REVIEW

Endocrine-Related Cancer (2012) **19** R1–R19

The renin–angiotensin system in the breast and breast cancer

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Abstract

Much evidence now suggests that angiotensin II has roles in normal functions of the breast that may be altered or attenuated in cancer. Both angiotensin type 1 (AT1) and type 2 (AT2) receptors are present particularly in the secretory epithelium. Additionally, all the elements of a tissue renin–angiotensin system, angiotensinogen, prorenin and angiotensin-converting enzyme (ACE), are also present and distributed in different cell types in a manner suggesting a close relationship with sites of angiotensin II activity. These findings are consistent with the concept that stromal elements and myoepithelium are instrumental in maintaining normal epithelial structure and function. In disease, this system becomes disrupted, particularly in invasive carcinoma. Both AT1 and AT2 receptors are present in tumours and may be up-regulated in some. Experimentally, angiotensin II, acting via the AT1 receptor, increases tumour cell proliferation and angiogenesis, both these are inhibited by blocking its production or function. Epidemiological evidence on the effect of expression levels of ACE or the distribution of ACE or AT1 receptor variants in many types of cancer gives indirect support to these concepts. It is possible that there is a case for the therapeutic use of high doses of ACE inhibitors and AT1 receptor blockers in breast cancer, as there may be for AT2 receptor agonists, though this awaits full investigation. Attention is drawn to the possibility of blocking specific AT1-mediated intracellular signalling pathways, for example by AT1-directed antibodies, which exploit the possibility that the extracellular N-terminus of the AT1 receptor may have previously unsuspected signalling roles.

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Introduction

In the treatment of breast cancer, the various ways of removing the effects of oestrogen, first by surgery and then by the use of drugs, such as tamoxifen and the aromatase inhibitors, which block the actions of oestrogens or prevent their formation, have been hugely successful (Barnes *et al*. 2004, Howell & Dowsett 2004, Jones & Buzdar 2004). Indeed, the critical association between oestrogens, oestrogen receptor (ER) expression and cancer is so entrenched in relation to the breast that the terms 'receptor-positive' or 'receptor-negative' tumours are a widely accepted shorthand for ER alone (e.g. Yaren *et al*. (2007)).

This long-established connection between oestrogen and breast tumours preceded the more general realisation that the misdirection of normal growth regulatory processes underlies many cancers. Subversion of growth factor receptor structure and function is a well-understood mechanism of oncogene action (Ross *et al*. 2004, Bianco *et al*. 2005, Hynes & Lane 2005, Pal & Pegram 2005, Zhang *et al*. 2005). In the breast, mechanisms that regulate tissue and tumour growth are multifactorial, and many hormones, growth factors and intracellular signalling pathways are involved (Haagensen 1986, Dickson *et al*. 1992, Hansen & Bissell 2000, Tucker 2000, Pollard 2001, Goffin *et al*. 2002, Singer *et al*. 2003, Lamote *et al*. 2004, Nicolini *et al*. 2006, Cheng *et al*. 2008). Several of these have been targeted for drug development, particularly in tumours that either do not contain ER or are unresponsive to anti-oestrogens.

The systemic renin–angiotensin system (RAS) and the generation of angiotensin II (Fig. 1) has as major roles the regulation of blood pressure, and the adrenal secretion of aldosterone (Mulrow 1999, de Gasparo *et al*. 2000, Kaschina & Unger 2003). The actions of angiotensin II in the regulation of vasoconstriction have even been used to facilitate better accessibility of

1351–0088/12/019–R1
DOI: 10.1530/ERC-11-0335
Online version via http://www.endocrinology-journals.org

