

# Renin Angiotensin System Components and Cancer: Reports of Association

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## Abstract

**Renin-Angiotensin System (RAS) is involved with hypertension and other cardiovascular diseases. However, the association of RAS components to cancer still causes suspicion. To try to clarify this, here we aimed to show this association for three important components: Angiotensin Converting Enzyme 1 (ACE1), Angiotensin Type 1 Receptor (AGTR1) and Angiotensin Type 2 Receptor (AGTR2). The first articles show that association of RAS components with cancer dates back to the 70's. ECA1 and AGTR1 have close association with cancer and ACE1 inhibitors or AGTR1 blockers are candidates to treatment of some tumors. Moreover, the action of AGTR2 is still controversial, but most studies show that the increased expression of AGTR2 can attack the cancer cells. In breast cancer, these components have also been widely studied and many works have shown that the correlation exists. Therefore specific target using these RAS components could be a beneficial, novel therapy to various tumors.**

## Keywords

**Renin-Angiotensin System, Angiotensin Converting Enzyme, Angiotensin Type 1 Receptor, Angiotensin Type 2 Receptor, Breast Cancer, Cancer**

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## 1. Introduction

The rennin-angiotensin system (RAS) and the generation of angiotensin II (Ang II) have major roles in the regulation of blood pressure and the adrenal secretion of aldosterone [1] [2]. Ang II, which is formed after conversion by Angiotensin-Converting Enzyme (ACE), acts preferentially by receptors type 1 or 2 (AGTR1 or AGTR2) [1].

The RAS plays an important role not only in homeostasis, but also in carcinogenesis. Recent epidemiological studies suggest that hypertensive patients with hyper-regulated functions of the RAS are at significantly increased risk for later development of cancer, with poor results. On the other hand, the inhibitors of RAS may reduce tumor growth, progression and metastasis [3].

Evidence suggests that Ang II possesses the role in physiological functions of the breast and that these could be modified or attenuated in cancer [4]. Furthermore, both AGTR1 and AGTR2 are mainly present in this secretory epithelium [5].

The binding of Ang II to AGTR1 induces the growth of breast cancer cells, and on the other hand triggering signaling by binding to the surface of AGTR2 causes an opposite effect, causing the growth inhibition and apoptosis [6].

Moreover, all elements of the tissue RAS (angiotensinogen, pro-renin, ACE, AGTR1, AGTR2, etc.) are present and distributed in different cell types. These results are consistent with the notion that stromal and myoepithelial elements are critical in the maintenance of normal epithelial structure and function. In illness, this system becomes disrupted, particularly in invasive carcinoma [7].

Therefore, the RAS can be involved both in normal and in abnormal physiology of the breast and other cancers. There is strong evidence that blocking the pathways of AGTR1, AGTR2 or inhibition of ACEs can have beneficial effects.

### 1.1. Renin Angiotensin System and Cancer

The effect of RAS in the pathophysiology of cancer has been analyzed and checked for almost 40 years, but the studies in past two decades have intensified. While studying the first associations of RAS components to cancer, we found that these date back to the 70 s. Initially, the evaluations of these components were focused in the kidney and cardiovascular system, and the first type of cancer in which this association was observed was in kidney [8].

In the following decades, it has been suggested that elevated serum ACE could be implicated with a worse prognosis for lung cancer and that this enzyme could be used as a prognostic indicator in this disease [9]. In other studies, the treatment with combined Ang II showed good clinical response in the patients with advanced gastrointestinal cancer and also with breast cancer [10] [11]. Between 1985 and 1990 several works showed that RAS components were correlated with other cancers (prostate, gastric, bladder, bronchial, breast, lung and neuroblastoma) [12] [13].

The research field of correlation of RAS components to various tumor types has not ceased, but rather from the late 90s to the current date increased interest of many researchers in this area was noted. So what would be the role of these hormones and Angiotensin receptors in the initiation, promotion, progression or even specifically inhibiting mammary tumor? To answer this question, there have been many studies. The signaling cascade that involves the components of the RAS has been implicated in enhanced survival and increased proliferation of tumor cells *in vitro* [7] [14]-[33].

Current literature also shows the association of RAS components (AGT, ACE, angiotensin II, and AGTR1 AGTR2, etc.) to various types of cancers (**Table 1**), namely: breast, endometrium, ovary, lung, gastric, prostate, colorectal, bladder, etc. [34]-[44].

