



The Role of Angiotensin-(1-7) in Cancer

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Introduction

One of the first indirect evidence for the role of Angiotensin-(1-7) [Ang-(1-7)] in cancer was that hypertensive patients treated with angiotensin-converting enzyme (ACE) inhibitors have a decreased risk of cancer [1] and ACE inhibitors cause a significant elevation in both tissue and circulating Ang-(1-7) [2–4]. Considering that Ang-(1-7) inhibits the growth of several cell lines [5–9], it has been suggested that the heptapeptide may also reduce the proliferation of cancer cells and tumors.

However, the direct role of Ang-(1-7) in tumor process was first described by Rodgers and coworkers [10, 11]. These authors showed that treatment with Ang-(1-7) accelerates hematopoietic recovery by increasing both the number of white blood cells and myeloid progenitors in the peripheral blood and bone marrow after chemotherapy [10, 11]. Soon after, Gallagher and Tallant [12] reported that Ang-(1-7) inhibits lung cancer cell growth through the activation of Mas receptor.

In this chapter, we summarize studies on the role of Ang-(1-7) in different types of cancer.

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Angiotensin-(1-7) in Lung Cancer

Lung cancer is one of the most frequent types of cancer in humans and a leading cause of death [13]. The high mortality rates have been associated with late diagnosis, which results in elevated frequency of metastasis [13]. Therefore, despite all developments in therapeutic approach, the investigation of novel treatments that control neoplastic cell migration, proliferation and metastasis is urgently needed.

In this regard, Ang-(1-7) has emerged as a potential therapeutic target [14]. The first evidence was provided by an *in vitro* study. Three lung cancer cell lines including human adenocarcinoma SK-LU-1 and A549 cells and non-small cell lung cancer SK-MES-1 cells were incubated with Ang-(1-7) to determine the effect of the heptapeptide on cell growth [12]. Ang-(1-7) potently inhibited the growth of all cell lines of lung cancer at subnanomolar concentrations [12]. The antiproliferative effect of Ang-(1-7) was associated with reduction in serum-stimulated phosphorylation of the MAP kinases ERK1/2 [12]. In addition, the inhibitory effect of Ang-(1-7) was mediated by Mas receptor, since it was blocked by the Mas receptor antagonist D-Ala⁷-Ang-(1-7) (A-779) and not affected by AT₁ or AT₂ [12]. *In vivo* evidence was obtained by the intravenous administration of Ang-(1-7) in mice with A549 human lung tumors [15]. Ang-(1-7) infusion was very well tolerated by the mice and resulted in a reduction of tumor volume by 30% compared to the size prior to treatment [15]. These findings were associated with a decrease in the proliferation marker Ki67 [15].

Two other mechanisms that may contribute to antitumor effect of Ang-(1-7) in lung cancer are cyclooxygenase 2 (COX-2) inhibition and antiangiogenic activity. COX-2 is overexpressed in 70–90% of adenocarcinomas [16]. Clinical trials with nonselective inhibitors of COX-2 decreased the risk for lung cancer, suggesting that a reduction in COX-2 is associated with inhibition of lung tumor growth [17, 18]. Ang-(1-7) significantly reduced COX-2 mRNA and protein in both A549 tumor xenografts and A549 cells in culture [15]. It should be pointed that Ang-(1-7) has significant advantages over the administration of nonselective and selective COX-2 inhibitors for lung cancer since the heptapeptide-mediated reduction in COX-2 is associated with antithrombotic and antiinflammatory activities without the side effects related to COX-2 inhibitors [19]. In regard to antiangiogenic activity, athymic mice with A549 lung tumors were injected daily with 1000 µg/kg of Ang-(1-7) for 5 days, followed by a 2-day drug-free, and sacrificed after 42 days [20]. Ang-(1-7) markedly decreased vascular endothelial growth factor (VEGF) protein and mRNA, vessel density and A549 lung tumor growth [20]. The antiangiogenic effect of Ang-(1-7) was also mediated by Mas receptor [20].

