

## Chapter 22

# Renin-Angiotensin System: A Potential Therapeutic Target for Colorectal Cancer



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**Abstract** The Renin-Angiotensin System (RAS) is associated with regulation of blood pressure, electrolyte balance, and hemostasis. It is implicated in cancer hallmarks because of its local expression in almost all of the body's tissues. RAS has recently been implicated in the progression of colorectal cancer (CRC) and subsequent liver metastasis. This review summarizes various RAS-associated cellular signaling pathways in colon cancer.

**Keywords** Renin-angiotensin system · Colorectal cancer · Liver metastasis · Angiotensin · Angiotensin-converting enzyme inhibitors · Angiotensin receptor blockers

## Introduction

Colorectal cancer is the world's third most prevalent malignancy and the fourth leading cause of cancer-related deaths, with approximately 9,40,000 new cases and 5,00,000 deaths reported each year [1]. CRC develops from the epithelial cells that line the colon and rectum. Colon cells replicate at a very high rate, with  $10^{10}$  epithelial cells changed every day. This rapid replication rate increases susceptibility of colon epithelium to mutation and, as a result, carcinogenesis [2]. CRC pathogenesis is a complex interaction of genetic predisposition and lifestyle factors. CRC subtypes are hereditary and non-hereditary, with the majority being sporadic and caused by a somatic mutation in response to environmental factors [3]. It can develop from a serrated hyperplastic polyp or an adenomatous polyp (AP) through the adenoma-carcinoma sequence, as well as from spontaneous mutations and inherited conditions. Although a single BRAF (B-Raf proto-oncogene serine/threonine kinase) mutation can cause CRC in serrated-type hyperplastic polyps, the bulk of colon cancers today are caused by an AP through the adenoma to carcinoma sequence [4]. Colonoscopy is

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used routinely by physicians to detect the presence of APs, and lesions can be studied by histological evaluation. Further, histological results are used to determine the cells' malignant potential [5]. Surgical resection offers the best chance of recovery. But, only about 20–25% of patients are candidates for surgery, and recurrence rates range from 40 to 70%. For the vast majority of these patients, palliative systemic chemotherapy is the preferred treatment option [6]. The primary cause of death from CRC is metastasis to the liver, which accounts for more than 70% of all deaths. In up to 30–40% of individuals with advanced CRC, the liver is the primary site of metastasis. 20–25% of CRC patients have detectable synchronous liver metastasis while primary diagnosis and another 40–50% will develop metachronous liver metastasis within three years of primary tumor resection [7]. Recent studies revealed variations in the compositions of the intestinal microbiota between CRC patients and healthy individuals [8].

Components of Renin-Angiotensin System (RAS), are renin, angiotensinogen (AGT), angiotensin I (Ang I), angiotensin-converting enzyme (ACE), angiotensin II (Ang II), angiotensin II type 1 receptor (AT1R), and angiotensin II type 2 receptor (AT2R). Recently, counter-regulatory axis of RAS is identified which comprises of angiotensin 1–7 (Ang 1–7), MAS Receptor (MASR), and angiotensin-converting enzyme 2 (ACE-2) [9]. Overactivation of RAS, which causes hypertension, raises the risk of cancer, cancer progression, and mortality in cancer patients [10]. Chronic inflammation and high levels of Vascular Endothelial Growth Factor (VEGF) during hypertension lead to endothelial dysfunction and angiogenesis, which may then act as auxiliary factors during cancer development [11]. Several studies have been conducted to investigate the role of RAS in the pathophysiology of CRC [12, 13]. Many renin-angiotensin system inhibitors have been shown to reduce the risk of cancer [14]. ACE inhibitors (ACEIs)/angiotensin II receptor blockers (ARBs) are RAS inhibitors that are used to treat hypertension. However, as more studies on RAS inhibitors have been conducted, it has been discovered that RAS inhibitors play a role not only in the treatment of hypertension but also in the treatment of colorectal cancer [15, 16].

