The Renin–Angiotensin System in Cancer: Mechanisms of Tumor Enhancement and Inhibition and Therapeutic Targets

Bachelor thesis
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Abstract

The renin–angiotensin system (RAS), traditionally known for its role in cardiovascular regulation, is increasingly recognized as a modulator of cancer biology. This thesis explores the dual role of RAS in oncology, i.e. on the one hand in tumor tumorigenesis / development and on the other hand in tumor suppression and evaluates its components as potential therapeutic targets. The classical RAS axis (ACE–Ang II–AT_1R) promotes tumor growth through activation of oncogenic pathways, angiogenesis, inflammation, and immune evasion. Conversely, the counter-regulatory arm—comprising ACE2, Ang-(1-5), Ang-(1–7), presumably the Mas receptor, and certainly AT_2R—exerts anti-proliferative and pro-apoptotic effects. Particular focus is given to the therapeutic potential of modulating these opposing pathways. While AT_1R antagonists and ACE inhibitors show promise in reducing tumor progression, AT_2R agonists and Ang-(1–7) may enhance tumor suppression. Recent evidence challenges the interaction of Ang-(1–7) with MasR, suggesting alternative mechanisms. This thesis proposes that Ang-(1–5), a downstream metabolite of Ang-(1–7), might induce these suppressive effects, either through MasR or AT_2R. Overall, dual modulation of RAS—suppressing pro-tumor and enhancing anti-tumor axes—represents a promising avenue for cancer therapy.

List of Abbreviations

Abbreviation	**Full Term**
ACE	Angiotensin-Converting Enzyme
ACE2	Angiotensin-Converting Enzyme 2
ACEi	ACE Inhibitor
ADH	Anti-Diuretic Hormone
Ang I	Angiotensin I
Ang II	Angiotensin II
Ang-(1–5)	Angiotensin-(1–5)
Ang-(1–7)	Angiotensin-(1–7)
Ang-(1–9)	Angiotensin-(1–9)
Ang III	Angiotensin III (Ang-(2–8))
Ang IV	Angiotensin IV (Ang-(3–8))
ARB	Angiotensin Receptor Blocker
AT_1R	Angiotensin II Type 1 Receptor
AT_2R	Angiotensin II Type 2 Receptor

CAF	Cancer-Associated Fibroblast
CHO	Chinese Hamster Ovary
COX-2	Cyclooxygenase-2
CSC	Cancer Stem Cell
DAG	Diacylglycerol
DRI	Direct Renin Inhibitor
ECM	Extracellular Matrix
EGFR	Epidermal Growth Factor Receptor
eNOS	Endothelial Nitric Oxide Synthase
EMT	Epithelial–Mesenchymal Transition
ERK1/2	Extracellular Signal-Regulated Kinase 1/2
G protein	Guanine Nucleotide-Binding Protein
GPCR	G Protein-Coupled Receptor
IL	Interleukin
IP3	Inositol Triphosphate
JAK	Janus Kinase
MAPK	Mitogen-Activated Protein Kinase
MasR	Mas Receptor
MCP-1	Monocyte Chemoattractant Protein-1
MrgD	Mas-Related G Protein-Coupled Receptor D
mTOR	Mechanistic Target of Rapamycin
NEP	Neprilysin
NF-κB	Nuclear Factor Kappa-light-chain-enhancer of Activated B Cells
NO	Nitric Oxide
NSAID	Non-Steroidal Anti-Inflammatory Drug
PIP2	Phosphatidylinositol 4,5-bisphosphate
PI3K	Phosphoinositide 3-Kinase

PKC	Protein Kinase C
PRR	(Pro)renin Receptor
RAS	Renin–Angiotensin System
RASi	RAS Inhibitor
ROS	Reactive Oxygen Species
SHP-1	Src Homology Phosphatase-1
STAT	Signal Transducer and Activator of Transcription
TGF-β	Transforming Growth Factor Beta
TME	Tumor Microenvironment
TNF-α	Tumor Necrosis Factor Alpha
VEGF	Vascular Endothelial Growth Factor

Introduction

The renin–angiotensin system (RAS) comprises a cascade of breakdown products from angiotensinogen including the peptide hormone angiotensin II and multiple receptors that regulate key physiological processes such as blood pressure, vascular tone, and fluid–electrolyte balance. It plays a vital role in maintaining hemodynamic stability, especially during hypovolemic states. The formation of the angiotensinogen-derived peptide cascade is initiated by the secretion of renin from juxtaglomerular cells in the kidney, which cleaves angiotensinogen (produced by the liver) into angiotensin I (Ang I). Angiotensin-converting enzyme (ACE) then converts Ang I into angiotensin II (Ang II), the primary active peptide of the system. Ang II exerts its classical effects via the angiotensin II type 1 receptor (AT_1R), inducing vasoconstriction, aldosterone secretion, sodium retention, and sympathetic nervous system activation—responses that collectively raise blood pressure (Figure 1) (Triebel & Castrop, 2024). Additionally, Ang II binds to the angiotensin II type 2 receptor (AT_2R), which mediates effects generally opposite to those of AT_1R, such as vasodilation and anti-proliferative signaling (Koh et al., 2023).