More recently, the expression pattern of microRNAs (miRNAs) in lung tumor cells has been investigated to elucidate the mechanisms by which Ang-(1-7) controls tumor migratory processes [21, 22]. It was found that miRNA-149-3p plays a role in cellular migration processes [21] and miRNA-513a-3p controls the protein level and molecular function of integrin-β8, thus reducing cell migration and inflammation [22]. Another recent line of investigation is the use viral vectors to

deliver Ang-(1-7). Chen and coworkers [23] constructed a mutant adeno-associated viral vector AAV8 (Y733F) that produced stable and highly efficient Ang-(1-7) expression in a xenograft tumor model. AAV8-mediated Ang-(1-7) overexpression inhibited tumor growth *in vivo* by downregulating Cdc6 and anti-angiogenesis. These findings provide useful information for future investigations on drug development.

Angiotensin-(1-7) in Breast Cancer

Among all the malignant diseases, breast cancer is considered as one of the most important causes of death in postmenopausal women, accounting for 23% of all cancer deaths [24]. There are three major types of breast cancer: estrogen receptor-positive (ER-positive) breast cancer, which can be treated with selective estrogen receptor modifiers (SERMs) or aromatase inhibitors; human epidermal growth factor receptor 2 (HER2)-overexpressing breast cancer, which can be treated with an antibody to the HER2 receptor; and triple-negative breast cancers, which lack both estrogen and progesterone receptors and also do not overexpress HER2, very frequently being refractory to conventional treatments [24]. In spite of targeted treatments for ER-positive and HER2-overexpressing breast cancers, there is still need for novel therapies for both primary and metastatic diseases.

The effect of Ang-(1-7) was first investigated in human ZR-75-1 ER-positive and BT474 ER-positive/HER2-overexpressing breast tumors [25]. Ang-(1-7) significantly reduced tumor volume and weight in both ZR-75-1 and BT474 breast tumors [25]. In addition, treatment with Ang-(1-7) markedly decreased fibroblast growth, interstitial fibrosis within the tumors and perivascular fibrosis surrounding tumor vessels, in association with a decrease in immunoreactive collagen I deposition [25]. The antifibrotic effect of Ang-(1-7) was associated with increase in MAP kinase phosphatase and reductions in phosphorylated ERK1/2 and in the production of transforming growth factor-beta (TGF- β) [25]. These findings indicate that Ang-(1-7) inhibits cancer-associated fibroblasts growth and tumor fibrosis in breast cancer.

The role of ACE2/Ang-(1-7)/MAS receptor axis was also investigated in the metastasis of breast cancer [26]. Yu and coworkers [26] detected that ACE2 protein level is negatively associated with the metastatic ability of breast cancer cells and breast tumor grade. Furthermore, stimulation of the ACE2/Ang-(1-7)/Mas receptor axis reduced breast cancer cell migration and invasion *in vivo* and *in vitro* by means of the inhibition of store-operated calcium entry and PAK1/NF- κ B/Snail1 pathways, and the induction of E-cadherin expression [26].

The counterregulatory role of Ang-(1-7) against deleterious actions of Ang II was also observed in breast cancer. In this regard, Cambados and coworkers [27] have investigated the effect of Ang-(1-7) on Ang II-induced protumorigenic features on normal murine mammary epithelial cells NMuMG and on breast cancer cells MDA-MB-231. Ang II stimulated PI3K/AKT pathway leading to epithelial-mesenchymal transition in NMuMG cells via AT₁ receptor activation [27].

Simultaneous administration of Ang II and Ang-(1-7) abolished the effects of Ang II in NMuMG cells. In addition, Ang-(1-7) annulled Ang II-induced migration and invasion of the MDA-MB-231 cells and inhibited proangiogenic process by reducing VEGF expression [27].