## **Renin-Angiotensin System-Associated Cellular Signaling Pathways in Colorectal Cancer**

In terms of cancer etiology, the mechanism of cancer development is a complex multi-stage process that involves sequential mutational events that occur concurrently with cancer progression [17]. Mutations in signaling pathways and genes that interact with RAS are involved in several tasks, including cell growth and survival. As a result, in a cancerous cell, these events will be interrupted [18]. The EGFR/MAPK, PI3K, and Wnt/ $\beta$ -catenin signaling pathways affect a variety of biological activities, including cell proliferation, differentiation, angiogenesis, apoptosis, and survival. These are some of the primary signaling pathways through which RAS protein functions.

### ***RAS and EGFR/MAPK in Colorectal Cancer***

When a ligand binds to receptor tyrosine kinase, the pathway is activated for the first time. For example, epidermal growth factor (EGF), whose receptor is EGFR. EGF releases from cell surface before it can bind with EGFR. This is accomplished through the use of the TACE/ADAM-17 enzyme, which cleaves transforming growth factor- $\alpha$  and amphiregulin, two EGF family ligands [19]. Following ligand binding, the receptor dimerizes and becomes phosphorylated. Following that, inside a cell, a protein complex is formed, with growth factor receptor-bound protein 2 (GRB2) attaching to the receptor while being bound by son of sevenless (SOS) [20]. SOS exhibits guanine nucleotide exchange factor activity after being attached to RAS. The RAF proteins (A-RAF, B-RAF, and C-RAF) can be recruited to the cell surface by active GTP-RAS [20]. It has been proposed that the Ras–Raf–ERK signaling pathway regulates cell growth, differentiation, and survival [20]. Malignant transformation and tumor progression results, if this pathway is faulty. A mutation in the RAS protein is one of the most common ways that the MAPK is activated; mutations in the KRAS protein are found in approximately 40% of all colorectal cancer (CRC) cases, whereas NRAS mutations are less common, accounting for 5% of all CRC cases. The most common mutations in KRAS and NRAS are found at codons 12, 13, and 61. These mutations can be found in early adenomas as well as cells with little potential for malignancy. Silencing these mutant codons results in a diminution of the tumorigenic features of diseased cells, according to both in vitro and animal studies [17]. BRAF mutates in the MAPK pathway, which appears to occur in about 5% to 10% of all colon cancer patients. The V600E mutation is the most common BRAF mutation in all cancers, including colorectal cancer [21]. As previously stated, the EGFR/MAPK signaling pathway has been linked to oncogenic processes and thus plays an important role in tumor growth and CRC progression [22]. This pathway's aberrant expression has been identified as a potential target for CRC treatment.

### ***RAS and PI3K in Colorectal Cancer***

PI3K/Akt is a critical intracellular signal pathway that regulates a wide range of cellular activities including cell growth, proliferation, differentiation, and migration. PI3K is divided into three classes, I–III, established on structural and functional differences. Type class IA contains two PI3K subunits, one regulatory (p85) and one catalytic (p110). Three genes, PIK3R1, PIK3R2, and PIK3R3, encode different isoforms of p85 as well as different types of p110 such as alpha, beta, gamma, and delta, which produce PIK3CA, PIK3CB, and PIK3CD, respectively [23]. Stimulating Ras activation or extracellular factors through RTK, causes PI3K activation. Cancer has been treated by inhibiting the PI3K/Akt pathway [24]. Akt phosphorylation has been linked to the downregulation of cell proliferation and apoptosis in human CRCs. Akt controls downstream targets like mTOR. Phosphatase and tensin

homologue protein (PTEN), a tumor suppressor molecule, dephosphorylates PIP3 and thus inhibits the PI3K pathway [23]. P110 is encoded by the gene PIK3CA. RAS mutations frequently coexist with PIK3CA exon 9 and 20 mutations. 15–25% of CRCs are thought to have PIK3CA mutations, which might lead to higher PI3K activity [25]. Overall, the PI3K signaling pathway has been shown to play a carcinogenic role in the initiation and progression of CRC. Several studies have found that inhibiting this pathway specifically causes a decrease in CRC cell growth and an increase in apoptosis [24].

