Antihypertensive drugs and risk of cancer: network meta-analyses and trial sequential analyses of 324,168 participants from randomised trials. Lancet Oncol. 2011;12(1):65–82. https://doi.org/10.1016/S1470-2045(10)70260-6.
104. Ruiter R, Visser LE, Van Duijn CM, Stricker BH. The ACE insertion/deletion polymorphism and risk of cancer, a review and meta-analysis of the literature. Curr Cancer Drug Targets. 2011;11(4):421–30. https://doi.org/10.2174/156800911795538147.
105. Sipahi I, Chou J, Mishra P, Debanne SM, Simon DI, Fang JC. Meta-analysis of randomized controlled trials on effect of angiotensin-converting enzyme inhibitors on cancer risk. Am J Cardiol. 2011;108(2):294–301. https://doi.org/10.1016/j.amjcard.2011.03.038.
106. Xi B, Zeng T, Liu L, Liang Y, Liu W, Hu Y, Li J. Association between polymorphisms of the renin-angiotensin system genes and breast cancer risk: a meta-analysis. Breast Cancer Res Treat. 2011;130(2):561–8. https://doi.org/10.1007/s10549-011-1602-3.
107. Mc Menamin UC, Murray LJ, Cantwell MM, Hughes CM. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in cancer progression and survival: a systematic review. Cancer Causes Control. 2012;23(2):221–30. https://doi.org/10.1007/s10552-011-9881-x.

108. Lin J, Chen J, Liu C. AGT M235T variant is not associated with risk of cancer. J Renin Angiotensin Aldosterone Syst JRAAS. 2015;16(2):448–52. https://doi.org/10.1177/1470320313496859.
109. Dai YN, Wang JH, Zhu JZ, Lin JQ, Yu CH, Li YM. Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers therapy and colorectal cancer: a systematic review and meta-analysis. Cancer Causes Control. 2015;26(9):1245–55. https://doi.org/10.1007/s10552-015-0617-1.
110. Yang H, Cai C, Ye L, Rao Y, Wang Q, Hu D, Huang X. The relationship between angiotensin-converting enzyme gene insertion/deletion polymorphism and digestive cancer risk: ınsights from a meta-analysis. J Renin Angiotensin Aldosterone Syst JRAAS. 2015;16(4):1306–13. https://doi.org/10.1177/1470320315585908.
111. Mao Y, Xu X, Wang X, Zheng X, Xie L. Is angiotensin-converting enzyme inhibitors/angiotensin receptor blockers therapy protective against prostate cancer? Oncotarget. 2016;7(6):6765–73. https://doi.org/10.18632/oncotarget.6837.
112. Shen J, Huang YM, Wang M, Hong XZ, Song XN, Zou X, Pan YH, Ling W, Zhu MH, Zhang XX, Sui Y, Zhao HL. Renin-angiotensin system blockade for the risk of cancer and death. J Renin Angiotensin Aldosterone Syst JRAAS. 2016. https://doi.org/10.1177/1470320316656679.
113. Sun H, Li T, Zhuang R, Cai W, Zheng Y. Do renin-angiotensin system inhibitors influence the recurrence, metastasis, and survival in cancer patients?: evidence from a meta-analysis including 55 studies. Medicine (Baltimore). 2017;96(13):e6394. https://doi.org/10.1097/MD.0000000000006394.
114. Li XY, Sun JF, Hu SQ. The renin-angiotensin system blockers as adjunctive therapy for cancer: a meta-analysis of survival outcome. Eur Rev For Med Pharmacol Sci. 2017;21(6):1375–83.
115. Abdeahad H, Avan A, Khazaei M, Soleimanpour S, Ferns GA, Fiuji H, Ryzhikov M, Bahrami A, Hassanian SM. Angiotensin-converting enzyme gene polymorphism and digestive system cancer risk: A meta-analysis based on 9656 subjects. J Cell Biochem. 2019;120(12):19388–95. https://doi.org/10.1002/jcb.28955.
116. Cheng Z, Liu Z. Renin-angiotensin system gene polymorphisms and colorectal cancer risk: a meta-analysis. J Renin Angiotensin Aldosterone Syst JRAAS. 2019;20(4):1470320319881932. https://doi.org/10.1177/1470320319881932.
117. Xiao Y, Dong Z, Zhu J, You J, Fan J. Association between ACE A240T polymorphism and cancer risk: a meta-analysis. J Int Med Res. 2019;47(12):5917–25. https://doi.org/10.1177/0300060519882559.
118. Zhou Q, Chen DS, Xin L, Zhou LQ, Zhang HT, Liu L, Yuan YW, Li SH. The renin-angiotensin system blockers and survival in digestive system malignancies: a systematic review and meta-analysis. Medicine (Baltimore). 2020;99(7):e19075. https://doi.org/10.1097/MD.0000000000019075.