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REVIEW

The alternative renin-angiotensin-system (RAS) signalling pathway in prostate cancer and its link to the current COVID-19 pandemic

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Abstract

Background The renin-angiotensinsystem is known to maintain blood pressure and body fluids. However, it hasbeen found to consist of at least two major constituents, the classic and thealternative pathway, balancing and supporting each other's signalling in a veryintricate way. Current research has shown that the renin-angiotensin system is involvedin a broad range of biological processes and diseases, such as cancer andinfectious diseases.

Methods and results We conducted aliterature review on the interaction of the renin-angiotensin system andprostate cancer and explored the research on the possible impact of theSARS-CoV-2 virus in this context. This review provides an update on contemporaryknowledge into the alternative renin-angiotensin system, its role in cancer,specifically prostate cancer, and the implications of the current COVID-19 pandemic on cancer and cancer care.

Conclusion In this work, we aimto demonstrate how shifting the RAS signalling pathway from the classic to thealternative axis seems to be a viable option in supporting treatment ofspecific cancers and at the same time demonstrating beneficial properties insupportive care. It however seems to be the case that the infection with SARS-CoV-2and subsequent impairment of the renin-angiotensin-system could exhibit seriousdeleterious long-term effects even in oncology.

Keywords Renin-angiotensin system · Prostate cancer · SARS-CoV-2 · MAS1 · Ang (1–7)

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Introduction

Often in physiology, seemingly simple enzymatic systems can regulate a host of pleiotropic and frequently contradictory actions. The renin-angiotensin system (RAS) for instance, has long time been studied for its important role in cardiovascular disease, and various pharmacological intervention principles have been identified to achieve the desired medical effects, such as lowering blood pressure. These include well-established treatment-modalities with angiotensin-converting-enzyme (ACE)-antagonists, selective angiotensin (AT) I antagonists, and diuretics [1].

The RAS itself can be subdivided into the classic and the alternative RAS (see Fig. 1).

The alternative RAS represents a powerful antagonist to the classic RAS, counteracting its effects on blood pressure, fluid and electrolyte homeostasis. Besides these well-known roles, a growing body of evidence has linked the RAS with the pathogenesis of cancer. However, in the same pleiotropic manner as its role in controlling vascular functions, the RAS signalling cascade exerts its actions both pro- and antineoplastic [2].

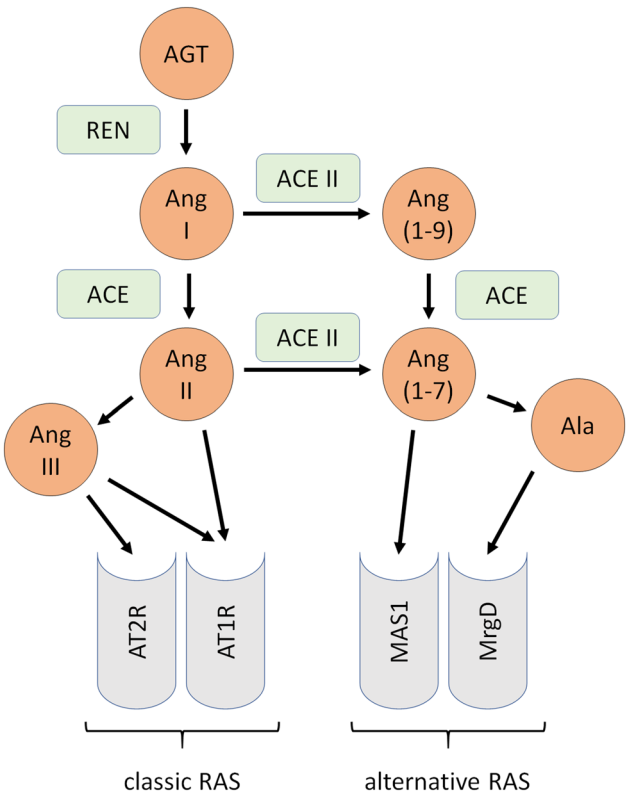

Fig. 1 Classic and alternative RAS signalling; *ACE* angiotensin converting enzyme, *AGT* angiotensinogen, *Ang* Angiotensin, *AT1R* angiotensin II type 1 receptor, *AT2R* angiotensin II type 2 receptor, *Ala* Alamandine, *MAS1* Mas-receptor, *MrgD* G-protein-coupled receptor Mas, *REN* renin