### ***RAS and Wnt/ $\beta$ -Catenin in Colorectal Cancer***

The Wnt/ $\beta$ -catenin signaling pathway has shown its role in a variety of biological processes, including embryonic development, tissue homeostasis, and carcinogenesis [26]. Excess Wnt/ $\beta$ -catenin signaling causes abnormal cell proliferation and inhibits apoptosis, which cause progression of colorectal cancer [27].  $\beta$ -Catenin degradation is usually mediated by the destruction complex, which is made up of the adenomatous polyposis coli protein (APC) and numerous other proteins in the absence of Wnts. Further, Wnt phosphorylation of LRP6 disrupts this destruction complex. The active  $\beta$ -catenin then translocates into the nucleus, where it binds to the TCF/LEF to trigger the production of target oncogenes namely cyclin D1 and c-Myc [28, 29]. Over 80% of CRCs have APC loss-of-function mutations, and roughly 5% have  $\beta$ -catenin activating mutations, which result in constitutive activation of the Wnt/ $\beta$ -catenin pathway and thus contribute to oncogenesis [30]. Recent research has shown that silencing Wnt3 significantly reduced the activation of the Wnt/ $\beta$ -catenin pathway and the proliferation of CRC cells with APC or  $\beta$ -catenin mutations [31]. The 350-amino-acid protein, (Pro)renin receptor ((P)RR) was first identified as a key component of the RAS and is widely expressed in the human body. Additionally, it performs the role of an adapter protein that associates with the Wnt receptor complex and aids in the activation of Wnt/ $\beta$ -catenin signaling independently of the renin-angiotensin system. Aberrant (P)RR expression, through the Wnt/ $\beta$ -catenin signaling pathway, enhances CRC carcinogenesis in the presence of constitutive pathway component mutations [32].

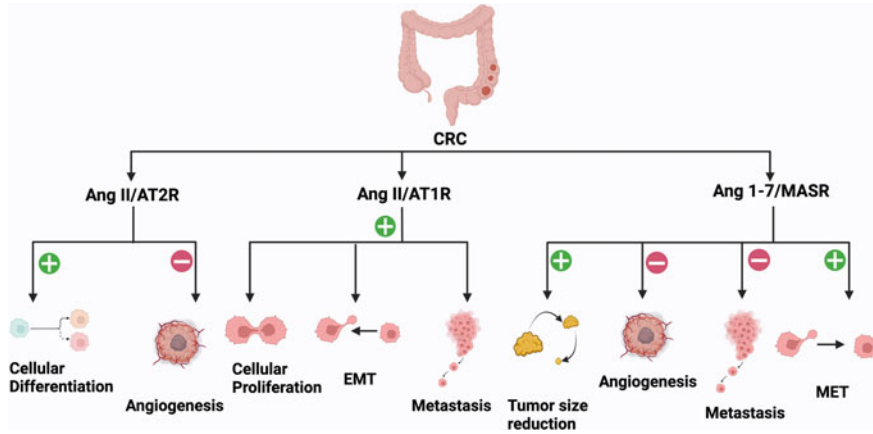
### **Role of Renin-Angiotensin System in Colorectal Cancer**

Novel physiologic functions of the renin-angiotensin system in the renal and cardiovascular systems have been well established. Recent research has looked into and identified RAS receptors and mediators in other tissues and organs of the body [33]. Components of the RAS system were also found in the lamina propria, lending credence to the hypothesis that the RAS also performs paracrine functions. AT2R is primarily stimulated at low Ang II concentrations, which stimulates colonic water

