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1 Introduction

Breast cancer is the most frequent cause of death by malignancy among women in developing countries, and the occurrence of distant metastasis is a critical event that limits the survival of patients with breast cancer. While targeted molecular therapies have considerably improved the management of primary breast tumors, these remain poorly effective for the treatment of distant metastases. The identification of molecular agents that may contribute to breast cancer cell dissemination and colonization is therefore essential for future development of new anti-metastatic therapeutic strategies.

In this chapter, we will describe the processes of breast cancer development and progression. We will next focus on Angiotensin II (AngII) as a novel interesting target against metastatic breast tumors. Finally we will present models and strategies to investigate AngII functions in experimental breast cancer metastasis.

1.1 Breast Cancer General Features

Breast cancer is the most common cancer among women affecting more than 1 million women worldwide. Each year, more than 450,000 patients die due to the disease (Jemal et al., 2011). Breast cancer is not a single disease. There are indeed several types of breast tumors that have diverse histopathology, genetic and genomic variations, and clinical outcomes (Vargo-Gogola and Rosen, 2007).

Multiple subgroups of tumors with different molecular signatures, prognosis and response to therapies have been identified. Currently, breast tumors can be classified into three major molecular subtypes associated with differences in therapy and clinical outcome (Sorlie et al., 2001; Higgins & Basselga, 2011):

- Luminal, or estrogen receptor positive tumors (ER+), are characterized by expression of estrogen receptor ER and progesterone receptor PR. This subtype concerns 70-80% of breast tumors and benefits from efficient hormonal therapy such as Tamoxifen or Aromatase inhibitors.

- HER2 (Human Epidermal growth factor Receptor 2) tumors are characterized by amplification of the ErbB2/HER2 oncogene and represent 10-15% of the tumors. Patients are treated with specific therapy targeting HER2 with monoclonal antibodies like Trastuzumab/Herceptin®.

- Triple negative tumors, that do express neither hormone receptors (ER, PR) nor HER2, belong to a heterogeneous molecular subtype which is the most aggressive, being highly proliferative and metastatic. Triple negative tumors represent only 10-15% of tumors but are responsible for 25% of deaths by breast cancer. Patients with triple negative breast tumors do not benefit from targeted therapy and remain of poor prognosis.

1.2 Breast Cancer Development and Progression

Breast cancer develops within epithelial cells of lobules and ducts of the breast. The transformation of breast epithelial cells is a combination of epigenetic and genetics changes. During this multistage process, control of proliferation and survival becomes deregulated allowing the emergence of breast tumors. As the tumor grows, the need in oxygen and nutrients increases and the center of the tumor becomes inaccessible to peripheral blood vessels, and thus hypoxic. Hypoxia activates neoangiogenesis necessary for tumor growth and progression. In highly aggressive tumors, some cells with metastatic properties initiate the metastatic program by detaching from the primary tumor, invading and migrating through the sur-
rounding matrix stroma until reaching the blood flow by intravasation. This is quite an efficient step since most of the disseminated metastatic cells succeed in reaching the circulation. However, metastasis remains an inefficient process (Luzzi et al., 1998). Among the large number of cancer cells that detach from the primary tumor and invade adjacent tissues to reach the bloodstream, most remain quiescent or die in the circulation. Few circulating tumor cells are able to cross the blood barrier and migrate toward distant organs to grow as a metastasis (Chambers et al., 2002) (Figure 1). Metastasis is thus initiated by cancer cell dissemination, but extravasation and colonization remain the critical steps of the whole process.

1.3 Breast Cancer Metastasis: A Complex and Fatal Disease

Patients with metastatic breast cancer receive chemotherapy, but most of the time patients suffer from treatment resistance and recurrence of the disease. There is an urgent need to identify molecular factors of breast cancer cell dissemination and colonization in order to develop new anti-metastatic therapeutic options.

Networks of genes altered in primary tumors have been shown to contribute to the metastatic path, leading to the notion of "metastasis gene signatures" (Nguyen et al., 2009). Among them, genes with pleiotropic effects that control both early and late stages of metastasis were classified as "metastasis progression genes" (Nguyen & Massagué, 2007) and are of high interest for novel efficient therapies against cancer metastasis. In addition to intrinsic metastasis gene signatures that predict the ability of tumor cells to colonize distant tissues, close interactions between circulating tumor cells and the host microenvironment are critical to the establishment of cancer cells at secondary sites (Fidler, 2003; Joyce & Pollard, 2009). Adaptative cancer cells can either proliferate to give rise to a micrometastasis, or remain latent in a dormant state. Reactivation of dormant cancer cells allows them to develop into a macrometastasis (Joyce & Pollard, 2009; Shibue & Weinberg, 2011). Breast cancer progression and metastasis strongly depend on the selection of adapted cancer cells and their close interactions with the stromal microenvironment (Figure 2).