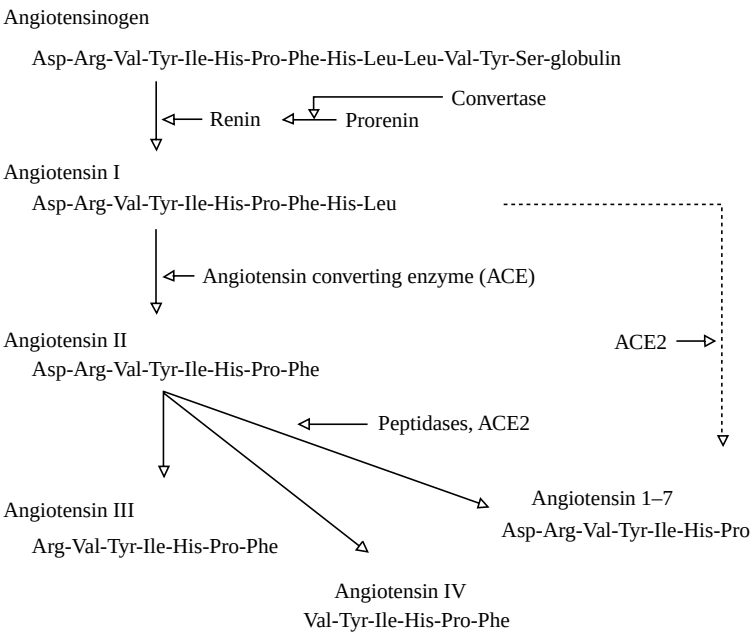

Figure 1 The renin–angiotensin system. In normal tissue, and in cancer, the major active hormone is usually considered to be angiotensin II, though angiotensins III and IV, and angiotensin 1–7 have also been implicated (see text).

chemotherapeutic drugs to tumours (Noguchi *et al*. 1988, Goldberg *et al*. 1990, Yamaue *et al*. 1990, Anderson *et al*. 1991). Angiotensins III and IV and angiotensin 1–7 may also be produced, and may act through the same two receptor types as angiotensin II, i.e. angiotensin type 1 and 2 (AT1 and AT2) receptors though with varying effectiveness (de Gasparo *et al*. 2000, Le *et al*. 2002). Angiotensin IV also acts through an insulin-regulated transmembrane enzyme designated as the AT4 receptor (Thomas & Mendelsohn 2003, Chai *et al*. 2004), and angiotensin 1–7 primarily through MasR, the product of the *Mas* oncogene (Neo *et al*. 2010).

Angiotensin receptors AT1 and AT2 are widespread, and they uniformly occur in secretory epithelia. In addition to its functions in the maintenance of blood pressure and hypertension, angiotensin II has also well-studied actions on electrolyte and water transport in the kidney, and elsewhere, including across other epithelial surfaces (Wong *et al*. 1990, Norris *et al*. 1991, Lees *et al*. 1993, Quan & Baum 1996, Wang & Giebisch 1996, Leung *et al*. 1997, Mahmood *et al*. 2002) where it also affects ciliary beat frequency (Saridogan *et al*. 1996*a*).

Importantly, in many tissues, including the cardiovascular system, adrenal cortex, kidney, liver and perhaps muscle and connective tissue, angiotensin II regulates cell turnover by promoting both cell proliferation and programmed cell death, perhaps predominantly through differential actions via the AT1 and AT2 receptors (Linz *et al*. 1989, Millan *et al*. 1989, Weber *et al*. 1991, Johnston 1992, Motz *et al*. 1992, Natarajan *et al*. 1992, Wolf & Neilson 1993, Booz & Baker 1995, Schorb *et al*. 1995, Quan & Baum 1996, Vinson & Ho 1998, Kaschina & Unger 2003, Carl-McGrath *et al*. 2007, Billet *et al*. 2008, Moreno & Bataller 2008, Kaschina *et al*. 2009).

Accordingly, it is appropriate to consider angiotensin II among the growth promoting and tissue modelling factors that may be subverted in cancer.

Angiotensin in cancer

Epidemiological evidence

Because angiotensin receptors are widely distributed in epithelia, their possible relevance to cancer, particularly carcinoma, is clear. It is now known that several different types of cancer express angiotensin receptors, and in particular, AT1 and AT2 receptors are expressed in breast cancer (Vinson *et al*. 1995, Marsigliante *et al*. 1996, Inwang *et al*. 1997, Kucerova *et al*. 1998, De Paepe *et al*. 2001, Fujimoto *et al*. 2001, Suganuma *et al*. 2005, Uemura *et al*. 2005*b*, Gonzalez-Zuloeta Ladd *et al*. 2007, Dolley-Hitze *et al*. 2010, George *et al*. 2010).