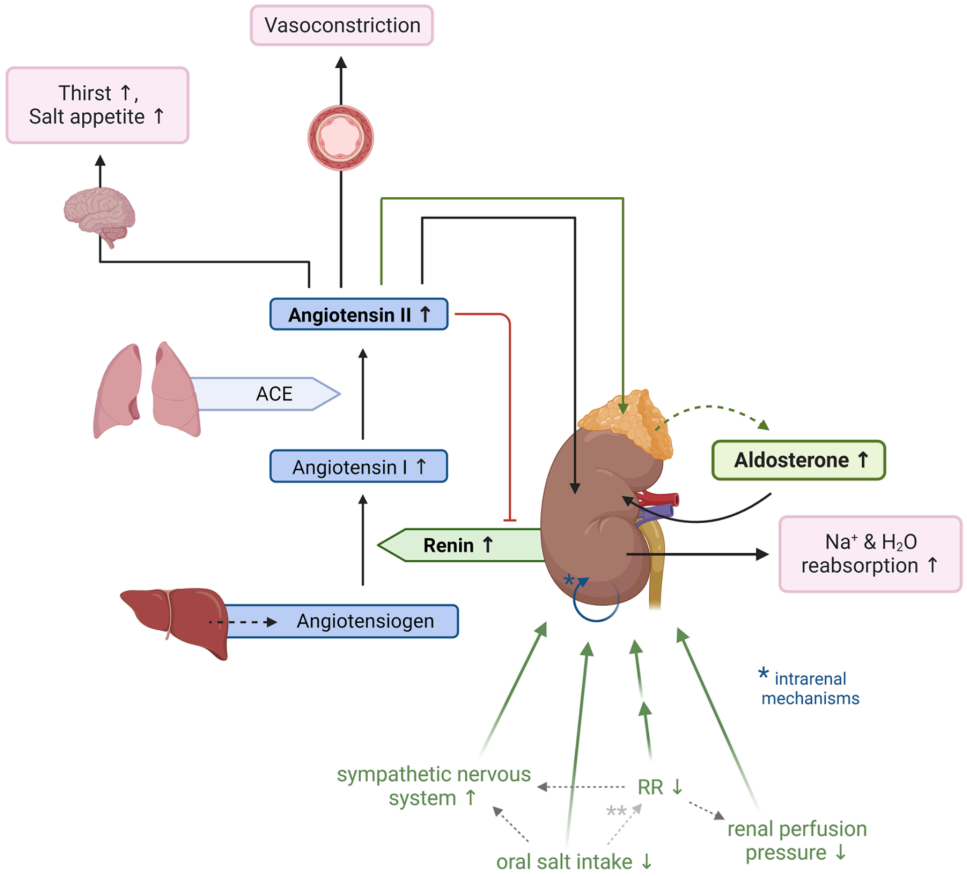

Figure 1. Regulation of the RAS and key effects of angiotensin II and aldosterone. The system is controlled by a complex network of factors that together maintain blood pressure and extracellular volume. Solid arrows represent stimulatory pathways, while blunt arrows indicate inhibitory effects. The figure illustrates the activating side of RAS regulation. * Denotes intrarenal mechanisms, including the baroreceptor and macula densa-mediated control of renin release. ** Refers to the influence of dietary salt intake on blood pressure, a response that varies between individuals due to salt sensitivity. Figure from Triebel & Castrop (2024)

Beyond these interactions, the counter-regulatory arm of the RAS involves the heptapeptide angiotensin-(1–7) [Ang-(1–7)], generated via ACE2-mediated cleavage of Ang II. Ang-(1–7) has been proposed to bind to the Mas receptor (MasR) (Figure 2) (Hassani et al., 2023), where it is believed to exert anti-inflammatory, anti-fibrotic, and anti-proliferative effects that counterbalance the classical RAS axis (Hassani et al., 2023; Koh et al., 2023), although not by all studies confirmed (Gaidarov et al, 2018). Both AT_2R and MasR activation are associated with protective mechanisms including vasodilation, reduced oxidative stress, and inhibition of cellular proliferation, especially in vascular and cardiac tissues (Shah et al., 2023; Triebel & Castrop, 2024). While the cardiovascular roles of these receptors are increasingly accepted, their involvement in cancer and other non-cardiovascular pathologies is the subject of ongoing investigation (Koh et al., 2023; Su et al., 2023).

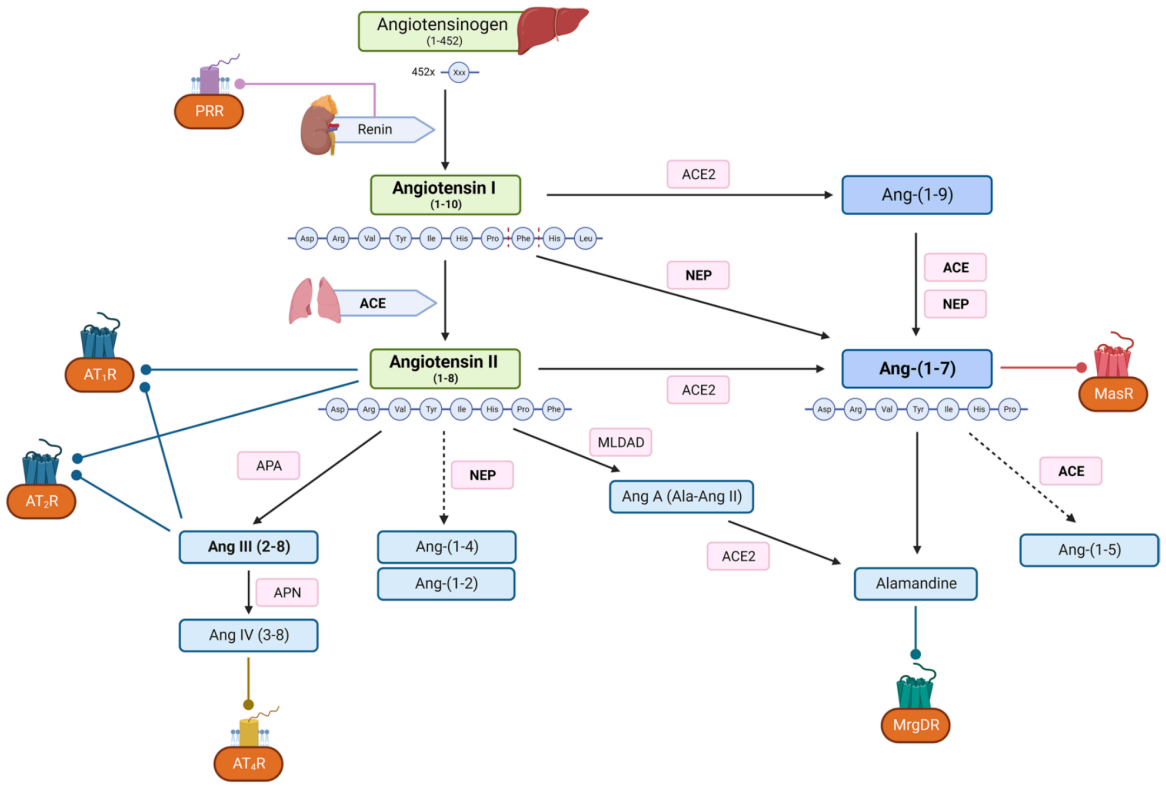

Figure 2 illustration of the RAS proteolytic cascade. Renin cleaves angiotensinogen into angiotensin I (Ang I), which is converted by ACE to the active angiotensin II (Ang II), acting on AT1 and AT2 receptors. Ang I can also be processed by NEP or ACE2 into Ang-(1–7), which is thought to signal via the Mas receptor, or further into alamandine, acting on MrgDR. Ang II can be converted into Ang III and thereafter into Ang IV, which binds AT4 receptors. Figure from Triebel and Castrop (2024).

Recent research has demonstrated that RAS activity is not restricted to systemic hemodynamics but also operates at a local level within tissues. Local or tissue-specific RAS components have been identified in the heart, brain, liver, kidneys, and even in tumors (Shah et al., 2023). In these settings, RAS influences processes such as inflammation, fibrosis, cellular proliferation, and apoptosis. Dysregulation of local RAS signaling is implicated in tumorigenesis through mechanisms including immune suppression, extracellular matrix remodeling, and enhanced angiogenesis (Hassani et al., 2023; Roth et al., 2019). These findings suggest that key RAS elements—particularly AT_2R and Ang-(1–7)/MasR—may be promising therapeutic targets in oncology (Koh et al., 2023). Therefore this thesis addresses the following main question:

Research Question

How is the renin–angiotensin system (RAS) involved in cancer, and which of its components could serve as relevant therapeutic targets?

To explore this topic, the thesis is structured around the following subquestions:

1. What are the physiological roles of the RAS system beyond cardiovascular regulation, particularly in cell growth, apoptosis, and inflammation?
2. How is RAS signaling altered in cancers, and which RAS components are commonly dysregulated?

3. What is the role of the classical RAS axis (ACE–Ang II–AT_1R) in promoting tumorigenesis?
4. What is the function of the counter-regulatory RAS axis (ACE2–Ang-(1–7)–MasR and AT_2R) in suppressing tumor progression?
5. Which RAS-related receptors and enzymes have emerged as promising therapeutic targets in oncology, and what is the current clinical status of pharmacological strategies aimed at modulating these components in cancer treatment?