Recent interest in this enzymatic system sparked with the discovery that several coronaviruses utilize one of its central constituents, the enzyme ACE II, as their entry point by binding to it via spike proteins [3]. The binding to and resulting depletion of ACE II is tilting the balance of this intricate system towards the classic RAS at the expense of the alternative pathway with potentially pathogenic consequences. This fostered research into the effects of established medications and repurposing medicines modulating this pathway [3]. To date, however, the data on this effort has been inconclusive.

First shown after the SARS outbreak of 2003, survivors exhibit increased susceptibility to infections, cardiovascular complications as well as an increased occurrence of various tumour types [4]. As SARS-CoV-2 utilizes the same underlying principle, it is to be expected that similar observations can be made in the aftermath of the current pandemic. Not only does the virus and its management impose logistical burdens, but the aforementioned tilting of the RAS balance may have a serious impact on the occurrence and progression of cancer. Possible mechanistic pathways have been investigated and described by Saha and Anirvan [5].

Prostate cancer itself is a severe disease, being the second most common type of cancer in men worldwide and is among the five leading causes of cancer death [6]. Primary treatment consists of either radical prostatectomy or radiation therapy, however a relevant proportion of patients develop metastases. Many different treatment options exist in the metastatic situation. The choice of treatment is dependent on multiple factors such as molecular and pathologic features of the cancer, localisation and number of metastases, and patient's choice. Nevertheless, androgen deprivation therapy still is the mainstay of management of advanced and metastatic prostate cancer. Because of the interplay between the RAS and the androgen receptor pathway [7], impacting the androgen receptor pathway should raise concerns about interfering with the RAS. A comprehensive picture on the mechanistic pathways linking cardiovascular disease and androgen deprivation has not yet been delineated, however, this seems to be a multi-facetted problem [8]. The possible interaction does not work one way only, as it has been shown that the mortality rate due to SARS-CoV-2 infection is significantly higher in prostate cancer (PCa) patients than in a cohort of male patients with any other malignancy [9]. On the other hand, patients receiving androgen depriving therapy exhibited a significantly lower risk of SARS-CoV-2 infection [10].

In this review, we present a summary of the contemporary knowledge of the role of RAS in PCa with a focus on the alternative RAS.

The classic RAS signalling cascade

Since the classic pathway of the RAS has been known for much longer, the bulk of research focussed on it, its constituents and their medicinal manipulation. In our opinion, current knowledge on the classic pathway has been summed up excellently by other authors [11, 12], so we quickly touch on this pathway only insofar as it relates to PCa.

Angiotensin (Ang) II, besides being a major constituent of the vascular homeostasis, can also activate signal cascades that affect classic hallmarks of cancer, such as inflammation, proliferation and angiogenesis [13]. Experiments in vitro and in mouse xenografts have shown that the AT1 receptor (AT1R) transduces its signalling cascade through mitogen-activated protein kinase (MAPK) and signal transducer and activator of transcription 3 (STAT3), so that blockade of AT1R leads to inhibition of both androgen-dependent and independent PCa cells activated by the epidermal growth factor (EGF) [12]. Consequentially, administration of selective AT1R inhibitors lead to inhibited growth and vascularization of PCa xenografts [12, 14]. Inhibition of AT1R has also been shown to improve vascular perfusion of cancers and thereby possibly increases delivery of chemotherapy [15]. These effects appear to be complementary to those of dedicated VEGF-directed drugs and further evaluation clearly is warranted.