Angiotensin-(1-7) in Prostate Cancer

Prostate cancer is the second most important cause of cancer deaths in men [28]. Treatment options for localized prostate cancer include surgery, radiation therapy, and hormone ablation therapy. Although treatment is encouraging for primary prostate cancer, metastatic prostate cancer, predominantly to the bone, is often fatal [28].

Ang-(1-7) was administered for 54 days to athymic mice with human LNCaP prostate cancer cells injected into the flank [29]. Ang-(1-7) treatment significantly reduced the volume and weight of LNCaP xenograft tumors [29]. Histological analysis of the tumor showed that Ang-(1-7) decreased Ki67 immunoreactivity, ERK1/2 activities and vessel density. The reduced angiogenesis was associated with less concentration of VEGF and of PlGF and increased levels of the soluble fraction of VEGF receptor 1 (sFlt-1). sFlt-1 acts as a decoy receptor that catches VEGF and PlGF, making the ligands unavailable to membrane-bound VEGF receptors and preventing activation of proangiogenic signaling [29].

In order to investigate the effect of Ang-(1-7) on metastatic prostate cancer to the bone, human PC3 prostate cancer cells were injected into the aortic arch of mice pretreated with Ang-(1-7) or into the tibia of athymic mice, subsequently administered with Ang-(1-7) for 5 weeks beginning 2 weeks after cancer cells injection [30]. When PC3 cells were injected, the mice developed tumors in the submandibular bone, the spinal column, or the long bone of the leg. In sharp contrast, pretreatment with Ang-(1-7) prevented metastatic tumor formation. Ang-(1-7) administered 2 weeks after human PC3 prostate cancer cells also attenuated intratibial tumor growth. In addition, bone marrow cells were extruded from the long bone of untreated mice, differentiated to induce osteoclastogenesis and treated with Ang-(1-7). The heptapeptide reduced by 50% osteoclastogenesis in bone marrow cells, suggesting that Ang-(1-7) treatment impedes the formation of osteolytic lesions to reduce tumor survival in the bone microenvironment [30].

Angiotensin-(1-7) in Hepatocellular Cancer

The effects of Ang-(1-7) were also investigated in hepatocellular carcinoma [31, 32]. For this purpose, H22 hepatoma-bearing mice were randomly divided into five groups: vehicle-treated group, mice receiving low-dose of Ang-(1-7), high-dose of Ang-(1-7), high-dose of Ang-(1-7) plus A779, and high-dose of Ang-(1-7) plus PD123319. Ang-(1-7) inhibited tumor growth in a time- and dose-dependent manner [31]. The antitumoral mechanisms elicited by Ang-(1-7) include reduction of

cell proliferation and of angiogenesis as well as induction of tumor cell apoptosis. The effects of Ang-(1-7) on tumor cell proliferation and apoptosis were reversed by coadministration with A779 or PD123319, whereas the effects on tumor angiogenesis were completely blocked by A779 but not by PD123319. Moreover, Ang-(1-7) downregulated mRNA for AT₁ receptor, upregulated mRNA for AT₂ and Mas receptors [31].

As previously described for lung cancer, the use viral vectors to deliver Ang-(1-7) was also employed in hepatocellular carcinoma also. Thus, the effects of Adeno-associated virus serotype-8 (AAV8)-mediated Ang-(1-7) overexpression were investigated in hepatocellular carcinoma [32]. The authors first generated three different mutants of AAV8 (Y447F, Y703F, Y708F) and evaluated in vivo transduction efficiencies. The antitumor effects of Ang-(1-7) delivered by Y703F, the most efficient vector, was evaluated in H22 hepatoma-bearing mice. AAV-Ang-(1-7) persistently inhibited angiogenesis and the growth of hepatocellular carcinoma [32].