Results

1. Physiological Roles of RAS Beyond Cardiovascular Regulation

1.1 Tissue Ras

Traditionally known for its role in blood pressure and fluid homeostasis, the renin-angiotensin system (RAS) is now recognized as a multifunctional regulator of a wide range of physiological and pathophysiological processes, including cell proliferation, apoptosis, inflammation, and fibrosis. In addition to its systemic actions, RAS components are expressed locally in various tissues including the heart, kidneys, lungs, liver, brain, and reproductive organs— where they act in autocrine, paracrine, or intracrine fashions to influence tissue-specific functions (Shah et al., 2023). These specific functions are mediated through several signaling pathways involving RAS components that contribute to cancer progression. Each pathway is initiated by a specific ligand binding to its corresponding receptor, which then triggers a cascade of intracellular events that ultimately influence gene expression and cell behavior.

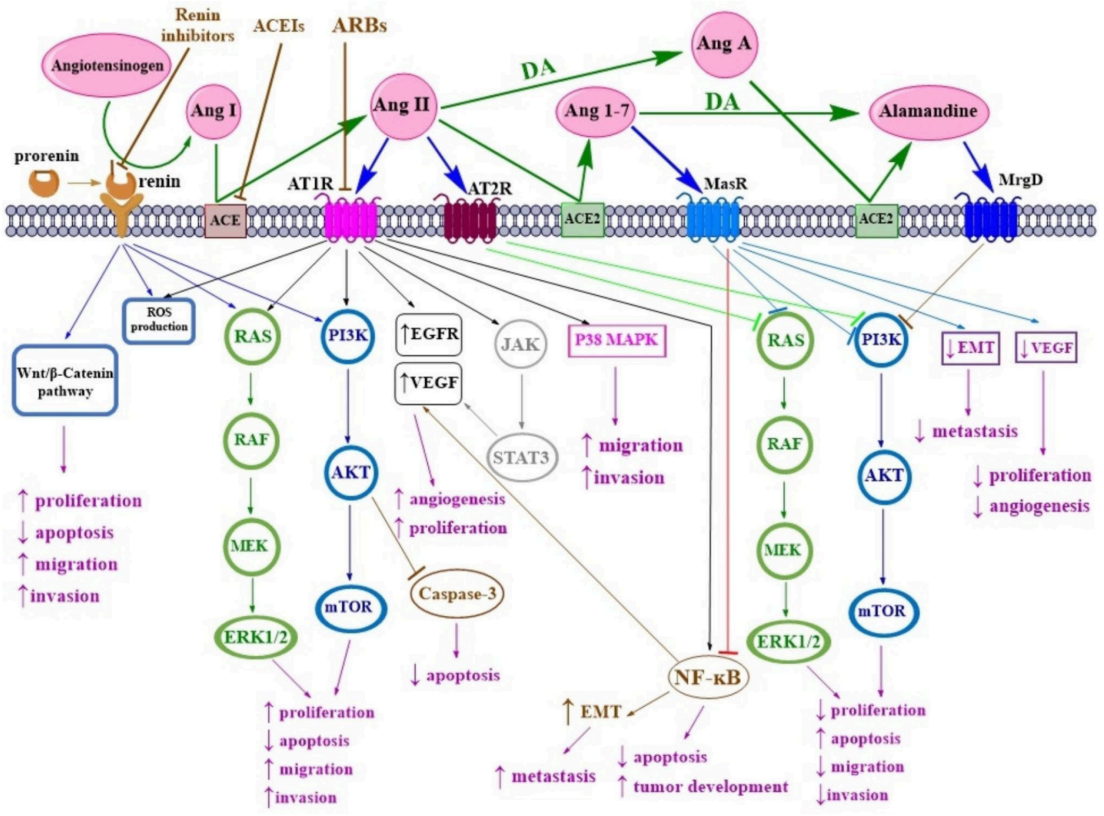

Figure 3. Angiotensin Derivatives, Receptor Interactions, and Cancer-Related Pathways. This figure illustrates the key angiotensin peptides, their associated receptors, and the downstream signaling cascades that regulate proliferation, apoptosis, and angiogenesis. It highlights the dual role of the renin–angiotensin system (RAS) in cancer. Pro-tumorigenic effects are primarily mediated by Ang II through AT_1R, while anti-tumorigenic activity is associated with Ang I/AT_2R, Ang-(1–7)/Mas, and alamandine/MrgD interactions. These receptor-ligand interactions influence critical oncogenic and tumor-suppressive pathways, notably the PI3K/AKT/mTOR and RAS/RAF/ERK1/2 cascades, which play pivotal roles in either promoting or inhibiting cancer progression. Figure from Hassani et al. (2023).

1.2 Angiotensin II stimulates the Angiotensin II type 1 receptor

One of the primary pathways is the Angiotensin II interaction with the Angiotensin II type 1 receptor. Ang II, a potent vasoconstrictor, binds to AT_1R, a G protein-coupled receptor located on the plasma membrane of various cell types. Upon binding, the receptor activates Gq proteins, which stimulate phospholipase C (PLC). This enzyme catalyzes the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP2) into inositol triphosphate (IP3) and diacylglycerol (DAG). IP3 increases intracellular calcium levels, while DAG activates protein kinase C (PKC) (Figure 3). These events lead to the activation of the MAPK pathway, specifically the Ras-Raf-MEK-ERK cascade. ERK then translocates to the nucleus, where it influences the transcription of genes involved in cell proliferation, differentiation, and survival. These transcription factors result in increased cell proliferation, differentiation, and survival (Hassani et al., 2023; Triebel & Castrop, 2024).

1.3 Angiotensin II also stimulates the Angiotensin II type 2 receptor

In contrast to the pro-growth effects mediated by AT_1R, the Ang II/AT_2R (Angiotensin II type 2 receptor) axis generally exerts anti-proliferative, pro-apoptotic, and anti-inflammatory effects. Ang II not only binds and activates AT_1R but also AT_2R, also a G protein-coupled receptor which activates fundamentally different signaling pathways than AT_1R does.

Upon stimulation, AT_2R recruits intracellular phosphatases such as SHP-1 (Src homology 2 domain-containing phosphatase-1) and PP2A (protein phosphatase 2A), which inhibit MAPK signaling by dephosphorylating ERK, MEK, and other kinases (Figure 3) (Peluso et al., 2023). AT_2R activation also inhibits the PI3K–Akt–mTOR pathway, a major signaling axis for cell growth and survival. SHP-1 and PP2A dephosphorylate Akt at Ser473 and Thr308, suppressing its kinase activity. This reduces downstream mTORC1 signaling, leading to decreased protein synthesis and cell proliferation (Figure 3) (Hassani et al., 2023).

In parallel, AT_2R promotes nitric oxide (NO) production via endothelial nitric oxide synthase (eNOS). NO stimulates soluble guanylate cyclase (sGC), increasing cyclic GMP (cGMP) levels and activating protein kinase G (PKG). PKG signaling further supports apoptosis and vasodilation and reduces oxidative stress (Peluso et al., 2018).

Finally, AT_2R may also engage β-arrestin-independent mechanisms and modulate signaling through receptor dimerization (Peluso et al., 2023), particularly under stress or in pathological states. These combined pathways enable AT_2R to counterbalance AT_1R-driven oncogenic processes by suppressing mitogenic and induce apoptosis signals (Peluso et al., 2023).