Figure 1: Scheme of tumor progression: Shown are the 4 majors steps of tumor progression namely growth, angiogenesis, invasion and metastasis. Blue cells represent epithelial cells over basement matrix (blue line); brown cells represent tumor cells; red cells are for endothelial cells.
Figure 2: Scheme of metastatic colonization: After extravasation (1), metastatic cancer cells (in brown) migrate and seed in the target organ where they interact with stromal cells (in yellow) and extracellular matrix (yellow curves) present in the microenvironment (2). At this stage, metastatic cells can die from apoptosis (3), remain dormant (4), or proliferate to give a micrometastasis (5) that develops into a macrometastasis (6).

Diffusible molecules such as cytokines or chemokines (CXCL12, CCL2) are key factors in the interplay between metastatic tumor cells and the host microenvironment, and play a decisive role in breast cancer metastasis (Muller et al., 2001; Qian et al., 2011). We have hypothesized that other small molecules such as vasoactive peptides (Angiotensins, Endothelins or Bradykinins), either produced locally or released in the blood flow, may trigger activating signals contributing in an autocrine or paracrine way to cancer cell extravasation, colonization and metastasis (Rodrigues-Ferreira et al., 2012a). In this review, we will present our recent studies investigating the effects of angiotensin II on breast cancer metastasis.

2 Angiotensin II as a New Potential Therapeutic Target

2.1 Angiotensin II and the Renin-angiotensin System

Angiotensin II (AngII) has been initially identified as the major biologically active peptide of the renin-angiotensin system (RAS), but it is now well established that other peptides derived from the RAS, namely Ang1-7, AngIII and AngIV, also display biological activities (Wright & Harding, 1997; Crowley & Coffman, 2012; Santos et al., 2012). All angiotensin peptides derive from a unique precursor, angiotensinogen (AGT), synthesized and released from the liver. In response to blood changes (such as decrease in blood pressure or plasma sodium level), the kidneys produce and release the renin protease which cleaves AGT into a decapeptide designated Angiotensin I (AngI). AngI is in turn cleaved by Angiotensin Converting Enzyme (ACE) to produce the octapeptide AngII. AngII can then be processed by either the Angiotensin Converting Enzyme 2 (ACE2) to produce Ang1-7, or by aminopeptidase A and N to produce AngIII and AngIV, respectively (George et al., 2010; Crowley & Coffman, 2012) (Figure 3). Angiotensin peptides, and in particular AngII, are produced in the plasma but also in several organs where a local RAS is active (Paul et al., 2006). Interestingly, angiotensin peptides exert diverse biological effects, such as vasoconstriction/vasodilatation, inflammation, proliferation and apoptosis, through binding to different receptors, namely AT1R, AT2R, AT4R and MAS-R (Santos et al., 2012; George et al., 2010) (Figure 3).
Both AngII and its cleavage product Ang1-7 have been shown to contribute to cancer processes, by different mechanisms. Studies reporting an effect of Ang1-7 acting though the MAS receptor have been recently reviewed (Santos et al., 2012) and their role in cancer have first been described by Tallant’s group (Gallagher et al., 2004, 2011; Soto-Pantoja et al., 2009). In this chapter, we will mainly focus on the effects of AngII in cancer progression.

2.2 AngII and Cancer

AngII is a major regulator of blood pressure and cardiovascular homeostasis, acting through activation of specific receptors AT1R and AT2R. These two subtypes of receptors belong to the superfamily of G-protein-coupled receptors, but have distinct distribution and intracellular signaling pathways (Nouet & Nahmias, 2000). Most of AngII actions involve the AT1R whereas AT2R often functions as a negative regulator of the AT1 subtype. Activation of the AT1 receptor triggers a large number of intracellular effectors leading to modulation of various cell processes, among which proliferation, migration, angiogenesis and inflammation, which are closely associated with tumor progression (Deshayes & Nahmias, 2005).