Angiotensin-(1-7) in Glioblastoma

Glioblastoma multiforme (GBM) is the most primary brain tumor, specially characterized with the damage of blood-brain barrier [33]. Ang-(1-7) inhibited the growth and invasiveness of GBM [34]. To investigate the mechanisms beyond antitumor effect of Ang-(1-7) in GBM, Liu and coworkers evaluated the crosstalk between Podocalyxin (PODX) and Ang-(1-7)/Mas receptor signaling in GBM cells, and examined its effect on GBM cell invasion and proliferation [35]. It has been previously reported that PODX enhances invasion in many human cancers including GBM. The authors found a significant negative correlation between the expression of PODX and Mas in GBM tumor tissues from 10 patients ($r = -0.768$, $p < 0.01$) [35]. The stable overexpression of PODX in LN-229 and U-118 MG human GBM cells decreased the mRNA and protein expression of Mas receptor, resulting in low density of Ang-(1-7)-binding Mas on the cell membrane. Overexpression and knockdown of PODX respectively reversed and enhanced the inhibitory effects of Ang-(1-7) on the expression/activity of matrix metalloproteinase-9 and cell invasion and proliferation in GBM cells. PODX inhibited Ang-(1-7)/Mas signaling by downregulating the expression of Mas through a PI3K-dependent mechanism in GBM cells. This effect increased GBM cell invasion and proliferation [35].

Besides the inhibitory effect of Ang-(1-7) on GBM growth, the heptapeptide significantly relieved the damage of blood-brain barrier in rats with intracranial U87 gliomas [36]. Furthermore, treatment with Ang-(1-7) restored the function of blood-brain barrier and avoided edema formation. Similarly, Ang-(1-7) also decreased U87 glioma cells barrier permeability in vitro. The protective effect of Ang-(1-7) on blood-brain barrier was associated with inhibition of JNK pathway and a consequent return of tight junction protein (claudin-5 and ZO-1) expression to normal levels both in rats and in U87 glioma cells [36].

Angiotensin-(1-7) in Other Cancers

Basal and interleukin (IL)-1 β -stimulated expression of components of ACE2/Ang(1-7)/Mas receptor axis were evaluated in U-2 OS and MNNG-HOS osteosarcoma cells analyzed as well as the effect of Mas receptor on proliferation and/or migration of these cells [37]. The two cell lines expressed Ang-(1-7)-generating peptidases, including ACE2, neutral endopeptidase 24.11 and prolyl-endopeptidase together with Mas receptor. IL-1 β stimulated mRNA and protein expression for Mas receptor, which was associated with a reduction of proliferation and migration. On the other hand, RNA-mediated knockdown of Mas expression led to increased cell proliferation, supporting a beneficial role of ACE2/Ang(1-7)/Mas receptor axis in the treatment of osteosarcoma [37].

The treatment of nasopharyngeal carcinoma (NPC) has been associated with several side effects [38]. Therefore, the investigation on novel treatment modalities for NPC is of utmost importance. It was found that Mas receptor is significantly upregulated in NPC specimens and NPC cell lines [39]. Viral vector-mediated expression of Ang-(1-7) markedly inhibited NPC cell proliferation and migration in vitro. These effects were mediated by Mas receptor since they were completely blocked by A-779 [39]. In addition, Ang-(1-7) significantly reduced the growth and the vessel density of human nasopharyngeal xenografts [39]. Mechanistic investigations revealed that, also in this tumor, Ang-(1-7) inhibited the expression of the proangiogenic factors VEGF and PlGF. The effects and signaling pathways involved in the Ang-(1-7)/Mas receptor axis in NPC were further investigated both in vitro and in vivo [40]. Ang-(1-7) inhibited cell proliferation, migration, and invasion in NPC-TW01 cells. Ang-(1-7) induced autophagy by increasing the levels of the autophagy marker LC3-II and by enhancing p62 degradation via activation of the Beclin-1/Bcl-2 signaling pathway with participation of the PI3K/Akt/mTOR and p38 pathways [40]. Pretreatment with Ang-(1-7) also inhibited tumor growth in NPC xenografts by stimulating autophagy, while no autophagy was observed following Ang-(1-7) posttreatment [40]. To sum up, Ang-(1-7) plays a role in autophagy downstream signaling pathways in NPC, supporting its therapeutic potential for reducing the incidence of primary NPC tumors and for preventing recurrent disease [40].