It also seems like angiotensin II and III may modify the expression of their corresponding receptors in PCa cell lines, most notably angiotensin II type 2 receptor (AT2R) [14].

Further exploration showed that the AT1 receptor is upregulated in most human PCa tissues versus normal prostate tissues [12]. Additionally, high AT1R expression negatively correlated with survival in patients with ovarian cancer [16]. This naturally posed the question, whether medicinal interference with already approved substances might have a positive impact on prognosis. An analysis of the Finnish Cancer Registry revealed that post-diagnostic use of angiotensin receptor blockers decreased the risk for death from PCa irrespective of Gleason score, risk group or metastatic state [17].

However, the use of antihypertensive drugs such as ACE inhibitors, β-blockers and diuretics were associated with a slightly increased risk for the development of PCa in general [18]. Moreover, it has been shown that Ang II can boost the migration tendency of aggressive PCa cells [14], thus potentially speeding up metastasis. This is supported by the observation that in many cancers, interference with the Ang II –AT1R axis shows its beneficial effects especially in recurrence and distant metastases [19]. The interplay of Ang II and other pathways, such as relaxin 2, also seems crucial in remodelling both the tumour microenvironment as well as the cancer cells itself by facilitating the transition from the androgen-dependent to the androgen-independent phenotype via modulation of the expression of androgen receptors [19].

The alternative RAS signalling cascade

The alternate signalling pathway, describing the actions of Ang (1–7) mediated through the G-protein coupled receptor MAS1 [20], has also been studied in the light of its cardiovascular effects. However, Ang (1–7) does not only bind to MAS1, interaction with constituents of the classic pathway, AT1R and AT2R, have also been shown, yet on a much smaller scale [21]. This is further emphasised by the fact that some of its cardiovascular effects can be nullified by both AT1R- and AT2R-inhibition [22]. In addition to MAS1, Ang (1–7) has been found to specifically bind to another member of the Mas-receptor family: MAS-related G protein-coupled receptor member D (MrgD) [23]. While MAS-deficient mice suffered from endothelial dysfunction under cardiovascular stress [24], they did not show a strong phenotype under physiological conditions [25], suggesting that signalling of Ang (1–7) may at least in part be compensated for by MrgD [23].

Ang (1–7) also, however, exhibits effects on cancer. While the role of the classic RAS seems to be well understood, the implications of Ang (1–7) are contradictory in different organ systems: Despite the fact it has been shown to exert anti-neoplastic properties in breast [26], colon [27] lung [28], pancreatic [29] and PCa [30], pro-neoplastic effects have been discovered in renal cell carcinoma [31, 32].

Similarly to the classic pathway, constituents of the alternative pathway are differentially expressed in neoplastic versus non-neoplastic tissues. ACE II expression has been shown to be downregulated in non-small-cell lung cancer (NSCLC) [28], hepatocellular carcinoma (HCC) [33], breast cancer [34], pancreatic cancer [35] and gallbladder cancer cells [36]. It is debatable whether the levels of ACE II expression can be utilized as prognostic marker, as it has been shown that these in fact correlate with outcome, at least in HCC and breast cancer [33, 37]. In addition to their cellular experiments, Zhang et al. also performed retrospective analyses on the expression of ACE II in human breast cancer samples [37]. They could show that ACE II expression in cancerous tissues was significantly decreased compared to normal tissue and patients with higher ACE II expression exhibited a better prognosis with regard to relapse free survival than those with lower expression (HR = 0.81). These findings have been confirmed in clear cell renal cell carcinoma (ccRCC), in addition to showing that Ang (1–7) might be the mediator of these effects [38]. Interestingly, treatment of ccRCC with small-molecule inhibitors of vascular endothelial growth factor receptor (VEGFR-TKI) decreased expression of ACE2. This was ameliorated by the combined

administration of VEGFR-TKI and Ang (1–7), which resulted in further suppressed tumour growth and improved survival. Given the fact that TKI targeting the VEGFR are in widespread use e.g. in RCC management, this combination should be further evaluated.