and sodium absorption. When exposed to high levels of Ang II, the AT1R-mediated pathway is primarily activated, inhibiting sodium reabsorption and/or stimulating sodium secretion [34]. The activation of AT1R may also influence colonic motility. Losartan, an AT1R inhibitor, downregulates the effect competitively, requiring a higher concentration to produce the same contractile effect [35]. Ang II stimulates sodium and water absorption and secretion via the AT1R and AT2R, respectively. It was discovered that RAS components are dysregulated in CRC, indicating that RAS plays a role in CRC pathology (Fig. 22.1). The liver is the site of most CRC metastasis, and angiotensinogen production there is normal, raising the possibility of RAS and its role in CRC metastasis. ACE, Ang II, and MASR were found to be upregulated in CRC liver metastasis, while AT1R was found to be inhibited when compared to normal liver tissue. Angiotensinogen generated by the liver is converted by ACE into Ang II, which induces angiogenesis and metastasis via the AT1R by upregulating VEGF and TGF- $\beta$ , respectively [34]. Ang II inhibits cell growth, invasion, and apoptosis in several CRC-derived cell lines. It has also been shown to increase cell growth and invitro invasion into type IV collagen while decreasing apoptosis in a dose-dependent manner. Although AT1R was found to be decreased in the liver during CRC metastasis, Kupffer cells (KCs) overexpressed AT1R, which promotes CRC liver metastasis [36]. AT1R deletion in CRC animal models resulted in decreased liver metastasis and downregulated TGF- $\beta$  production in KCs, showing that KCs increases liver metastasis by inducing TGF- $\beta$  production via AT1R signaling [36]. RAS inhibitors have been linked to lower risk and mortality from CRC. Treatment with ACEIs and ARBs was found to improve recurrence-free survival in early-stage CRC and left-sided CRC cases. Overexpression of the AGTR1 gene, on the other hand, was associated with poor recurrence-free survival in the advanced stages [37]. Furthermore, ARBs were able to improve both overall survival and progression-free survival (PFS) in individuals with metastatic CRC who received first-line chemotherapy [38].

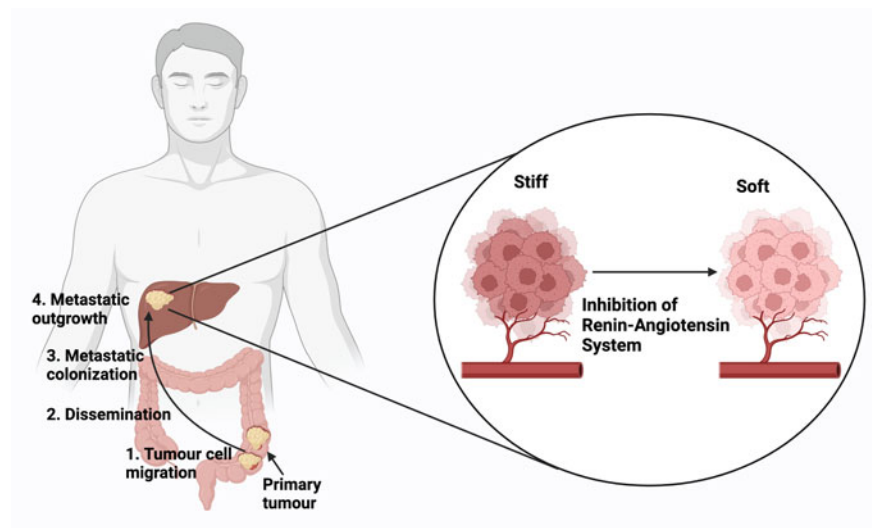
## **Renin-Angiotensin System in Colorectal Cancer Liver Metastasis**

In up to 30–40% of individuals with advanced illness, the liver is typically the primary metastatic location for CRC, it may be the only site of spread (Fig. 22.2) [39]. In response to tissue injury and hypoxia, the local RAS is up-regulated in the liver [40]. Ang II promotes the expression of a variety of growth and pro-angiogenic factors, including VEGF. Other RAS components mediate counter-regulatory effects of Ang II/AT1R signaling, which has proliferative and angiogenic effects. Activation of the AT2R, which is expressed more than the AT1R in primary CRC, inhibits angiogenesis and cellular proliferation [41]. In liver injury, the expression of an ACE homologue, ACE2, is increased [42]. This enzyme directly produces the peptide Ang-(1–7) from Ang II and indirectly from Ang I. Ang-(1–7) antagonizes some Ang



**Fig. 22.1** The role of renin-angiotensin system components in colorectal cancer. CRC-colorectal cancer, MET- mesenchymal-epithelial transition, EMT- epithelial-mesenchymal transition, Ang I-angiotensin I, Ang II-angiotensin II, AT1R-angiotensin II type 1 receptor, AT2R-angiotensin II type 2 receptor, Ang 1-7-angiotensin 1-7, MASR-MAS Receptor