### 1.2. Angiotensin Converting Enzyme 1 (ACE1) in Cancer

ACE is a cell surface zinc metallopeptidase that is differentially expressed in various tumors, and plays a role in malignant cell proliferation, tumor cell migration, angiogenesis, and metastatic behavior. The effects of the ACE gene on the risk of oral cancer was suggested and it was showed that the ACE gene polymorphisms may be associated with increased susceptibility to oral precancerous lesions and oral cancer lymph node metastasis [45]. ACE polymorphisms (I/D) also would be associated with hepatocellular carcinoma (HCC), breast and endometrial cancer, indicating that the polymorphism ACE I/D would lead to progression of HCC in the Chinese population [24] [36] [46].

Moreover another studies also demonstrated association of ACE with multiple myeloma and lung cancer [47] [48].

**Table 1.** RAS components actions in different types of cancer.

RAS COMPONENTS	ACTIONS	CANCER TYPES
ACEI	Cell proliferation	Oral
	Tumor cell migration	Hepatocellular carcinoma
	Angiogenesis	Breast
	Metastatic behavior	Endometrial Myeloma Lung
AGTR1/Ang II	Pro-inflammatory	Prostate
	Pro-angiogenic	Melanoma
	Proliferative	Pancreatic
	Anti-apoptotic	Myeloma
	Metastatic	Breast
AGTR2/Ang 1-7	Mitogenic	Lung
	Attenuate tumor growth	Human renal clear cell carcinoma
	Correlate disease-free survival	Pancreatic
	Negative regulator in growth	Prostate
	Induce apoptosis	Pancreatic ductal carcinoma
		Lung adenocarcinoma Leiomyoma Uterinomioma

ACE inhibitors (ACEI) and angiotensin blockers (ARBs) may have antitumor properties. Chae *et al.* (2013) investigated whether the use of ACEI/ARBs affects clinical outcomes of patients with primary breast cancer who received neoadjuvant anthracycline-based and taxane. Survival outcomes were observed between users and non-users of ACE inhibitors (ACEI) or inhibitors of AGTR1 (ARB) [49].

### 1.3. Angiotensin II Receptor Type 1 (AGTR1) and Cancer

After reports of a lower prevalence of cancer in hypertensive patients receiving ACE inhibitors, the biological action of Ang II on the development or progression of cancer has been the subject of several studies. Recently, the widespread use of AGTR1 blockers has contributed more compelling information about the involvement of Ang II in carcinogenesis. Interestingly, there is growing evidence that the RAS is involved in development of various cancers. From basic and clinical data Uemura & Kubota (2009) believe that ARBs have an ability to slow the rise of prostate specific antigen (PSA), especially in hormone-refractory cancer and suppress the incidence of prostate cancer, implying that the ARB could have a preventive activity for this cancer [50].

The AGTR1 signaling is generally pro-inflammatory, pro-angiogenic, proliferative and anti-apoptotic. And it was showed that the novel antagonist compound AGTR1 (2-(4-((2-nitro-5-propyl-1H-benzo[d]imidazol-1-yl)methyl)-1H-indol-1-yl) benzoic acid) have efficient *in vitro* antiproliferative and *in vivo* antitumor activities. Da *et al.* (2012) according to preliminary pharmacological characteristics observed for this compound, it was considered a candidate for the development of anticancer drugs [51]. Fujita *et al.* (2002) observed that another antagonist of AGTR1, the TCV-116 inhibited tumor growth, angiogenesis associated with tumors and metastases in a murine model. These results suggested that this AGTR1 antagonist inhibits angiogenesis, growth and metastasis of tumors highly dependent receptor blockade [52]. Therefore, these authors concluded that blocking the signaling AGTR1 could become an effective new strategy for cancer chemoprevention [22].

The stimulation of vascular endothelial growth factor receptor (VEGF), a transmembrane glycoprotein results in mitogenesis. Within this family of receptors, one containing the domain VEGFR 2/kinase inserted appears to be upregulated, especially during tumorigenesis. Piastowska-Ciesielska *et al.* (2013) showed correlation between the expression of AGTR1 and those containing VEGFR-2 kinase domain receptor in endometrial carcinoma [53].

The Ang II is involved in tumor growth, however, the exact mechanism is not known. The AGTR1 is expressed on the platelet surface, and these contribute to tumor growth. Amano *et al.* (2013) hypothesized that the interaction of platelets with cancer cells through AGTR1 signaling would promote the development of metastases. The results reported by these authors suggest that signaling AGTR1 play a critical role in tumor metastasis through interactions with the endothelial and tumor cells mediated by P-selectin on platelets and, through the

production of VEGF and SDF-1 dependent of AGTR1A signaling [54].