A beneficial role of Ang-(1-7) was also reported in head and neck squamous cell carcinoma (HNSCC) [41]. Hinsley and coworkers showed that Ang II promotes the invasion and migration of HNSCC cells both in an autocrine manner. The effects of Ang II were mediated by AT₁ receptors and inhibited by Ang-(1-7) [41].

Angiotensin-(1-7) for Cancer Pain and Side Effects of the Treatment

Besides antitumor actions, Ang-(1-7) may also be useful to control cancer pain [42] and side effects secondary to radiation therapy [43].

Several solid tumors metastasize to the bone and induce intense pain. Cancer-induced bone pain is often severe due to accentuated inflammation, rapid bone

degradation, and disease progression [44]. Opioids are recommended to manage this pain, but these medications may enhance bone loss and increase tumor proliferation [44]. The antinociceptive effect of Ang-(1-7) was investigated in a murine model of breast cancer-induced bone pain. Breast cancer cells were implanted into the femur of BALB/c mice [42]. Spontaneous and evoked pain behaviors were examined before and after acute and chronic administration of Ang-(1-7). Cancer inoculation increased spontaneous pain behaviors by day 7. Both single injection and sustained administration of Ang-(1-7) significantly reduced pain. Preadministration of A-779 impeded this reduction, while pretreatment with an AT₂ receptor antagonist had no effect. However, the use of an AT₁ antagonist potentiated the antinociceptive effect of Ang-(1-7). Ang-(1-7) via Mas receptor activation significantly attenuated pain without the side effects seen with opioids [42].

Radiation-induced fibrosis of musculoskeletal tissue is a common complication of radiation therapy for extremity soft-tissue sarcoma, without a strategy for prevention and treatment [45]. In this regard, Ang-(1-7) was tested as a radioprotectant agent for radiation-induced fibrosis and stiffening of irradiated muscles [43]. Male CD-1 mice were randomized to three treatment groups: control, simulated sarcoma radiation therapy to the gastrocnemius and soleus muscles, or radiation therapy along with continuous Ang-(1-7) infusion initiated 3 days before radiation therapy. Ang-(1-7) attenuated radiation-induced fibrosis, stiffening, and reduced the production of profibrotic cytokines that were elevated in mouse skeletal muscles after radiation therapy [43].

Clinical Trials with Ang-(1-7) or TXA127

A total of nine clinical trials with Ang-(1-7) or TXA127 are registered in NIH (3 completed, 3 withdrawn, 2 active and 1 terminated). TXA127 is a pharmaceutical grade formulation of the naturally occurring peptide Ang-(1-7), which Tarix Pharmaceuticals is developing for the treatment of a number of diseases.

The first trial registered was a phase I study that treated patients with metastatic or unresectable solid tumors with Ang-(1-7) [46]. Eighteen patients were enrolled in this trial. Dose-limiting toxicities found at the 700 microg/kg included stroke (grade 4) and reversible cranial neuropathy (grade 3). Other side effects were generally mild. One patient developed a 19% reduction in tumor measurements. Three additional patients showed clinical benefit with stabilization of disease lasting more than 3 months. Ang-(1-7) administration reduced circulating levels of plasma placental growth factor (PlGF) levels in patients with clinical improvement, but not in patients without clinical benefit [46]. Further results of this trial were not reported or published ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier: NCT00471562).

The second completed clinical trial is a phase II study on the role of Ang-(1-7) as second-line therapy or third-line therapy in treating patients with metastatic sarcoma that cannot be removed by surgery ([ClinicalTrials.gov](https://clinicaltrials.gov) Identifier: NCT01553539). This study enrolled 20 adult patients with different types of sarcoma. Patients received Ang-(1-7) subcutaneous once daily in the absence of

disease progression or unacceptable toxicity. Results revealed low rate of significant adverse effects and slight reduction in the concentrations of VEGF and PIGF at day 22 after the beginning of the treatment with Ang-(1-7).