1.4 The controversial Angiotensin-(1-7)-mediated activation of the Mas receptor

Another important axis is the Angiotensin-(1-7) to Mas receptor (MasR) pathway. Angiotensin-(1-7), a heptapeptide derived from Ang II via ACE2 or from Ang I via neprilysin, is thought to bind to MasR, a G protein-coupled receptor distinct from AT_1R and AT_2R. It is thought that the activation of MasR leads to downstream signaling where it inhibits pathways like PI3K/Akt and ERK1/2 , although with more nuanced regulatory outcomes compared to AT_1R (Figure 3). This pathway promotes nitric oxide production, reduces reactive oxygen species, and has anti-inflammatory, anti-fibrotic, and anti-proliferative properties (Hassani et al., 2023). Whether or not these effects are MasR -dependent remains an area of active research, with some evidence pointing toward alternative receptor interactions or indirect mechanisms. In particular, recent findings mechanistically complicate the proposition that Ang-(1-7) would activate MasR. A study by Gaidarov et al. (2018) challenges the assumption

that Ang-(1–7) acts directly through MasR. Their data show no evidence of direct binding or functional activation of recombinant MasR by Ang-(1–7) across multiple signaling platforms, including G protein activation, β-arrestin recruitment, Erk1/2 phosphorylation, and receptor internalization. Furthermore, Ang-(1–7) did not antagonize MasR agonist-induced signaling. Instead, this study suggests that Ang-(1–7) may exert its effects by antagonizing Ang II at AT_1R, effectively blunting Ang II-induced proliferation and signaling cascades, including in rat aortic endothelial cells. While this casts doubt on MasR as a direct mediator of Ang-(1–7) activity in recombinant systems, broader literature still mentions a role where MasR binds Ang-(1–7) and induces anti-inflammatory, anti-fibrotic, and anti-proliferative properties (Hassani et al., 2023; Su et al., 2023).

1.5 Activation of the prorenin receptor may lead to transcription of oncogenes

The prorenin receptor (PRR), another key component of the RAS, mediates cross-talk with the Wnt/β-catenin signaling pathway. Binding of prorenin to PRR enhances Wnt receptor complex stability and prevents degradation of β-catenin (Figure 3). Accumulated β-catenin translocates to the nucleus, where it activates transcription of oncogenes such as MYC and CCND1. This mechanism is particularly relevant in cancer stem cell maintenance and tumor initiation (Roth et al., 2019).

1.6 Summary of the Physiological Roles of RAS

altogether, angiotensin II, acting via AT_1R, promotes cell growth and survival through MAPK activation (Hassani et al., 2023; Triebel & Castrop, 2024). In contrast, AT_2R signaling induces nitric oxide production and phosphatase activity, leading to apoptosis and anti-inflammatory effects (Peluso et al., 2023). Angiotensin-(1–7), typically linked to Mas receptor signaling, contributes to anti-proliferative effects, though recent evidence suggests it may act indirectly by antagonizing AT_1R (Gaidarov et al., 2023). Additionally, prorenin receptor (PRR) activation enhances Wnt/β-catenin signaling, supporting stemness and tumor progression (Roth et al., 2019).

2. RAS Dysregulation in Cancer

2.1 Shift Toward a Tumor-Promoting RAS Profile

The renin–angiotensin system (RAS), traditionally known for its role in cardiovascular regulation, is now increasingly implicated in cancer biology. In numerous malignancies, RAS signaling becomes disrupted, shifting from its physiological, homeostatic function toward a pro-tumorigenic state (Hassani et al., 2023). This shift is characterized by the upregulation of the classical axis, while the counter-regulatory arm is frequently suppressed or functionally impaired (Koh et al., 2023; Su et al., 2023).

2.2 RAS Signaling Supports Tumor Growth via Cancer Stem Cells and the Tumor Microenvironment

An important dimension of RAS involvement in cancer lies in its regulation of cancer stem cells (CSCs). These cells possess high tumorigenic potential, contribute to tumor heterogeneity, mediate resistance to conventional therapy, and play a pivotal role in relapse. RAS components have been found to be expressed in CSC populations, where they support stemness, proliferation, and survival (Roth et al., 2019). Consequently, RAS modulators are

being explored as a strategy to therapeutically target CSC-driven tumor maintenance and progression (Roth et al., 2019; Koh et al., 2023).

Beyond CSCs, components of RAS are present in a variety of non-malignant cells within the tumor microenvironment (TME), including endothelial cells, fibroblasts, macrophages, neutrophils, and T lymphocytes (Hassani et al., 2023). These cells often engage in paracrine RAS signaling, which contributes to immunosuppression, stromal remodeling, and angiogenesis. The integrated effect of local RAS activation within the TME is a permissive niche that facilitates tumor expansion and immune evasion (Su et al., 2023; Maranduca et al., 2023).

2.3 Overexpression of Classical Axis Components

The tumor-promoting effects of RAS are primarily mediated through the overexpression of classical axis components. Ang II, the principal effector of this axis, is often elevated in cancerous tissues. It induces oxidative stress, activates pro-inflammatory cytokine production, and contributes to extracellular matrix remodeling and fibrosis, all of which are conducive to tumor progression (Shah et al., 2023).

ACE, which converts Ang I to Ang II, is frequently upregulated in both malignant and fibrotic pathologies, such as chronic hepatitis and idiopathic pulmonary fibrosis. In cancer, this may contribute to the desmoplastic and inflammatory stroma typical of aggressive tumors (Koh et al., 2023). The AT_1R is also commonly overexpressed and has been proven in driving cell proliferation, angiogenesis, and inflammatory signaling. Its upregulation is often associated with advanced tumor grade, increased microvascular density, and poor prognosis (Su et al., 2023).

2.4 Suppression of Counter-Regulatory Pathway

The downregulation of the angiotensin II type 2 receptor (AT_2R) is a common feature in various cancers and is associated with the loss of critical tumor-suppressive functions. Under normal physiological conditions, AT_2R counterbalances the effects of the angiotensin II type 1 receptor (AT_1R) by promoting apoptosis, inhibiting proliferation, and reducing inflammation. However, in malignancies such as colorectal, pancreatic, and prostate cancers, AT_2R expression is often reduced or absent, which shifts the balance toward AT_1R-driven tumorigenic signaling (Moll, 2024; Hassani et al., 2023). This loss of AT_2R activity contributes to uncontrolled cell growth, enhanced angiogenesis, and impaired apoptotic responses. Moreover, experimental studies using AT_2R agonists, such as LP2, have demonstrated that restoring AT_2R activation can inhibit tumor progression by inhibiting key signaling pathways like PI3K/Akt and mTOR, further highlighting the functional consequences of its downregulation (Peluso et al., 2023; Wagenaar & Moll, 2023).

RAS Pathway	Dysregulated Components	Effect on Cancer
ACE–Ang II–AT_1R	↑ ACE, ↑ Ang II, ↑ AT_1R	Promotes tumorigenesis
ACE2–Ang-(1–7)–MasR	↓ ACE2, possibly non-functional MasR	Loss of anti-tumor effects

Ang II–AT_2R	↓ AT_2R	Reduces apoptosis & suppression of growth

Table 1 Possibilities of RAS Components that can be Dysregulated. Dysregulation is indicated by upward or downward pointing arrows in front of a component.