The association of AGTR1 with several cancers was showed [55]. In prostate cancer, Ang II via AGTR1 can induce cell proliferation and show that AGTR1 blockers could be used in the treatment of prostate cancer and its chemoprevention [56] [57]. In melanoma cancer cells, the activation of AGTR1 increases the expression of metalloproteinases 2 and 13 (MMP) and also VEGF in melanoma cells. This is an important conclusion because of the great importance of these factors in the invasion of melanoma cells and the possibility of blockade of AGTR1 for the treatment of cancer [58]. In pancreatic cancer, the authors found a significant system generator of local angiotensin in these tumor cell lines, which operates of intracrine manner, that is, inside the cells. Furthermore, this Ang II produced intracellularly has aggressiveness role in the pancreatic cancer and is a potential target for therapeutic agents [59]. And finally, the AGTR1 is expressed in myeloma cells from patients with leukemia of bone marrow and possess role in the genesis of this cancer and promoting erythropoiesis [60].

#### 1.4. Angiotensin II Receptor Type 2 (AGTR2) and Cancer

Despite the significant level of expression in cancer cells, the role of AGTR2 in the progression of this disease remains poorly understood. Clere *et al.* (2009) investigated the involvement of AGTR2 in tumorigenesis, hypothesizing a role in the proliferation and/or tumor angiogenesis. These researchers showed That AGTR2 has new mechanisms by which promotes the growth of the tumor, favoring both the proliferation of malignant cells and tumor angiogenesis [61].

In prostate cancer, the activation of AGTR2 can be associated and potentialized by the blockade of AGTR1 [62]. The AGTR2 is expressed and is located in the prostate tissue and, in addition, evaluated their role in cellular morphology and number of prostatic epithelial cells in primary culture. These authors showed a decreased number of cells of non-tumor prostate after selective stimulation of the AGTR2, suggesting that this receptor may play a protective role against the development of prostate cancer. So, the use of a selective agonist AGTR2 could represent a new approach for the prevention and treatment of prostate cancer [62].

In the target gene delivery therapy, the transfection efficiency and toxicity are concerns that continue to be a challenge for this effective gene therapy [63]. In their studies of nanoparticles formulated a vector for delivery of AGTR2 gene in tumor target in the setting of intratracheal administration for therapy of lung cancer. Notably, expression of the gene in tumor tissues persisted at least 14 days after intratracheal administration. In addition, administration of this vector showed markedly attenuate tumor growth. Taken together, these results provide a proof of concept for preclinical a new gene delivery system that delivers and effective strategy for managing intratracheal gene therapy of lung cancer using the AGTR2 as target [63].

In human renal clear cell carcinoma (RCCC), it was observed that expression of AGTR2 correlated with disease-free survival. Therefore, blocking these receptors could offer directions to new anti-RCCC therapy [64].

Pancreatic cancer is one of the most aggressive human malignancies with a very poor prognosis. To assess the effect of expression of AGTR2 in the growth of carcinoma of the pancreas, Doi *et al.* (2010) investigated the growth of graft of pancreatic ductal carcinoma in wild-type mice deficient for either the AGTR2 (AGTR2 knockout mice, or mice with inactivated this gene). The results suggest that Ang II regulate the growth of pancreatic carcinoma cells by modulating functions of stroma cells of the host. In addition, the signaling AGTR2 functions as a negative regulator in growth of carcinoma cells in the pancreas. These results indicate that AGTR2 in stromal fibroblasts would be a potentially important for the action of chemotherapeutic agents in the treatment of pancreatic cancer target [65].

Functional AGTR2 receptors are present in prostate cancer cells and inhibit the stimulation induced by epidermal growth factor. Li *et al.* (2011) evaluating apoptosis of cancer cells induced by over expression of AGTR2 in the prostate. The data obtained by these authors suggest that the ability of increased expression AGTR2 induce apoptosis in prostate cancer may have therapeutic implications, and would suggest that this receptor a promising new target for gene therapy of prostate cancer [66].