The receptor of Ang (1–7), MAS1, can be upregulated in colon cancer [27]. It has been discussed, however, that this is not a marker of oncogenic processes itself, but rather part of a general activation of the RAS in cancer [27]. Further data from breast and oesophageal cancer supports this notion, as upregulation of MAS1 has been shown to represent a positive prognostic marker [39]. However, siRNA mediated knockout of MAS1 increased proliferation of osteosarcoma cells [40]. Taken together, most of the evidence suggests that the classic RAS plays a pro-neoplastic role in the development of cancers that can (partly) be ameliorated by the alternative RAS pathway.

Both for its effects on the vascular system and cancer itself, Ang (1–7) has been investigated as a medication in trials in cancer patients. It was found to exert positive effects on multilineage cytopenia as well as demonstrating clinical benefit and shrinking of some tumour types [41]. These results have also been observed in PCa, albeit in mouse models only [42]. Stimulation of MAS1 with a selective agonist has been found to exhibit favourable effects, too, such as delaying the development of cancers and mitigating cancer cachexia [43]. A summary of selected experiments on the role of the alternative RAS can be found in Table 1.

Another receptor also capable of binding Ang (1–7), MrgD, was found upregulated in lung cancer tissue and its main ligand, beta-alanine, enhanced spheroid formation in vitro [44]. It is unclear, however, whether these affects are solely contributable to beta-alanine and whether Ang (1–7) results in a different signalling.

The intracellular signal transduction cascade of MAS1 as shown below (see Fig. 2) follows both the MAPK/ERK and the AKT/mTOR signalling cascades.

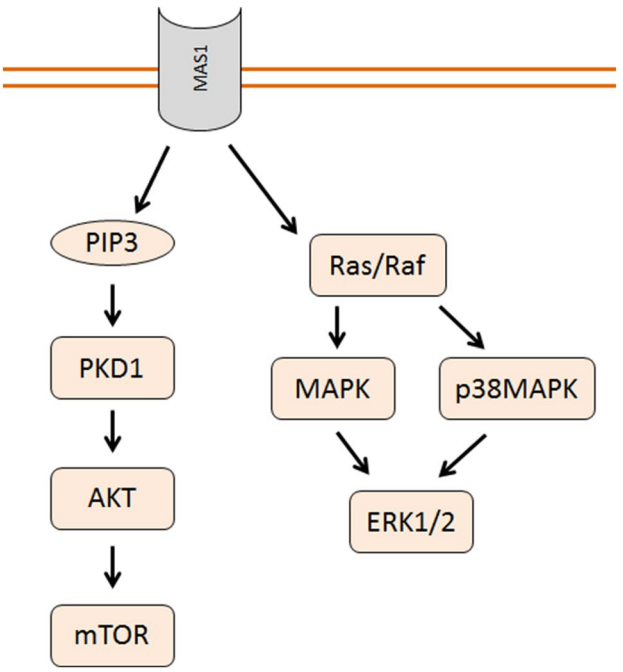

Fig. 2 Downstream signalling cascade from MAS1; *AKT* protein kinase B, *ERK* Extracellular signal-regulated kinase, *MAPK* mitogen-activated protein kinase, *mTOR* mammalian target of rapamycin, *PKD1* protein kinase D1, *PIP3* Phosphatidylinositol (3,4,5)-trisphosphate, *Raf* rapidly accelerated fibrosarcoma, *Ras* rat sarcoma kinase

Prostate cancer within the context of the current COVID-19 pandemic

As it has recently been found that SARS-CoV-2 enters its host cells by ACE II in a TMPRSS2 (transmembrane protease serine subtype 2)-dependent manner [3], implications on the functioning of the RAS, especially the alternative RAS were expected. While the expression of TMPRSS2 is influenced by androgens, data on its manipulation are contradictory at best. Mechanistically one could argue that downregulation of the receptor ACE II induced by androgen-depriving therapy (ADT) for instance, may have a protective effect against the virus. While this was found to be the case in one study [10], another study demonstrated different, contrary results [51]. This could be in part due to population differences among the subjects observed, as well as the clinical settings and thus needs confirmation. Additionally, it was found that lower testosterone plasma levels are able to predict worse clinical outcome of the infection, suggesting a more favourable role of androgens during the course of the infection [52].