2.5 Summary of the Oncogenic Shift

Overall, the dysregulation of RAS in cancer reflects a shift in the balance between tumor-promoting and tumor-suppressive signaling. The predominance of the ACE–Ang II–AT_1R axis, coupled with suppression of ACE2, AT_2R, and possibly MasR activity, establishes a molecular environment that favors oncogenesis. This imbalance drives chronic inflammation, fibrotic remodeling, immune evasion, and abnormal cellular proliferation, contributing to both primary tumor growth and metastatic potential (Hassani et al., 2023; Koh et al., 2023; Su et al., 2023).

3. Pro-Tumor Effects of the Classical RAS Axis

3.1 Activation of Oncogenic Signaling Pathways

The classical RAS axis—comprising ACE, Ang II, and AT_1R—is a central promoter of tumorigenesis. When Ang II binds to AT_1R, it activates several key oncogenic pathways such as MAPK/ERK, PI3K/AKT/mTOR, and NF-κB. These cascades drive uncontrolled proliferation, inhibit programmed cell death, and enhance cell survival under stress conditions (Figure 4) (Hassani et al., 2023; Koh et al., 2023; Su et al., 2023). This signaling framework is commonly hijacked in many cancer types to support rapid tumor growth and progression.

3.2 Induction of Angiogenesis and Metastasis

AT_1R signaling also promotes the expression of vascular endothelial growth factor (VEGF), a potent pro-angiogenic molecule that plays a critical role in the development of new blood vessels. These vessels supply tumors with oxygen and nutrients, enabling further growth and increasing metastatic potential. Elevated VEGF levels, often driven by Ang II, are linked to more aggressive tumors and poorer clinical outcomes (Su et al., 2023; Khoshghamat et al., 2021).

3.3 Inflammatory Microenvironment and Immune Evasion

In addition to promoting angiogenesis, Ang II contributes to a pro-inflammatory tumor microenvironment by stimulating the release of cytokines such as MCP-1 and COX-2. These factors support chronic inflammation, suppress anti-tumor immune responses, and contribute to a microenvironment that enables immune evasion and facilitates tumor progression (Shah et al., 2023; Hassani et al., 2023).

3.4 The Role of the (Pro)renin Receptor (PRR)

The (pro)renin receptor plays a synergistic role by enhancing local Ang II production and independently activating tumor-promoting signaling pathways. Notably, PRR can trigger the Wnt/β-catenin and MAPK cascades, both of which are associated with cancer cell stemness, therapy resistance, and tumor recurrence (Roth et al., 2019; George et al., 2010). Its activity within cancer stem cells underscores its relevance as a therapeutic target.

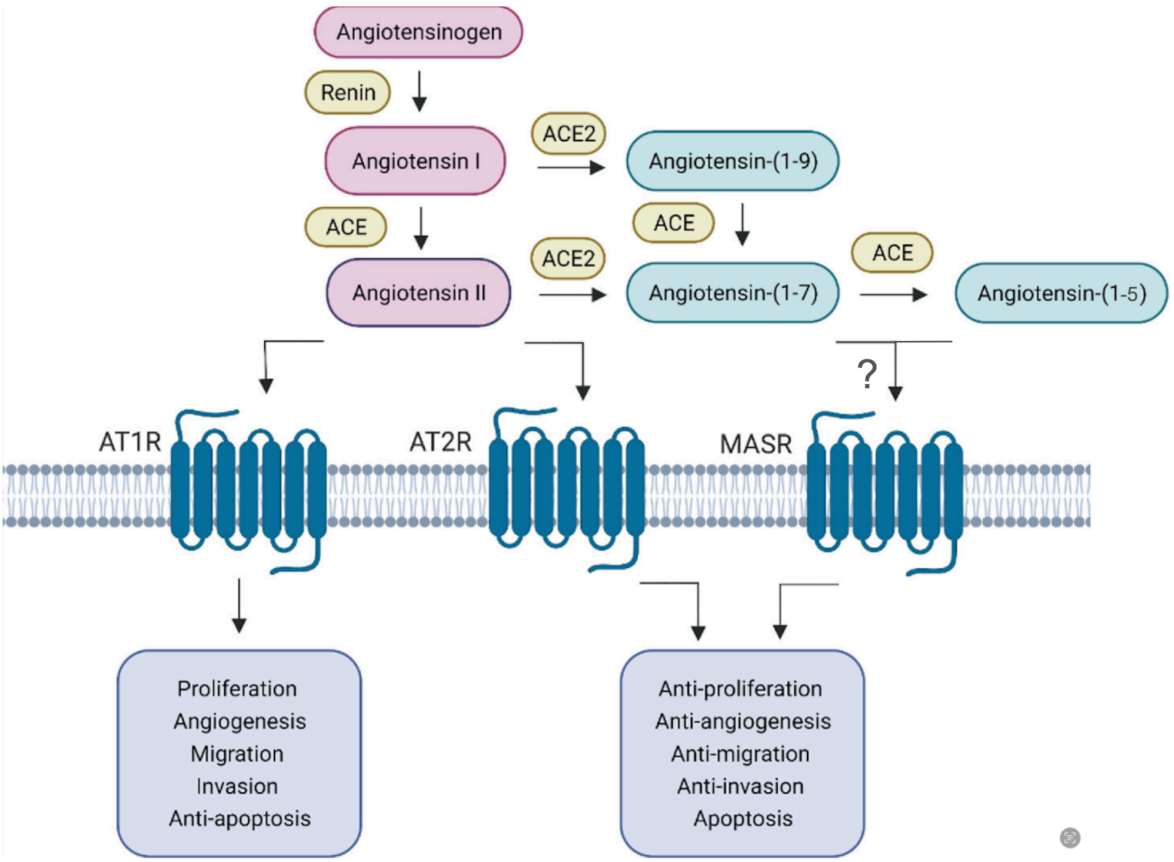

Figure 4 Effects of AT_1R AT_2R and MasR.
Key components of the renin–angiotensin system (RAS) include Ang I, Ang II, Ang-(1–7), ACE, ACE2, AT_1R, AT_2R, and the Mas receptor. Activation of the classical axis, in which Ang II binds to AT_1R, promotes angiogenesis, tumor cell proliferation, migration, invasion, and metastasis. In contrast, Ang II binding to AT_2R has anti-proliferative, anti-angiogenic, and anti-metastatic effects. Similarly, Ang-(1–7), acting through the Mas receptor, inhibits tumor progression by reducing proliferation, migration, and angiogenesis, although this is not completely certain. Adapted from Su et al. (2023)

4. Tumor-Suppressive Role of the Counter-Regulatory RAS Axis

4.1 ACE2 and Ligand Conversion

ACE2 serves as a counter-regulator of classical RAS activity by degrading Ang II and producing Ang-(1–7). This enzymatic switch reduces oncogenic signaling while increasing levels of Ang-(1–7), which is associated with anti-inflammatory, anti-fibrotic, and anti-proliferative effects (Triebel & Castrop, 2024; Shah et al., 2023). The resulting shift in the RAS balance supports tumor-suppressive signaling.

4.2 AT_2R-Mediated Anti-Tumor Activity

The AT_2R pathway complements the role of ACE2 in suppressing tumor growth. Upon activation, AT_2R recruits phosphatases such as SHP-1 and PP2A, which inhibit the MAPK and PI3K/AKT pathways—key signaling routes in cancer progression. AT_2R also promotes nitric oxide production and activates apoptotic pathways via p38 MAPK and caspase-3.