Indirect patient evidence supports the role in cancer (Deshayes & Nahmias 2005). Thus, the AT1 receptor has been reported to be up-regulated in various hyperplastic and cancer tissues (De Paepe *et al*. 2001), though not according to all reports (Dinh *et al*. 2002). Additionally, polymorphisms in angiotensinogen, AT1 receptors and angiotensin-converting enzyme (ACE) have been associated with breast cancer risk (Koh *et al*. 2003, 2005, Arima *et al*. 2006, Gonzalez-Zuloeta Ladd *et al*. 2007, Yaren *et al*. 2007, van der Knaap *et al*. 2008, Mendizabal-Ruiz *et al*. 2011). Such polymorphisms have recently been extensively reviewed and discussed (Xi *et al*. 2011). One widely studied polymorphism is a 278 bp *Alu* insertion/deletion (I/D) polymorphism in intron 16 of the *ACE* gene that apparently accounts for 50% of the variability in circulating ACE levels (Rigat *et al*. 1990). Though earlier studies suggested that this had no strong predictive value (Haiman *et al*. 2003), more recently the DD phenotype has been associated with increased risk and poor prognosis in breast cancer (Gonzalez-Zuloeta Ladd *et al*. 2005, Yaren *et al*. 2007, van der Knaap *et al*. 2008, Rosenthal & Gavras 2009). Interestingly, the same ACE polymorphism may also increase risk in benign prostatic hyperplasia (BHP) and prostate cancer, whereas the A1166C substitution in the AT1 receptor increases BHP risk alone (Sierra Diaz *et al*. 2009). Conversely, the C allele carriers have reduced breast cancer risk (Mendizabal-Ruiz *et al*. 2011). Three further AT1 receptor substitutions (A168G, C535T and T825A) have also been associated with reduced breast cancer risk (Koh *et al*. 2005).

More direct patient evidence has been elusive. The first report of the potential utility of ACE inhibitors in preventing cancer development was that of Lever *et al*. (1998) who surveyed data from patients receiving these medications for other reasons, but their findings were not confirmed by others (Meier *et al*. 2000, Li *et al*. 2003, Gonzalez-Perez *et al*. 2004, Ronquist *et al*. 2004, Fryzek *et al*. 2006, Rosenthal & Gavras 2009), nor, in similar patient studies was the use of angiotensin II antagonists in any way linked with the disease (Fryzek *et al*. 2006, Teo 2011). One report suggests that candesartan, an AT1 receptor blocker, when used at a dose similar to that used in patients for other reasons, has beneficial effects in prostate cancer, in that circulating prostate-specific antigen is reduced (Uemura *et al*. 2005*a*), though this study does not appear to have been repeated. Others have even suggested a modest increase in cancers of all types in patients receiving angiotensin receptor blockers (Sipahi *et al*. 2010), though this too has been contested (Volpe *et al*. 2011). The failure to make such associations may depend on variations in gene expression, and patients with low ACE expression phenotype may have poorer breast cancer outcomes than high ACE-expressing subjects (Yaren *et al*. 2007), though again there appear to be conflicting findings (Yaren *et al*. 2007, van der Knaap *et al*. 2008). Nevertheless, RAS inhibiting drugs may benefit high ACE-expressing patients but not others (van der Knaap *et al*. 2008). It is possible that anti-RAS drugs are more effective in combination. In patients with advanced pancreatic cancer receiving the nucleoside analogue gemcitabine, lower doses of losartan and other RAS inhibitors were effective in improving outcomes (Nakai *et al*. 2010). One way in which this might occur has been described by Diop-Frimpong *et al*. (2011). Drawing on previous work (Stylianopoulos *et al*. 2010) demonstrating the effect of collagen fibre networks, such as those that occur in connective tissue, on the diffusion of drugs, Diop-Frimpong *et al*. (2011) demonstrated that losartan blocks collagen I production by breast carcinoma-associated fibroblasts, potentially facilitating drug accessibility.

In contrast to the patient data, both ACE inhibitors and AT1 receptor antagonists are effective *in vitro*: they inhibit growth in many different types of tumour cells, including breast cancer cells (Chen *et al*. 1991, Reddy *et al*. 1995, Small *et al*. 1997, Rivera *et al*. 2001, Uemura *et al*. 2008, Inigo *et al*. 2009, Ino *et al*. 2011). In experimental animals *in vivo*, on the other hand, for example in xenografts of SKOV-3 ovarian tumour in mice or of C6 rat glioma cell tumours in rats, much higher doses of candesartan and losartan, respectively, were needed to demonstrate tumour regression than those generally used in patients (Rivera *et al*. 2001, Suganuma *et al*. 2005). It is perhaps because high doses are required when these drugs alone are used that the epidemiological studies on patients receiving antihypertensive treatment for cardiovascular disease show no benefit in incidence of cancer.