Strategies to investigate AngII functions in cancer include either blockade of AngII production with ACE inhibitors, or inhibition of AngII signaling pathways with Angiotensin receptor blockers (ARBs) (Deshayes & Nahmias, 2005). Of note, these drugs are widely used in the clinics to efficiently treat hypertensive patients. A retrospective cohort study performed by Lever and co-workers aimed to assess the risk of cancer in hypertensive patients receiving ACE inhibitors or other antihypertensive drugs. They showed that long-term use of ACE inhibitors may protect against cancer (Lever et al., 1998). In an independent study of 1051 cases, users of ACE inhibitors or ARBs were shown to have significantly reduced risks in developing basal and squamous cell carcinomas (Christian et al., 2008). These findings have been challenged by a recent meta-analysis that suggested that ARBs medication may be associ-
ated with a modest increase in cancer risk (Sipahi et al., 2010). However, these results have not been further validated by other groups, which rather found no effect of ARBs related to the risk of cancer (Bangalore et al., 2011; Connolly et al., 2011). These results might reflect the heterogeneity of patient cases included in the studies. Regarding breast cancer, the use of ACE inhibitors or ARBs has not been associated with breast cancer risk (Li et al., 2003; Fryzek et al., 2006; Chae et al., 2013; Sørensen et al., 2013), but with significant reduction of breast cancer recurrence (Chae et al., 2011). Furthermore, attempts to correlate RAS polymorphism with breast cancer risk have not been conclusive and require further investigation (Gonzalez-Zuloeta Ladd et al., 2007; Xi et al 2011). Whether angiotensin receptors variation or blockade has beneficial effects in cancer patients still remains a matter of debate. This question needs to be better explored in distinct subpopulations of tumors classified according to histological, molecular and clinical characteristics, and according to the expression of different RAS components.

In breast tumors, most components of the classical RAS including angiotensinogen, angiotensin converting enzyme and angiotensin receptors are locally expressed (De Paepe et al., 2001; Tahmasebi et al., 2006; Herr et al., 2008; Inwang et al., 1997; George et al., 2010). Interestingly, a large-scale meta-analysis performed on 31 breast cancer profiling datasets has revealed overexpression of AT1 receptor in 10-20% of invasive breast tumors (Rhodes et al., 2009). Such studies highlight the potential use of ARBs as novel therapeutic agents against a subpopulation of breast cancer.

ARBs and ACE inhibitors have been assayed both in cancer cells and in mouse experimental models to characterize AngII functions in tumor growth, angiogenesis and metastasis. It is well established that AT1 receptor activation by AngII induces cell proliferation in several cell types including cancer cells (Deshayes & Nahmias, 2005). In agreement, ARBs such as losartan or candesartan were shown to inhibit cell proliferation in vitro and tumor growth in mice xenografts (Chen et al., 2012). Tumor growth reduction in response to ARBs is associated with reduced tumor vascularization (Fujita et al., 2002 and 2005), which is essential to the progression of primary tumors as well as initiation of metastasis.

Local production of AngII was shown to facilitate tumor progression and lymph node metastasis (Carl-McGrath et al., 2007; Kinoshita et al., 2009). Evidence for a role of AT1 receptor on cancer cell metastasis came from in vivo studies of lung models of metastasis. Cancer cells were injected into the tail vein of mice perfused with the ARB Candesartan. Inhibiting AngII signalling strongly reduced lung metastasis (Miyajima et al., 2002; Fujita et al., 2005), although it was not clear whether ARBs were acting on tumor cells or on the stromal microenvironment. The role of AT1R in the tumor microenvironment has been investigated by comparing the growth and the vascularization of tumors injected subcutaneously into wild type (WT) or AT1R knockout mice (Egami et al., 2003; Fujita et al., 2005; Imai et al., 2007). Tumor growth and tumor-associated angiogenesis were strongly reduced in AT1R null mice indicating that the AT1R of host cells contributes to both tumor growth and angiogenesis. Of interest, the results show that AT1R-dependent tumor growth requires tumor angiogenesis that is promoted by AT1R-induced VEGF synthesis, a well known angiogenic factor. Furthermore, AT1R is highly expressed in the stromal tissue surrounding the tumors, in particular in tumor-associated macrophages TAMs. Macrophage infiltration, as well as levels of TAMs-released VEGF, was strongly reduced in AT1R null mice, supporting the hypothesis that host AT1R might also participate in inflammation-related tumor angiogenesis to maintain tumor growth (Egami et al., 2003; Fujita et al., 2005; Deshayes & Nahmias, 2005).