These effects lead to reduced proliferation, increased apoptosis, and decreased angiogenesis (Figure 4). In preclinical studies, AT_2R agonists like Compound 21 have significantly lowered tumor volumes and vascular density (Peluso et al., 2018; Peluso et al., 2023; Moll, 2024).

4.3 Ang-(1–7) and the Mas Receptor

Although Ang-(1–7) has demonstrated anti-tumor effects, its interaction with MasR remains controversial. In recombinant systems, Ang-(1–7) does not activate MasR signaling, as evidenced by the lack of G protein activation, β-arrestin recruitment, and ERK phosphorylation (Gaidarov et al., 2018). These findings suggest that Ang-(1–7) may not act via direct MasR stimulation but rather through indirect mechanisms—possibly by antagonizing Ang II-induced AT_1R signaling (Figure 4). Despite this, *in vivo* studies continue to show tumor-suppressive effects, pointing to a complex, context-dependent mechanism that warrants further research (Gaidarov et al., 2018).

5. RAS Components as Therapeutic Targets and Pharmacological Strategies

The renin–angiotensin system (RAS), traditionally studied for its role in cardiovascular homeostasis, has been increasingly implicated in tumor biology. Key components such as angiotensin II type 1 receptor, prorenin receptor, and angiotensin-converting enzyme are now associated with hallmark features of cancer including proliferation, angiogenesis, inflammation, and immune evasion (George et al., 2010; Hassani et al., 2023; Su et al., 2023). Figure 5 shows potential targets in the RAS system to treat cancers.

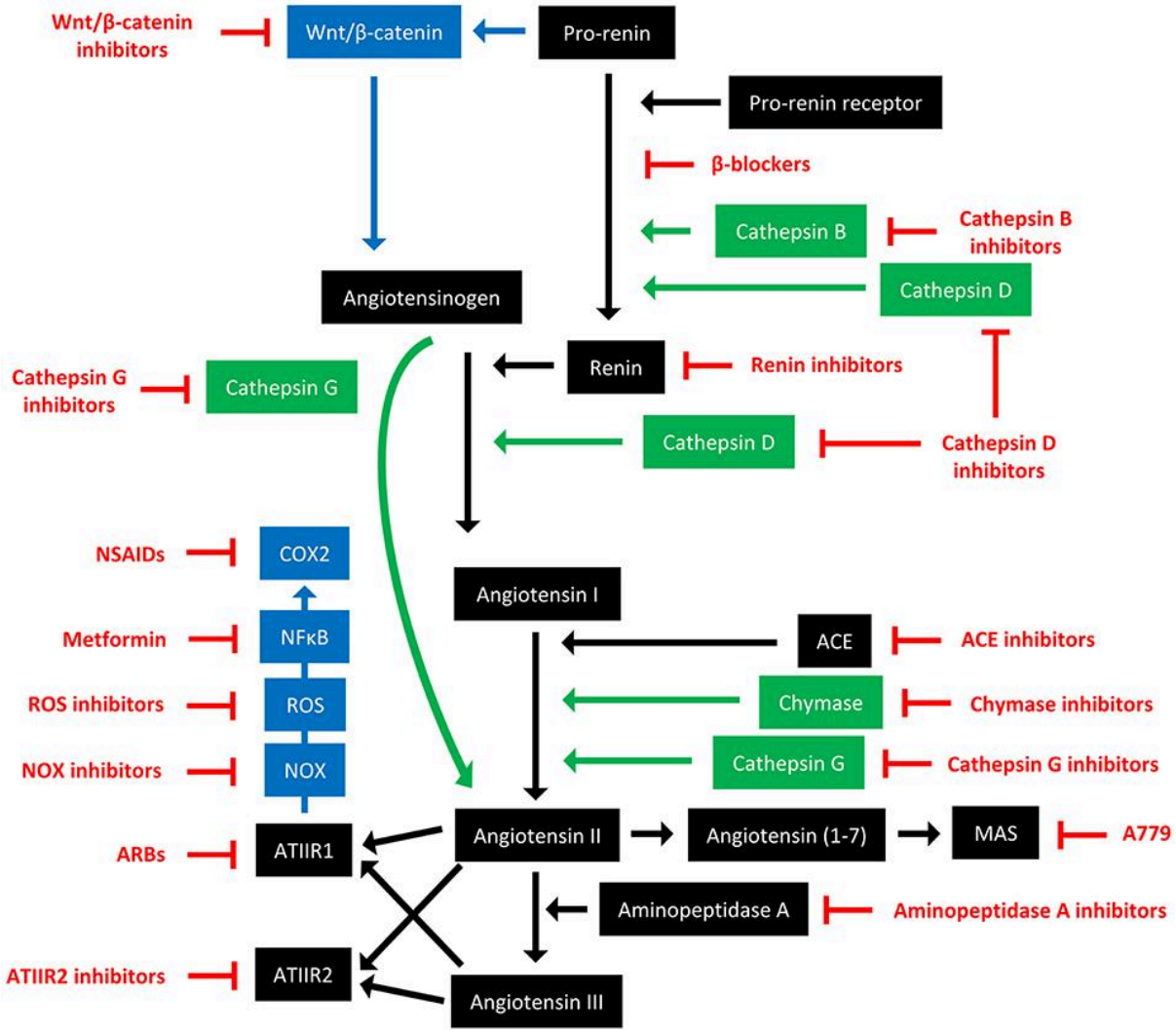

Figure 5. The renin–angiotensin system and its targets
The renin–angiotensin system influences blood pressure, stem cell regulation, and cancer progression. It contains bypass mechanisms, such as cathepsins and chymase (indicated in green), that enhance system redundancy. Additionally, RAS intersects with various inflammatory and developmental pathways (blue), contributing to diverse biological effects. Several steps within this network are pharmacologically targetable using specific inhibitors (red). Key components include ACE , ARBs (AT_1R blockers), and modulators of reactive oxygen species (ROS) and inflammation such as NSAIDs (non-steroidal anti-inflammatory drugs). Figure from Roth et al. (2019).

5.1 Targeting Pro-Tumor Pathways: PRR and AT_1R

In cancer, the classical RAS axis (ACE–Ang II–AT_1R) facilitates tumor progression by activating downstream signaling pathways such as MAPK/ERK and PI3K/AKT, promoting cellular proliferation, angiogenesis, resistance to apoptosis, and extracellular matrix remodeling (George et al., 2010; Hassani et al., 2023).

AT_1R is a validated target for pharmacological intervention. Angiotensin receptor blockers (ARBs) like losartan, candesartan, and valsartan can inhibit tumor-promoting pathways and are shown to reduce vascular endothelial growth factor (VEGF) expression and matrix metalloproteinase activity in preclinical models (Figure 6) (Roth et al., 2019; Hassani et al., 2023; Su et al., 2023). ARBs have also been observed to lower tumor interstitial pressure and improve drug delivery in solid tumors by normalizing abnormal vasculature and reducing fibrosis (Roth et al., 2019).

Parallel to AT_1R, the (pro)renin receptor (PRR) has emerged as a promising but underexplored oncogenic target. PRR can initiate Ang II-independent signaling cascades such as MAPK/ERK1/2 and Wnt/β-catenin, driving proliferation, stemness, and epithelial–mesenchymal transition (Hassani et al., 2023; Triebel & Castrop, 2024). RNA interference and experimental PRR inhibition have shown reductions in tumor growth and invasiveness in vitro and ex vivo (Triebel & Castrop, 2024; Hassani et al., 2023), although further in vivo validation is needed.