Endogenous AGTR2 is capable of mediating apoptosis in cardiovascular tissues. Pickel *et al.* (2012) explored the anticancer effect of this receptor by its overexpression in lung adenocarcinoma cells *in vitro* using adenovirus (Ad), FuGENE, and nanoparticles vectors [67]. Transfection of the AGTR2 gene through nanoparticles markedly increased expression of AGTR2 and resulted in the death of A549 lung tumor cells. These results indicate that the overexpression of this receptor effectively attenuates the growth of adenocarcinoma cells through the intrinsic apoptosis. Therefore, the authors suggest that nanoparticles can be used as a vector to deliver genes

AGTR2 and would be effective in the targeted lung adenocarcinoma therapy [67].

The AGTR2 is plentiful in the fetus and decreases rapidly after birth. The uterus expresses this receptor abundantly, even in adults, suggesting a role in reproduction. To explore the roles and regulation of AGTR2 in human uterus and to examine whether its expression is related to the characteristics of proliferation of leiomyoma [68]. Matsumoto *et al.* (1996) studied the expression of genes of Ang II receptors in myometrium of pregnant and nonpregnant obtained from patients undergoing gynecological surgery for uterine myoma. The receptor binding studies showed that AGTR2 agonists bind with high affinity to the receptor and are expressed in human myometrium and uterine leiomyoma [68].

### 1.5. Angiotensin Converting Enzymes 1 and Angiotensin II Receptor Type 1 and 2 (ACE1 and AGTR1 and 2) in Breast Cancer

There have indicated that RAS plays an important role at various stages of cancer progression. The presence of RAS components was shown in normal tissue and breast cancer. Insertion/deletion (I/D) polymorphism is an ACE and A1166C is a type of AGTR1 polymorphism which has been linked to various diseases such as cardiovascular diseases. Namazi *et al.* (2010), in their study sought to substantiate the putative importance of ACE and AGTR1 about the biology of breast. These authors investigated the influence of their genetic polymorphisms in cancer progression and showed that the polymorphism of the ACE (I/D) would associated with the expression of HER-2 and AGTR1 polymorphism (A1166C) that would associate the stage of patients with breast cancer [21].

In a recent study we conclude that changes in circulating levels of ECA1/AngIIECA2/ Ang-(1-7) determine the magnitude of the inflammatory response that an individual can trigger and the variation in ACE1 and 2 plasma level measurements in the blood of breast cancer patients suggests an association with the process of mammary carcinogenesis. Thus, is possible that RAS is associated with the process of mammary carcinogenesis by both genotypic variations of RAS components and by circulating levels of ACEs [69].

ECA1 seems to be associated with advanced stages of the disease and, on the other hand, the ACE2 seems to be more associated with the early stages, giving it a protector status against cancer. These ACEs plasma levels data here presented, combined to other recent observations that Ang-(1-7) attenuates lung cancer metastasis, has a protective effect by inhibiting cell proliferation [70] [71] and that genetic polymorphisms of the RAS components are associated with gynecological cancer risk and progression [24] [36] give another piece of evidence that the RAS may be associated with breast cancer.

Both AGTR1 and AGTR2 are present in tumors. Experimentally, acting through AGTR1AngII increases the proliferation and angiogenesis of tumor cells, and through AGTR2, inhibiting, blocking its production or function. Epidemiologic evidence on the effect of expression levels of ACE or distribution of ACE or AGTR1 variants in many cancers gives indirect support to these concepts. Furthermore, Vinson *et al.* (2007) believe it is possible that there is a process for the therapeutic use of high doses of ACE inhibitors and blockers AGTR1 in breast cancer, as well as by agonists can be AGTR2, although latter needs to be better investigated. Attention is called to the possibility of blocking signaling pathways mediated by AGTR1, for example, with antibodies directed against AGTR1 exploiting the possibility that the N-terminal extracellular AGTR1 may have signaling functions previously unsuspected [4].

Response rates to chemotherapy in patients with breast cancer are highly variable. De Ronde *et al.* (2013) studied genes associated with resistance to chemotherapy and found that among the five resistance markers identified was the AGTR1. The presence of these genes can lead to a better understanding of the mechanisms involved in resistance to chemotherapy and thereby contribute to the development of more specific and effective drugs [5].

The AGTR1 promotes tumor invasion, migration, angiogenesis and metastasis. Chen *et al.* (2013) explored the potential antitumor effects of AGTR1 antagonists in breast cancer [6]. These authors found that Ang II promoted cell proliferation and hyper-regulated the expression of vascular endothelial growth factor A (VEGF-A) in mammary tumor cells MCF-7. Furthermore, they found that losartan hiporregulated the expression of VEGF-A in MCF-7 cells treated with Ang II. Candesartan hiporregulated the expression of VEGF-A in mice bearing xenografts of MCF-7 and inhibited tumor growth and angiogenesis. The expression of AGTR1 and VEGF-A was correlated with increased microvessel density in 102 patients with breast cancer. The data presented by these authors suggest that AGTR1 antagonists may be useful to suppress breast cancer by inhibition of Ang II [6].