The discovery of the zinc metalloprotease ACE2 introduced a new aspect of angiotensin signalling (Donoghue *et al*. 2000). ACE2 preferentially hydrolyses angiotensin I to angiotensin 1–9, and angiotensin II to angiotensin 1–7 (Fleming *et al*. 2006; see Fig. 1). Angiotensin 1–7 has properties different from those of angiotensin II and may oppose angiotensin II functions. In particular, it is antiproliferative and reduces fibrosis in breast tumours, and angiogenesis in lung tumours (Menon *et al*. 2007, Soto-Pantoja *et al*. 2009, Cook *et al*. 2010, Gallagher *et al*. 2011), and has been used with benefit in phase I patient trials (Petty *et al*. 2009).

Angiogenesis

Additionally, although both ACE inhibitors and AT1 receptor antagonists may be effective on animal tumours *in vivo*, the results are more ambiguous than *in vitro*, and at least in part could be due to their anti-angiogenic actions (Volpert *et al*. 1996, Fujimoto *et al*. 2001, Fujita *et al*. 2002, 2005, Yoshiji *et al*. 2004, Kosaka *et al*. 2007, De Paepe 2009, Miyajima *et al*. 2009). The important part played by angiogenesis in the development of cancer has frequently been emphasised. There is considerable evidence that cancer growth and spread is angiogenesis dependent, tumour cells themselves can produce angiogenic factors and inhibition of angiogenesis can limit tumour growth (Weidner 2004, Sharma *et al*. 2005, Clapp *et al*. 2009), including in the breast (Heffelfinger 2007, Groves *et al*. 2011). It is difficult to assess the importance of this process in relation to the direct effects of angiotensin II on tumour growth and cell proliferation. Certainly, angiotensin II is involved in angiogenesis. Several *in vitro* studies have shown that vascular endothelial growth factor (VEGF) expression is stimulated by angiotensin II or inhibited by ACE or angiotensin blockers in tumour cells, including squamous cell (Yasumatsu *et al*. 2004) ovarian (Suganuma *et al*. 2005), prostate (Kosaka *et al*. 2007) and rat pituitary tumour cells (Ptasinska-Wnuk *et al*. 2007). Similar conclusions have been reached from *in vivo* studies. Thus, AT1 receptor expression and angiogenesis were correlated in ovarian tumours and in astrocytomas (Ino *et al*. 2006, Arrieta *et al*. 2008). Angiotensin II supported VEGF production and angiogenesis in xenografts of ovarian cancer cells (Suganuma *et al*. 2005) and AT1 receptor blockade inhibited both of these actions in xenografts of ovarian and gastric tumour cells (Suganuma *et al*. 2005, Huang *et al*. 2008). AT1 receptor blockade also inhibited angiogenesis in murine Lewis lung tumours (Imai *et al*. 2007) and through this means enhanced the effectiveness of radiation treatment in murine melanoma (Ohnuma *et al*. 2009, Otake *et al*. 2009) and in murine renal tumours (Miyajima *et al*. 2009). However, in *in vivo* studies in which S-180 murine sarcoma cell tumours were developed in AT1a receptor null mice, angiogenesis, along with VEGF expression, was both reduced and partially refractory to AT1 receptor blockade when compared with normal tissue. Hence, host angiotensin II activity is instrumental in supporting angiogenesis in host stromal cells in addition to any effect it has on the cancer cells themselves (Fujita *et al*. 2002, 2005, Imai *et al*. 2007).

Actions of angiotensin II on breast cancer cells

As in other tissues, angiotensin II acts on the AT1 receptor to promote cell proliferation in breast cancer cells (Muscella *et al*. 2002). The AT1-mediated signalling involves the protein kinase C (PKC, zeta and iota)/Ca^{2+}/inositol trisphosphate (IP3) pathways, and also extracellular signal-related kinase (ERK) activation (Greco *et al*. 2002*a*,*b*, 2003, Muscella *et al*. 2003, 2005). Angiotensin II also activates Na^{+}/K^{+} ATPase (Muscella *et al*. 2002, 2005).

Angiotensin II has further possible roles involved in cell adhesion and invasion. Specifically, again acting via the AT1 receptor, it inhibits expression of integrin subtypes $\alpha 3$ and $\beta 1$ and also binding to and invasion through components of the extracellular matrix. In contrast to its actions on proliferation, these effects of angiotensin II may be regarded as potentially beneficial (Puddefoot *et al*. 2006). Consequently, RAS blockade may not always be entirely an appropriate therapy in cancer, perhaps also explaining its apparent lack of benefit in patients. Conflicting evidence on the efficacy of anti-RAS treatment has also been discussed in the context of cardiovascular disease (Magy *et al*. 2005).