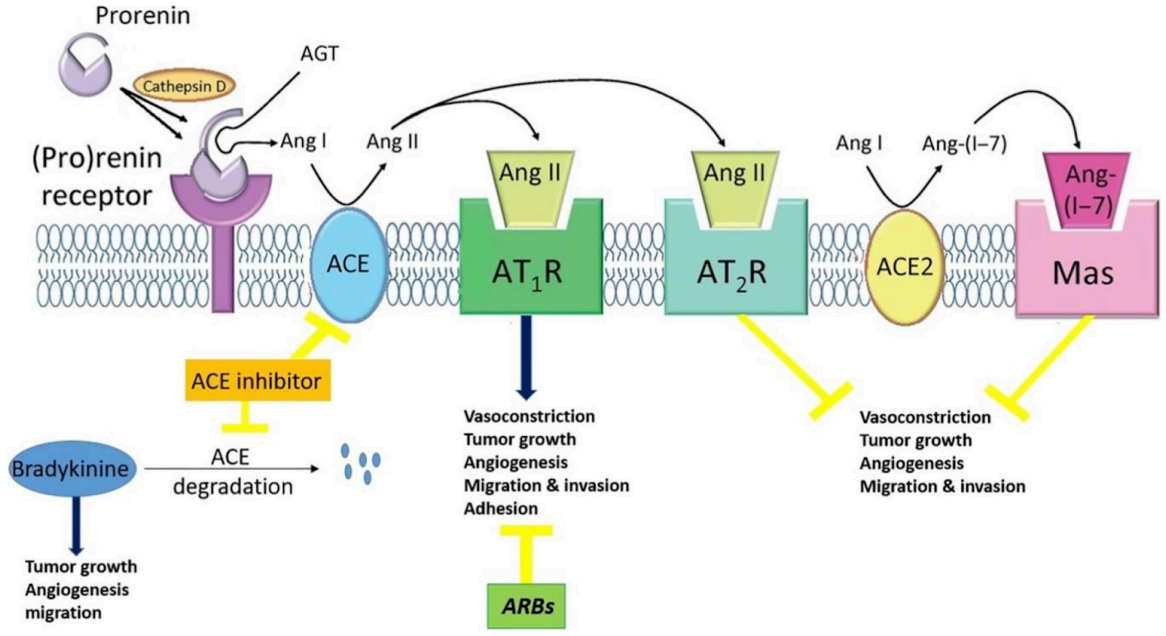

Figure 6. Overview of the renin–angiotensin system in cancer and ACE and AT_1R as targets.
Prorenin activates the RAS cascade, leading to Ang II production via ACE. Ang II promotes tumor growth, angiogenesis, and invasion through AT_1R, while AT_2R and the Ang-(1–7)/Mas axis counteract these effects. ACE inhibitors and ARBs block pro-tumor signaling. ACE2 shifts the balance toward anti-tumor pathways. Yellow lines indicate points of inhibition. Figure from Khoshghamat et al, (2021)

5.2 Enhancing Anti-Tumor Pathways: AT_2R and MasR

Counter-regulatory components of the RAS, including AT_2R and the Mas receptor (MasR), act in opposition to the classical axis. The AT_2R mediates anti-proliferative, pro-apoptotic, and anti-inflammatory effects via activation of phosphatases like SHP-1 and PP2A, and downstream signals such as p38 MAPK and caspases (Moll, 2024; Hassani et al., 2023). Its stimulation can result in reduced tumor cell viability, inhibition of angiogenesis, and increased sensitivity to chemotherapeutics (Peluso et al., 2023; Su et al., 2023).
Compound 21 (C21), a selective AT_2R agonist, has been studied in models of lung, breast, and pancreatic cancer, where it significantly reduced tumor volume and vascular density while promoting apoptosis and modulating the tumor microenvironment (Su et al., 2023; Moll, 2024). LP2 another selective AT_2R agonist, has demonstrated potent anti-tumor effects in colorectal cancer xenografts, particularly in KRAS-mutated models (Namsolleck et al., 2023; Namsolleck et al., 2021)
Angiotensin-(1–7) has been proposed to exert anti-tumor effects, particularly through inhibition of VEGF signaling, matrix remodeling enzymes, and the PI3K/AKT pathway. These actions have been observed in models of breast, lung, and prostate cancer and have been associated with reduced tumor growth, angiogenesis, and metastasis (Su et al., 2023;

Hassani et al., 2023). While the Mas receptor (MasR) has been suggested as the primary mediator of Ang-(1–7)'s actions, this role remains uncertain (Gaidarov et al., 2018). However, the same study showed that Ang-(1–7) can inhibit Ang II-induced AT_1R signaling in rat aortic endothelial cells, suggesting a functional antagonism of AT_1R as a potential mechanism for its observed effects. Therefore, while MasR may contribute to Ang-(1–7) signaling in certain contexts, its direct role as the primary receptor remains unconfirmed.

5.3 Clinical and Translational Applications

ARBs and ACE inhibitors (ACEIs), beyond their cardiovascular indications, have shown clinical benefits in oncology. Retrospective studies have associated long-term use of ARBs and ACEIs with improved survival and reduced progression in colorectal, breast, ovarian, and prostate cancers (Cho et al., 2020; Koh et al., 2023). For instance, in ovarian cancer, ARB use correlated with significantly prolonged overall survival (Cho et al., 2020).
Combination therapies are also being evaluated. ARBs such as losartan have demonstrated the ability to remodel the fibrotic stroma, enhance perfusion, and improve chemotherapeutic drug delivery in desmoplastic tumors such as pancreatic cancer (Khoshghamat et al., 2021; Roth et al., 2019).
Ang-(1–7) is currently under clinical investigation as a therapeutic peptide. Its administration in preclinical cancer models leads to suppressed tumor growth, reduced microvessel density, and enhanced apoptosis (Su et al., 2023). Importantly, these effects are thought to be mediated through MasR-dependent signaling and suppression of ERK and AKT pathways (Hassani et al., 2023).

5.4 Strategic Outlook: Dual-Axis Modulation

Given the opposing roles of the classical and protective RAS axes, a dual-modulation strategy holds strong therapeutic promise. Simultaneous inhibition of AT_1R/PRR and activation of AT_2R/MasR could offer synergistic anti-tumor effects—suppressing tumor growth, normalizing the vasculature, improving immune infiltration, and enhancing response to chemotherapy or immunotherapy (George et al., 2010; Koh et al., 2023).
As the field advances, personalized treatment plans based on RAS receptor profiles and cancer subtypes may optimize clinical outcomes.

6. Discussion, Conclusions and Perspectives

6.1 RAS in cancer

The renin–angiotensin system (RAS), traditionally known for its role in cardiovascular regulation, is increasingly recognized as a key modulator in cancer biology. This discussion evaluates the dual role of RAS components in promoting and suppressing tumorigenesis, and explores the therapeutic potential of targeting these mechanisms. To frame this analysis, it is essential to revisit the central research question: How is the renin–angiotensin system (RAS) involved in cancer, and which of its components could serve as relevant therapeutic targets? This overarching question was addressed through five subquestions, each aimed at elucidating a specific aspect of RAS function in oncogenesis.