A remaining question is whether AngII produced locally may also directly act on tumor cells to promote tumor growth and metastasis.
3 Experimental Models to Study AngII and its Receptors in Breast Cancer Metastasis

3.1 Experimental Mouse Models of Metastasis

“Classical metastasis” experiments are performed by orthotopic injection of cancer cells that are allowed to grow and spontaneously form metastases. This model recapitulates all steps of cancer metastasis from primary tumor dissemination to distant organ colonization and constitutes the most relevant model of metastasis, but kinetics are very long and results are hardly reproducible due to variation of mouse response.

An alternative model of metastasis consists in injection of cancer cells directly in the blood flow. This model recapitulates the late rate-limiting steps of the metastatic process, i.e. extravasation and colonization. Cancer cells can be inoculated either by tail vein injection, in the case of lung metastasis experiments, or by intracardiac injection to promote the dissemination of cancer cells throughout the whole body including the lungs, bones and brain which are the major sites of breast metastases.

With no labelling of cancer cells, metastases can only be detected by histological or Polymerase Chain Reaction (PCR) analysis of selected tissues at the end of the experiment, which makes it difficult to monitor the establishment of metastatic foci in bones and soft organs. To follow and identify tumor cells in the whole organism, we used breast cancer cells stably expressing high levels of luciferase. Luciferase is an enzyme that reacts with its substrate luciferin to generate a photon. The number of photons released is proportional to the number of cancer cells. Bioluminescence is a powerful alternative to fluorescence labelling which is of weak sensitivity due to its high signal-to-noise ratio. Major limitation remains poor spatial resolution, light scattering and absorption by the tissue, although partially circumvent by three-dimensional imaging. Thus Bioluminescence Imaging (BLI) allows noninvasive real time follow up of tumor growth and metastasis formation at distant site in living mouse.

3.2 Model to Target AngII in Breast Cancer Cells Metastasis

To investigate the role of AngII on breast cancer metastasis, and address the question of whether locally produced AngII may act directly on tumor cells to promote tumor progression, we used the D3H2LN sub-line derived from the metastatic and triple negative breast cancer cells MDA-MB-231, expressing high levels of luciferase (Jenkins et al., 2005). D3H2LN cells are of particular interest for the study of breast cancer cell progression both in vitro and in vivo since they are highly invasive and metastatic. After intracardiac injection into nude mice, these cells rapidly disseminate and colonize distant organs including the brain, the lungs and the bones (Jenkins et al., 2005).

In our experiments, D3H2LN cells were exposed for 24 hrs to 100nM of AngII in vitro, before being injected intra-cardiacally into the bloodstream of nude mice (Rodrigues-Ferreira et al., 2012a). Such strategy allowed us to evaluate the effects of AngII on cancer cells while avoiding any direct effect of the peptide on the host microenvironment. Injection efficiency was monitored immediately after intra-cardiac injection by acquisition of luminescence in whole mice. Injection was considered successful when cancer cells propagated though the left ventricle reached the blood flow and labeled the whole animal (Figure 4). Only mice with successful injection were included in the study.
The establishment of tumor micrometastases in various organs was then evaluated by intravital bioluminescent imaging. Nineteen days after intracardiac injection all mice harbored metastases confirming high aggressiveness of the D3H2LN cell line. However, tumor cells exposed to AngII acquired a more aggressive behavior since at least one metastasis was already detectable in 86% of mice at day 9 as compared to only 40% for control mice, without any preferential tropism. Furthermore, AngII pre-treatment not only increased the percentage of mice with metastasis, but also increased the number of detectable metastatic foci per mouse (Figure 5) as well as the total number of tumor cells disseminated in the whole body, as assessed by quantification of bioluminescence (Rodrigues-Ferreira et al., 2012a).
Our results indicate that D3H2LN breast cancer cells exposed to AngII show increased metastatic potential \textit{in vivo} and are more prone to rapidly establish at distant organs. As AngII can be locally produced both in blood flow and cancer tissues, we hypothesize that this local production may accelerate the metastatic progression of breast cancer cells. Furthermore, we showed that direct exposure of breast cancer cells to AngII contributes to the metastasis process by increasing tumor-endothelial cell adhesion, trans-endothelial migration and motility (Rodrigues-Ferreira \textit{et al.}, 2012a). Of interest, AngII concomitantly regulates a set of genes that ultimately influence the host microenvironment to facilitate cancer cell extravasation, adaptation to the soil and subsequent metastatic colonization. Among those genes, we have identified a set of genes related to MAP Kinase (MAPK1), a major effector of cell proliferation, and another one connected to matrix metalloproteases (MMP2/9), well-known mediators of cell invasion and matrix remodeling (Rodrigues-Ferreira \textit{et al}, 2012a) (Figure 6). These results are in agreement with \textit{in vitro} and \textit{in vivo} effects of AngII and suggest that AngII may contribute to the cross-talk between tumor cells and their microenvironment to potentiate the metastatic colonization process. This model supports the notion that targeting AngII production or action using ACE inhibitors or ARBs, respectively, may represent an interesting therapeutic option to prevent metastatic progression of invasive breast tumors.