Many hypotheses have been put forward to explain the increased infection rates of males versus females [53], but most are speculative so far. The overall differential expression of TMPRSS2 between males and females for instance has been found to be very similar in lung tissue and one common driver of PCa, the fusion of TMPRSS2 and ERG has so far not been found to elicit any differential infection patterns or influence the severity of the infection. The influence of this fusion gene in prostate cancer therefore might warrant further exploration.

The depletion of ACE II upon SARS-CoV-2 infection [54] is expected to mitigate the alternative RAS signalling, thereby skewing the resulting signal more in favour of the potentially deleterious classic RAS pathway [5]. The resulting effects have been studied in the aftermath of the 2003 epidemic of the very similar SARS-CoV with the consequential spike of incidences of various cancers and other inflammatory diseases [55]. Many open questions still remain and are worth pursuing.

Table 1 Effects of the alternative RAS signalling pathway on cancer

Cancer	Model	Manipulation	Results	References
Breast	In vitro	ACE II overexpression	↓ Proliferation ↓ Vascularisation ↓ Migration ↓ Metastasis ↓ pVEGFR2	[37]
Breast	In vivo	MAS1 analysis	MAS1 low: ↑ Tumour growth ↑ Metastasis ↑ Grading	[39]
Pancreas	Murine	MAS1 stimulation	↓ Muscle atrophy ↓ Weight loss ↑ Locomotor activity ↓ Tumour development	[43]
Colon	In vivo	MAS1 analysis	↑ MAS1 expression in neoplastic tissue	[27]
Lung	Murine	Addition of Ang (1–7)	↓Tumour growth ↓ Vessel density ↓ VEGF	[45]
Lung	In vitro	Addition of Ang (1–7)	↓ Migration ↓ Invasion ↓ MMP-2 & -9	[46]
Nasopharynx	Murine	Addition of Ang (1–7)	↓ Tumour growth ↓ Vessel density ↓ VEGF/↓ PlGF	[47]
Nasopharynx	Murine	Addition of Ang (1–7)	↑ Autophagy	[48]
Prostate	Murine	Addition of Ang (1–7)	↓ Metastasis ↓ VEGF ↓ Tumour growth ↓ Osteoclastogenesis	[30]
Prostate	Murine	Addition of Ang (1–7)	↓ Tumour growth ↓ Proliferation ↓ Intratumoral vessel density ↓ VEGF/↓ PlGF/↑ sFlt-1	[42]
Prostate	In vitro	Addition of Ang (1–7)	↓ Proliferation ↓ Apoptosis ↑ AT2R / ↑MAS1 ↓ ESR1 / ↑ ESR2 Modulation of NF-kB Modulation of IKK Modulation of MMP-2 & -9	[49]
Prostate	In vitro	Addition of Ang (3–7) Addition of Ang (1–9)	↑ Growth ↑ Mobility ↑ ESR1/↑ ESR2 ↓ Colony size ↑ AR expression (in PC3)	[50]

AR androgen receptor, *ESR oestrogen receptor, IKK IκB kinase, MMP Matrix metallopeptidase, NF-kB Nuclear Factor kappa-light-chain-enhancer of activated B cells, PC3 human prostate cancer cell line, PlGF placental growth factor, pVEGFR2 phosphorylated receptor 2 of the vascular endothelial growth factor, sFlt-1 soluble fms-like tyrosine kinase-1, VEGF vascular endothelial growth factor*