The third completed clinical trial is a phase IIb, multicenter, randomized, double-blind, placebo-controlled study comparing safety and efficacy of two dose levels of TXA127 when administered during 6 cycles of combination gemcitabine and platinum-based chemotherapy ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00771810) Identifier: NCT00771810). This study intends to investigate the effectiveness of TXA127 for the mitigation of severity and/or incidence of thrombocytopenia, as well as safety when administered as a self-injected, subcutaneous solution. TXA127 was administered to patients with breast cancer in the adjuvant setting to determine the effect of Ang-(1-7) on cytopenia [47]. No dose-limiting toxicities were reported, and Ang-(1-7) reduced thrombocytopenia and lymphopenia [47]. Patients with ovarian, Fallopian tube, or peritoneal carcinoma receiving gemcitabine and carboplatin or cisplatin were also treated with TXA127. Once more, Ang-(1-7) reduced thrombocytopenia following gemcitabine and platinum chemotherapy [48]. These data suggest that Ang-(1-7) may be beneficial in attenuating multilineage cytopenias following bone marrow-toxic chemotherapy.

The three withdrawn clinical trials were phase II studies and had the objective to investigate the role of Ang-(1-7) or TXA127 in hematologic malignancies. The first registered study aimed to examine the safety and the efficacy of TXA127 to enhance engraftment in pediatric patients undergoing single or double umbilical cord blood transplantation ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01554254) identifier: NCT01554254). The second study aimed to evaluate the efficacy of TXA127 to reduce the incidence (Grade II-IV) of acute Graft-versus-Host Disease (aGVHD) in adult subjects undergoing double umbilical cord blood transplantation ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01882374) identifier: NCT01882374). The third study had the purpose to evaluate the efficacy of TXA127 to reduce the incidence (Grade II-IV) of aGVHD in adult subjects undergoing allogeneic peripheral blood stem cell transplantation ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01882387) identifier: NCT01882387). In these three studies, no results were reported, and the studies were withdrawn before participants were enrolled.

The two active clinical trials are investigating the role of TXA127 in hematologic malignancies. The first registered is a randomized, double-blind, placebo-controlled study phase II with the purpose to determine the safety and effectiveness of TXA127 in accelerating the time it takes for patients to recover their platelet counts following an Autologous Peripheral Blood Stem Cell transplant ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01121120) identifier: NCT01121120). The second is a phase I study with the aim to examine the safety and efficiency of TXA127 (two injected doses: 300 or 1000 mcg/kg/day for 28 days) in enhancement of engraftment in adult double cord blood transplantation for the treatment of a variety of hematologic malignancies for whom there is no available therapy with substantive antidisease effect ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01300611) identifier: NCT01300611). No results are posted for both studies.

The single terminated clinical trial was a phase 1 study that aimed to determine safety and tolerability of TXA127 (300, 600, or 900 µg/kg daily by subcutaneous injection) in thrombocytopenic subjects with low or Intermediate-1 risk myelodysplastic syndrome ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01362036) identifier: NCT01362036). No results were reported.

Concluding Remarks

Studies in vitro and in vivo experimental models showed that Ang-(1-7) reduced proliferation of human cancer cells and xenograft tumors. The antitumor effect of Ang-(1-7) was due to reduction of angiogenesis, cancer-associated fibrosis, osteoclastogenesis, tumor-induced inflammation, and metastasis, as well as inhibition of cancer cell growth and proliferation. In clinical trials, Ang-(1-7) was well tolerated with limited toxic or quality-of-life side effects and showed clinical benefit in cancer patients with solid tumors. In conclusion, these findings so far suggest that Ang-(1-7) may act as chemotherapeutic agent, reducing cancer growth and metastases by pleiotropic mechanisms as well as targeting the tumor microenvironment. Further clinical trials are needed to confirm safety, and to determine doses and clinical indications.

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