First, it became clear that the RAS, beyond its well-known role in cardiovascular regulation, plays an important role in cell proliferation, apoptosis, and inflammation — all key processes in cancer biology. It was then shown that RAS signalling is often dysregulated in cancer, with

upregulation of the classical axis (ACE–Ang II–AT_1R) and downregulation or impairment of the counter-regulatory axes (ACE2–Ang-(1–7)–MasR and AT_2R).

The classical axis promotes tumorigenesis through enhanced proliferation, angiogenesis, inflammation, and immune evasion. In contrast, the counter-regulatory arms exert tumor-suppressive effects, including induction of apoptosis, inhibition of angiogenesis, and reduction of fibrosis. These actions are particularly attributed to AT_2R and potentially MasR activation.

Furthermore, several RAS components — including AT_1R, AT_2R, MasR, ACE, and ACE2 — have emerged as promising therapeutic targets. Evidence from preclinical models suggests that angiotensin receptor blockers, ACE inhibitors, and selective AT_2R agonists (such as Compound 21) may reduce tumor progression and enhance treatment response.

In conclusion, this thesis shows that the RAS plays a dual role in cancer: the classical pathway promotes tumor growth, whereas the alternative axes suppress it. Therapeutic strategies that shift the RAS balance toward its protective arms may offer a novel and promising avenue for cancer treatment.

6.2 Tumor-Promoting Effects of the Classical RAS Axis

The classical ACE–Ang II–AT_1R axis has been consistently linked to tumor progression. Angiotensin II (Ang II), through activation of the AT_1R, enhances cell proliferation, survival, angiogenesis, and inflammation while promoting fibrosis and immune evasion (Koh et al., 2023; Su et al., 2023). These effects are mediated by key oncogenic signaling cascades such as MAPK/ERK, PI3K/AKT, and NF-κB, and are evident across various cancers, including breast, colorectal, gastric, and pancreatic tumors (Hassani et al., 2023). The upregulation of AT_1R in tumors is often associated with a worse prognosis and increased vascularization.

Furthermore, the (pro)renin receptor (PRR) contributes to tumorigenesis by stabilizing renin activity and activating alternative proliferative pathways such as Wnt/β-catenin, particularly in cancer stem cells (Roth et al., 2019). These findings highlight the classical RAS as a robust pro-tumorigenic pathway.

6.3 Tumor-Suppressive Functions of the Counter-Regulatory RAS Axis

In contrast, the ACE2–Ang-(1–7)–MasR and Ang II–AT_2R axes are generally associated with tumor-suppressive effects. AT_2R activation inhibits proliferation and induces apoptosis through phosphatase recruitment (e.g., SHP-1, PP2A), NO production, and activation of p38 MAPK and caspase-3 (Peluso et al., 2023). Preclinical studies using selective AT_2R agonists such as Compound 21 (C21) have demonstrated reduced tumor volume, angiogenesis, and fibrosis in models of colorectal and pancreatic cancer (Moll, 2024; Su et al., 2023).

Angiotensin-(1–7), traditionally seen as the key ligand of the Mas receptor (MasR), has shown anti-proliferative and anti-angiogenic effects in various tumor models, including hepatocellular carcinoma and breast cancer (Hassani et al., 2023; Roth et al., 2019). These effects have been attributed to inhibition of VEGF, modulation of ERK and PI3K/AKT pathways, and reduction of inflammatory cytokines.

6.4 Controversies and Receptor Specificity

Despite these promising findings, the mechanism by which Ang-(1–7) exerts its effects remains unclear. A pivotal study by Gaidarov et al. (2018) found no evidence that Ang-(1–7) activates MasR in recombinant systems. The peptide failed to induce G protein signaling, β-arrestin recruitment, or ERK phosphorylation, suggesting that its action may not be mediated by MasR, at least in vitro. Instead, Ang-(1–7) appeared to antagonize AT_1R and AT_2R responses, suggesting an indirect mode of action. These findings cast doubt on the assumption that MasR is the primary receptor for Ang-(1–7), especially in cancer. However, in vivo models continue to show biological effects of Ang-(1–7), suggesting receptor context, cell type, or secondary signaling may still play a role.

6.5 Personal Viewpoint: A Role for Ang-(1–5)?

The receptor-mediated activity of angiotensin-(1–7) [Ang-(1–7)] remains controversial, particularly concerning its interaction with the Mas receptor (MasR). Although MasR antagonists such as D-Ala^7-Ang-(1–7) and D-Pro^7-Ang-(1–7) have been used to infer MasR-mediated effects, there is no direct evidence that these peptides or Ang-(1–7) itself bind MasR with high specificity (Yu et al., 2016). Gaidarov et al. (2018) further demonstrated that Ang-(1–7) fails to activate signaling pathways via recombinant MasR and does not bind directly to the receptor, calling into question its designation as a MasR ligand. In this context, the downstream metabolite angiotensin-(1–5) [Ang-(1–5)] may emerge as a biologically relevant player. Structurally related yet smaller than Ang-(1–7), Ang-(1–5) was recently identified as a potent endogenous agonist of the angiotensin type 2 receptor (AT_2R), suggesting its functional relevance within the protective arm of the RAS (Souza-Silva et al., 2024). While its activity at MasR remains unexplored, the AT_2R-mediated effects of Ang-(1–5) warrant further investigation, particularly in the context of anti-proliferative and anti-inflammatory signaling.

6.6 Therapeutic Potential of Dual RAS Modulation

The therapeutic implications of RAS modulation in cancer are considerable. Several retrospective studies have linked ACE inhibitors (ACEi) and angiotensin receptor blockers (ARBs) with improved survival in cancer patients (Cho et al., 2020; Khoshghamat et al., 2021). These agents are thought to mitigate AT_1R-driven tumor growth, inflammation, and angiogenesis. Combining AT_1R blockade (via ARBs or ACEi) with stimulation of the protective arms—using AT_2R agonists (e.g., C21 or LP2) or Ang-(1–7) may provide synergistic benefits. LP2, in particular, represents a dual-function therapeutic that offers AT_2R specificity, metabolic stability, and synergism with standard therapies, which could optimize dual-axis modulation approaches (Wagenaar & Moll, 2025; Namsolleck et al., 2021, 2022). This dual-axis modulation strategy reduces tumor-promoting signaling while enhancing anti-proliferative and pro-apoptotic responses (George et al., 2010; Hassani et al., 2023). Moreover, blocking AT_1R or inhibiting ACE may elevate substrate availability for ACE2-mediated Ang-(1–7) formation, indirectly amplifying its protective effects (Roth et al., 2019). Preclinical data suggest that such combinations may normalize the tumor microenvironment, enhance immune infiltration, and improve drug delivery—especially in fibrotic or immune-excluded tumors (Hassani et al., 2023; Su et al., 2023).

6.7 Clinical and Future Perspectives

Despite encouraging evidence, clinical implementation remains limited. The efficacy and safety of combining ARBs/ACEi with AT_2R agonists or Ang-(1–7) require validation in

cancer-specific trials. Furthermore, the functional role of Ang-(1–5), and whether it can serve as a therapeutic ligand for MasR, remains a novel hypothesis awaiting experimental verification. Personalized approaches based on RAS component expression in tumors may help identify patients most likely to benefit from RAS-targeted therapies. As understanding of the RAS in oncology expands, the system may prove to be a versatile target—not just for cardiovascular health, but for cancer prevention and therapy as well.

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