Summary

The bulk of the evidence so far shows that the classic RAS exhibits pro-tumorigenic properties, while the alternative RAS mostly displays anti-tumorigenic ones. Even though some mechanistical questions remain, RAS has been identified as a feasible drug target not only in cardiovascular disease, but in cancer as well [56]. As aldosterone is the final player in the RAAS, regulating not only blood pressure and volume, but also triggering migratory stimuli on

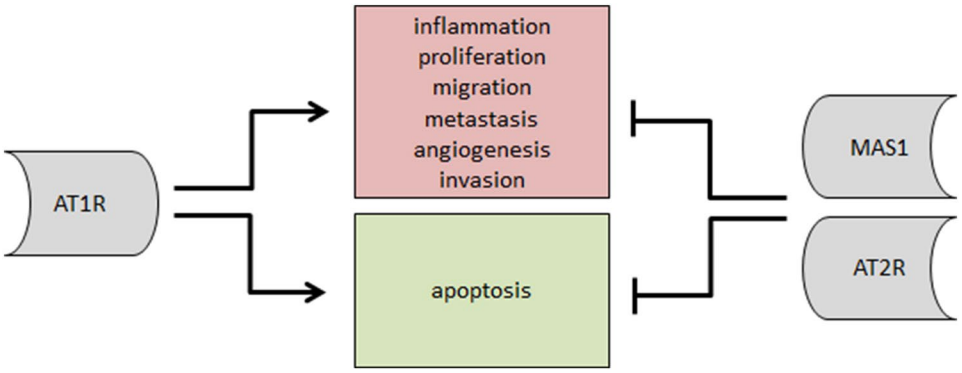

Fig. 3 Interplay of AT1R, MAS1 and AT2R

hormone-dependent PCa cells [57] it again demonstrates the importance of this pathway in the pathology of PCa. This conclusion is not new, as it has been discouraged to use drugs influencing the aldosterone axis in PCa before [58].

Even though Ang II signalling can trigger apoptosis [59] and signalling through MAS1 seems to prevent it [49], the deleterious effects of the classic RAS signalling cascade appear to outweigh those of the alternative pathway on cancer by far. Taken together, skewing the RAS signalling pathway from the classic to the alternative axis seems to be a viable option if not in preventing, but at least in treating specific cancers and at the same time demonstrating beneficial properties in supportive care (see Table 1; Fig. 3).

In the light of the current pandemic situation, cancer patients are among the most vulnerable and therefore careful consideration needs to be placed on not only how to protect them from the disease, the impact of their medication on and susceptibility to the virus but also on the possibility of Covid-19 convalescents later becoming cancer patients themselves [4, 5].

Further research on the influence of RAS on PCa and its modulation is warranted. This in fact can lead to an improved molecular understanding and novel, personalised treatment options. Lung cancer to date is at the forefront of targeted approaches to specific mutations, but it has been shown that PCa, too, yields various, sometimes already actionable mutations. Already, survival with PCa has been improved by the introduction of novel therapeutics [60], with a better molecular understanding of the pathogenesis and development of resistance, further improvement is to be expected.

Conclusion

While much has been investigated into the role of the classic RAS signalling pathway, data on the interplay between the alternative RAS and PCa still is fragmentary.

Taken together, while a SARS-CoV-2 infection poses a clear and acute danger to cancer patients in general, possible short term and long-term effects due to the interplay of SARS-CoV-2 with the RAS might be a danger for cancer patients as well. We suggest to further explore the oncogenic role of the classic RAS and alternative RAS, in particular with a focus on the androgen signalling pathway in prostate cancer. In light of the current pandemic a better understanding of the classic RAS and alternative RAS will improve both SARS-CoV-2 management and oncologic care.

Author contributions FS: Data collection and management, literature research, data analysis, manuscript writing and editing. HB, MM, SS, AO, SP, MWK: Manuscript editing. BG: Data collection. ASM: Idea, manuscript editing, critical revision. MCR: Idea, manuscript writing and editing, data collection.

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Declarations

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