Jethon *et al.* (2012) examined the correlation between the intensity of expression and the expression of the AGTR1 linfoangiogenics markers in cancers of the breast invasive ductal (IDC, invasive ductal breast cancers). These authors found a positive correlation between AGTR1 and VEGF-A and -D, which points to possible stimulatory action of Ang II expression in which may result in the increased linfoangiogenese invasive ductal breast carcinoma [72].

Chronic stress and a high fat diet are well documented risk factors associated with RAS in the development of breast cancer. Several recent studies have focused on the role of AGTR1 and cell proliferation in cancer development. Du *et al.* examined the hypothesis that Ang II promotes the proliferation of breast cancer cells through activation of AGTR1, which could play an important role in promoting the growth of breast cancer, and on the other hand, AGTR1 blockers inhibit proliferation by antagonizing the AGTR1. The level of AGTR1 expression was significantly hyper-regulated in breast cancer cells studied by means immunohistochemical assays but no correlation between the AGTR1 expression and the ER/PR/Her-2 expression was observed. The results obtained by these authors suggest that inhibitors of AGTR1 may be useful in using a strategy of prevention and therapy for the treatment of breast cancer [73].

With the advent of “personalized medicine” has changed profoundly the research and treatment of cancer. This individualization is paramount objective to identify the specific genetic events and/or epigenetic (that may be therapeutic targets) that direct the patient to a treatment of breast cancer differently, rather than assuming that all women with breast cancer have the same disease [74].

Ateeq *et al.* (2009) hypothesized that, among so many approaches in the literature, either in research on biochemical and molecular approach or in studies with genetic focus (polymorphisms), would need to assess the modulation of response AGTR1 and develop a monoclonal antibody against the extracellular domain of this receptor. Furthermore, it might be more appropriate to explore the different sites involved in AGTR1 ligand binding and transactivation of other important receptors such as the estrogen. Despite the abundant data supporting the therapeutic target this receptor, there is currently no monoclonal antibody directed to human clinical trials. In addition, these authors believe that a subgroup of patients can benefit from targeted therapy with inhibitors of AGTR1, for example, losartan. Rhodes *et al.* also recommend that AGTR1 antagonists may indeed be a viable therapy option for women that hiperexpressedAGTR1in breast tumors [23].

Recent studies have revealed that AGTR1 is a potential therapeutic target in breast cancer, but even then the subtype AGTR2 role in this disease has remained largely neglected. Rodrigues-Ferreira *et al.* (2012) described the generation and characterization of a novel cell model of human invasive breast (D3H2LN-AGTR2) that express high levels of stable human AGTR2 (Flag-hat2) cancer. These cells exhibit binding sites for high affinity Ang II. Total binding can be displaced by AGTR2 selective antagonist PD123319, but not AGTR1 antagonist, losartan selective. These investigators developed a new tool for investigating the functions of AGTR2 in breast cancer cells, regardless of activation AGTR1 [75].

## 2. Conclusions

This study shows that the action of the RAS in various cancers was investigated more than 40 years and around 20 years in breast cancer, specifically. The work presented here shows that these components, in particular ECA1, AGTR1 and AGTR2 are closely linked to cancer and can be used as targets in the fight against cancer. For this one can use ECA1 or AGTR1 blockers or potentiating actions of the AGTR2; the latter is known to be a protector against the cancer.

Therefore, we conclude that there is a correlation of these components of RAS to the cancer and the focus in the study of these components can indeed give us possibilities and solutions in development of new drugs or treatments for this very important disease that has victimized many people all over the world.

Therefore, the RAS can be involved both in the normal and in abnormal physiology of the breast and other cancers. There is strong evidence that blocking the pathways of AGTR1, AGTR2 or inhibition of ACEs can have beneficial effects.

So we can say that clinical studies on this topic will be important to confirm these evidences obtained in basic research in different populations, since it seems that the genetic and population factor, *i.e.* the different polymorphisms related to these genes present in the population has great influence on the prognosis and treatment of cancer.

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## Conflict of Interest Statement

None declared.

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