II-induced effects, via the MASR [43]. CRC cells with angiotensin-activating ability produce abundant Ang-2 from AGT in the liver and cause liver metastasis [44]. Several RAS components are expressed in primary CRC, and blocking the RAS inhibited tumor growth in a mouse model of CRC liver metastasis [45]. RAS expression changes significantly in the tumor-bearing captopril-treated liver and in CRC metastasis. Captopril treatment reduced ACE expression in CRC liver metastasis. Following captopril treatment, angiotensinogen expression is lower in CRC liver metastasis and lower in the liver surrounding tumors [1]. Treatment with captopril alters the spatial and temporal infiltration of tumor lymphocytes expressing CD3<sup>+</sup> and CD4<sup>+</sup>. It modulates T cell subpopulations that infiltrate into tumor and liver tissues in different ways [46]. In a mouse model of CLM, both captopril and irbesartan significantly inhibited tumor growth [45]. Anti-hypertensive drugs that target the renin-angiotensin system (anti-RAS) in combination with bevacizumab have been shown to significantly improve anti-angiogenic efficacy in CRC liver metastasis. Anti-RAS blocks the contraction of fibroblasts and the deposition of ECM, which prevents liver metastasis from hardening and increasing bevacizumab's anti-angiogenic effect [44]. Diabetes has been linked to angiotensin activation and the progression of CRC liver metastasis. The expression of renin and chymase in CRC cells provides an angiotensin activation mechanism. Cathepsin D produces Ang I from AGT instead of renin in cardiac myocytes, fibroblasts, and vascular smooth muscle cells. Renin expression was found in both HT29 and CT26 cells, and it was dose-dependently related to glucose concentration. Levels of intracellular Ang II are dramatically raised by a high glucose concentration in cardiac fibroblasts by increasing renin levels. Clinical data showed high tumoral renin concentrations, high tumoral Ang II concentrations, and liver metastasis in diabetic cancer patients [47].



**Fig. 22.2** Schematic representation of the role of the renin-angiostensin system in Colorectal cancer liver metastasis. Colon cancer metastasis to the liver occurs when tumor cells migrate and colonize from the colon to the liver, resulting in metastatic spread. The renin-angiostensin system is involved in liver metastasis, and inhibiting it reduces metastatic stiffness, hence boosting the anti-angiogenic effect

## Renin-Angiotensin System Targeting Therapy for Colorectal Cancer

According to recent research, drugs that target paracrine hormone systems that promote tumor formation may give an alternate or supplementary therapeutic option in CRC patients. Long-term inhibition of the renin-angiostensin system in hypertensive patients is related to a lower incidence of numerous human malignancies [16]. The angiotensin I converting enzyme is a critical enzyme in the RAS, converting the physiologically inactive angiotensin (Ang) I precursor to Ang II, the RAS's primary effector peptide. Renin-angiostensin system inhibitors' potential protective impact is gaining attention due to their potential involvement as chemopreventive medications against colorectal cancer. A variety of renin-angiostensin system inhibitors have been shown to reduce the risk of colorectal cancer (Table 22.1) [48, 49]. Recent research shows that Ang II/AT1R signaling has proliferative and angiogenic effects, while additional RAS components have counter-regulatory effects. Activation of the AT2R, which is expressed more than the AT1R in primary CRC, for example, suppresses angiogenesis and cellular proliferation [41].

The renin-angiostensin system has been widely studied in the context of liver and renal fibrosis. Ang II, the major effector of the RAS, has been demonstrated to stimulate TGF- $\beta$ 1 and NF- $\kappa$ B signaling pathways in inflammatory diseases such as hepatic and renal fibrosis [50]. Studies on renal fibrosis showed that multiple