\textbf{Figure 6}: Networks of genes regulated by AngII centered around AngII precursor Angiotensinogen AGT. This network was obtained using the Ingenuity Pathway Analysis (IPA) software. Shown are the two main groups of connected genes associated to Metalloproteases 2 and 9 (MMP2/9 on the left) or to MAP-Kinase 1 (MAPK1 on the right).

\textbf{3.3 Model to Target AT2 Effects on Breast Cancer Cells}

It is generally admitted that AT1 receptor activation is responsible for most of the reported effects of AngII. Studies of AngII in cancer were mainly performed using AT1 receptor antagonists. But it is important to keep in mind that antagonizing the AT1 receptor by ARBs leaves the AT2 receptor fully available for activation by local AngII. As AT2 receptor levels have also been shown to be increased in ductal and invasive breast carcinomas (De Paepe \textit{et al.}, 2002), it is essential to determine whether the AT2 receptor may antagonize, or mimic, the effects of the AT1 subtype on cancer cells. To date, results from the literature about AT2 receptor functions in cancer remain controversial. It has been shown that AT2 receptor
expression or activation reduces growth of pheochromocytomas as well as pancreatic and lung carcinomas (Brown et al., 2006; Doi et al., 2010; Pickel et al., 2010). In agreement, exogenous administration of AT2 receptor by nanoparticles significantly attenuates lung cancer growth in an orthotopic model of tumor grafts in syngenic mice (Kawabata et al., 2012). In addition, activation of AT2 receptor with the agonist CGP42112A reduces colorectal liver metastasis (Ager et al., 2010), suggesting that AT2 receptor activation might provide a novel strategy to inhibit tumor growth. However, in some other studies, AT2 receptor expression is rather correlated with poor prognosis and its blockade is associated with delayed tumor progression (Arrieta et al., 2008; Clere et al., 2010). As both subtypes of angiotensin receptors are concomitantly expressed in cancer cells and tissues, relative expression of each subtype in addition to their ability to dimerize may trigger different signalling and thus contradictory responses. Hence, establishment of a model to specifically address the function of AT2 receptor independently of the AT1 subtype is of particular interest.

To study the implication of AT2 in breast cancer, we generated a human breast cancer cell line stably expressing high amounts of human AT2 receptors at the plasma membrane. We chose the previously described, breast cancer D3H2LN cell line (Jenkins et al., 2005), and we first evaluated the expression level of the angiotensin receptors by RT-PCR (Reverse Transcription PCR) and their presence at the cell surface by radiolabelled AngII binding experiments. Our results indicate that D3H2LN cells express very low levels of endogenous AT2 receptor transcripts as assessed by RT-PCR and no detectable binding sites for I125-labeled AngII (Rodrigues-Ferreira et al., 2012b).

We then designed an expression vector for the AT2 receptor (Rodrigues-Ferreira et al., 2012b). To facilitate AT2 receptor detection, we used a Flag-tagged human AT2 receptor (Flag-hAT2), which can be revealed by immunofluorescence and immunoprecipitation using anti-Flag antibodies. We reasoned that by tagging the receptor at the extracellular N-terminus, we would also be able to easily detect its expression at the plasma membrane. To maximize the expression efficiency, the Flag-hAT2 receptor sequence was cloned into a modified lentiviral vector that allows high levels of AT2 receptor expression, together with concomitant expression of the green fluorescent protein (GFP). GFP serves both as a positive control for infection efficiency, and as a valuable tool for the sensitive detection of the infected cells by FACS and immunofluorescence studies.