**Table 22.1** List of renin-angiotensin system inhibitors tested for colorectal cancer

Targets	Drugs	Study outcome	Disease model	Reference
ACE	Captopril	Despite increasing Wnt signaling, captopril lowered the expression of downstream Wnt target genes, including c-myc and cyclin-D1 in a mouse model of colorectal cancer liver metastasis	MoCR-treated CBA mice	[52]
		Through anti-angiogenesis and pro-tumor apoptosis, captopril therapy regresses CRCLM in the regenerating liver without affecting liver recovery following large partial hepatectomy	MoCR-treated CBA mice	[54]
	Enalapril	Enalapril significantly increased the sensitivity of CRC cells to 5-FU at therapeutically acceptable dosages without causing additional damage, and the synergistic effect is due to synergistically decreasing proliferation, angiogenesis, and NF- $\kappa$ B/STAT3-regulated proteins	SW620-treated BALB/c nude mice; HCT116 and SW620 cell lines	[55]
ARB	Candesartan	Candesartan decreased tumor growth by decreasing fibrosis and increasing ROS generation when combined with 5-FU. Modulating Cyclin D1, MMP3/9, and E-cadherin inhibited tumor cell growth and migration	CT26 cells-treated BALB/c mice; CT26 and SW480 cell lines	[56]
	Telmisartan	Telmisartan suppressed cell growth and lowered cell viability in colon cancer cell lines in a dose-dependent manner	HT29, SW480, and SW620 cell lines	[53]
		Telmisartan inhibits cell proliferation by blocking HB-EGF-CTF nuclear translocation and blocks cell growth in colon cancer cells	HT29, HCT116, CaCo2, and SW480 cell lines	[57]

(continued)



**Table 22.1** (continued)

Targets	Drugs	Study outcome	Disease model	Reference
	Losartan	Losartan inhibited tumor development while increasing tumor cell necrosis. Losartan-treated animals had less metastasis and angiogenesis, as evidenced by decreased tumor vasculature and suppressed matrix metalloproteinase-2 and -9 activity	CT26 cells-treated BALB/c mice; CT26 cell line	[58]
	Irbesartan	Irbesartan reduces the development of colitis-associated CRC by inhibiting MCP-1 production and the concentration of CCR2 <sup>+</sup> inflammatory monocytes and fibrocytes in the inflamed colon	AOM/DSS-treated mice	[59]

ACE-angiotensin-converting enzyme, ARB-angiotensin receptor blockers, CRC-colorectal cancer, CRCLM-colorectal cancer liver metastasis, NF- $\kappa$ B-nuclear factor kappa-light-chain-enhancer of activated B cells, STAT3-Signal transducer and activator of transcription 3, ROS-reactive oxygen species, 5-FU-5-fluorouracil, MMP3-matrix metalloproteinase-3, HB-EGF-CTF-Heparin-binding epidermal growth factor-like growth factor carboxy-terminal fragment, MCP-1-Monocyte chemoattractant protein-1, DSS-dextran sulfate sodium

RAS genes in renal tissue are regulated by the Wnt/ $\beta$ -catenin pathway. Furthermore, ICG-001, a small molecule inhibitor of Wnt signaling, was able to reduce kidney fibrosis [51]. In a mice model of colorectal cancer liver metastasis, RAS inhibition by captopril could modify the Wnt/ $\beta$ -catenin pathway and EMT/MET in the context of liver regeneration following partial hepatectomy [52]. AT1R blocker, Telmisartan had antiproliferative and apoptotic effects in human colon cancer cells at therapeutic blood concentrations, and telmisartan had potency at least similar to pioglitazone, a complete PPAR $\gamma$  agonist. PPAR $\gamma$  blockade with GW9662 did not completely reverse pioglitazone's antiproliferative and apoptotic effects in human colon cancer cells. PPAR $\gamma$  inhibition boosted antiproliferative and apoptotic effects in the telmisartan-treated cells [53].

## Conclusion and Future Perspectives

In most malignancies, the ACE/Ang II/AT1R axis plays a tumorigenic role, whereas the ACE-2/Ang 1-7/MASR axis plays an antitumorigenic role. Furthermore, ACEIs and ARBs have been shown to enhance colorectal cancer outcomes. RAS activation

is a critical component of colorectal cancer for disease development and liver metastasis. In addition, Renin-angiotensin system blockade is a promising therapeutic for colorectal cancer liver metastases. Because of their potential role as chemopreventive drugs against CRC, RAS inhibitors' potential protective impact is gaining attention, however, there are still few studies that examine this association. More research is needed to confirm the significance of the renin-angiotensin system in colorectal cancer and its potential as a therapeutic target.

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