Lentiviral particles containing Flag-hAT2 were used to transduce D3H2LN cells. Transduction efficiency of stably infected D3H2LN-AT2 cells was evaluated by flow cytometry measuring GFP positive cells. More than 99% of the cells transduced with the AT2 lentiviral vector were positive for GFP expression, indicating that almost all infected cells had incorporated the construct (Figure 7 left).

**Figure 7:** Left: FACS analysis of GFP positive cells. Grey filled area represents parental D3H2LN cells (Ctrl) and white area represents infected D3H2LN-AT2 (AT2) cells. Right: Biochemical validation of Flag-AT2 expression by western blot in total cell lysate (upper panel) or in anti-Flag immunoprecipitation fraction (lower panel) revealed by an anti-Flag-HRP antibody.
We then performed western blotting and immunoprecipitation analyses using anti-Flag antibodies to evaluate whether D3H2LN-AT2 cells also expressed detectable amounts of the AT2 receptor. As shown in Figure 7 (right), anti-Flag-HRP antibodies revealed the expression of Flag-hAT2 receptor in D3H2LN-AT2, but not in parental D3H2LN cells. To investigate whether the ectopically expressed Flag-hAT2 receptor was able to bind AngII with high affinity at the cell surface of D3H2LN-AT2, competition binding experiments were performed on intact cells using tritium labeled AngII (³H-AngII) in the presence of increasing concentrations of unlabelled AngII. Results revealed a classical competition binding profile in D3H2LN-AT2 cells indicating the presence of a single population of receptors for AngII (Rodrigues-Ferreira et al., 2012b). In agreement, total binding of radiolabelled AngII to D3H2LN-AT2 cells could be displaced by 75% by adding an excess of the selective AT2 receptor antagonist PD123319, but not in the presence of an excess of the AT1 receptor antagonist losartan (Figure 8).

![Figure 8: Maximum binding obtained in the presence of the AT1 receptor antagonist Losartan (LOS) or AT2 receptor antagonist PD123319 (PD), as compared to control (CTRL).](image)

These results indicate that AT2 is the major AngII binding site in D3H2LN-AT2 cells and that ectopically expressed Flag-hAT2 receptors in D3H2LN breast cancer cells are correctly folded at the plasma membrane, and are able to bind the natural agonist.

We report the generation and characterization of a novel model of human invasive breast cancer cells (D3H2LN-AT2) that express high amounts of Flag-tagged human AT2 receptor at the plasma membrane. These cells also express GFP and luciferase, which makes them suitable for fluorescence and bioluminescence studies in vitro and in vivo. Of interest, D3H2LN-AT2 cells do not express detectable AT1 binding sites, as evaluated by radioligand binding assay, and overexpression of AT2 in breast cancer cells does not modulate levels of membrane AT1 receptors. This model allows the characterization of AT2 functions independently of those related to AT1 receptor activation, which is of great interest in the context of AT1 blockade by ARBs. The cellular model presented here offers a unique opportunity to evaluate the consequences of AT2 receptor activation and blockade on breast cancer proliferation, invasion and migration, as well as on tumor growth and metastasis formation. This model is of particular interest with the emergence of novel non-peptidic selective agonists of the AT2 receptor such as compound 21 (Wan et al., 2004; Unger & Dahlöf, 2010).
4 Conclusion

Data accumulated over the past two decades have highlighted important effects of the AngII vasoactive peptide in cancer, acting both on tumor cells and the host micro-environment. In this chapter, we summarize our recent studies indicating that AngII facilitates breast cancer metastasis by contributing to the cross-talk between cancer cells and the host stroma. While AT1 receptor blockade by ARBs is clearly beneficial in animal models, relevance to human cancer still remains to be evaluated and further studies should focus on selected populations of tumors overexpressing RAS components. Whether AT2 receptor activation may be beneficial or detrimental to cancer progression remains controversial; this question should benefit from a novel cellular model of breast cancer metastasis recently developed in our laboratory. Altogether, studies summarized here may translate into new therapeutic strategies against cancer, using blockers of the renin angiotensin system which are already used in the clinics as anti-hypertensive drugs with mild side effects.

References