Angiotensin II, ER and growth factors

Because of the well-known importance of ER and growth factors and their interrelationship in breast cancer, it is relevant to examine their interactions with the RAS. The interrelationship between the RAS and ER is complex. Depending on the tissue, oestrogen has varyingly been reported to down-regulate AT1 receptors, in rat pituitary and hypothalamus (Seltzer *et al*. 1992, Kisley *et al*. 1999) and dog kidney, myocardium, liver and adrenal (Owonikoko *et al*. 2004; see also Fischer *et al*. (2002), but to up-regulate them at other sites, including rat kidney (Baiardi *et al*. 2005) and sheep uterine artery endothelium (Sullivan *et al*. 2005). Consistent with RAS up-regulation by oestrogen, intensity of AT1 receptor staining is most intense in the periovulatory period in human fallopian tube and uterine epithelia (Saridogan *et al*. 1996*a*,*b*) and the AT2 receptor is also high during the proliferative phase in human myometrium (Pucell *et al*. 1987, Mancina *et al*. 1996), as it is in the rat ovary (Pucell *et al*. 1987, Mancina *et al*. 1996). However, such changes do not necessarily reflect the functions of the RAS as a whole and other RAS components may respond independently, for example renin and ACE activities are reduced in various tissues by oestrogen (Fischer

et al. 2002), though angiotensinogen is increased (Gordon *et al*. 1992, Klett *et al*. 1993, Fischer *et al*. 2002). Oestrogen stimulates plasma renin activity (PRA) and RAS activity in sheep (Magness *et al*. 1993), though in women high PRA is associated with the luteal phase (Sealey *et al*. 1994, Chapman *et al*. 1997, Chidambaram *et al*. 2002). In breast duct cancer cells, angiotensin II treatment *in vitro* reduces ER and increases PR (Small *et al*. 1997).

The relationship between ER and AT1 is thus incompletely resolved. It may be that angiotensin II signalling is more significant in ER-negative breast tumours (Herr *et al*. 2008), in which a role has been postulated for AT1 receptors in the non-genomic response to oestrogen (Lim *et al*. 2006), though there is a subset of ER-positive (and ERBB2-negative) tumours that shows marked overexpression of AT1 receptors (Rhodes *et al*. 2009). This appears to contrast with vascular smooth muscle cells in which the ER blocker raloxifene (in the presence of oestradiol) inhibited angiotensin II-stimulated proliferation (Wang *et al*. 2007).

Angiotensin receptor signalling also interacts with growth factors in breast cancer cells. Thus, ERKs are activated by angiotensin II directly via PKC and indirectly via epidermal growth factor receptor (EGFR)-mediated phosphatidylinositol-3 kinase/serine-threonine protein kinases (PI3-kinase/Akt/mTOR/p70S6K1) signalling pathways (Greco *et al*. 2002*b*, 2003, Chiu *et al*. 2005, Han *et al*. 2007). In more detail, the AT1 receptor, linked to Gq/11, signals both by Ca^{2+}/IP3 and by diacylglycerol-linked events, and also by tyrosine kinase activation, including via EGFR-linked PI3-kinase and Akt signalling, with subsequent activation of ERK1 and ERK2 (Greco *et al*. 2003, Shah *et al*. 2004, Han *et al*. 2007, Kim *et al*. 2009). Such EGFR activation is at least in part mediated via angiotensin II-stimulated metalloproteinase activity (Liebmann 2011, Smith *et al*. 2011; see below). There is extensive crosstalk with other receptors, including insulin and growth factor signalling pathways (Shah *et al*. 2006, Redondo *et al*. 2007, Escano *et al*. 2008, Muscogiuri *et al*. 2008, Olivares-Reyes *et al*. 2009, Arellano-Plancarte *et al*. 2010). Conversely, the AT2 receptor is thought to activate phosphatase activity and block AT1 receptor-mediated intracellular signalling events, including phospholipase activation and the phosphorylation of signalling components. These pathways have been extensively discussed elsewhere (de Gasparo *et al*. 2000, de Gasparo 2002, Kaschina & Unger 2003, Deshayes & Nahmias 2005, Louis *et al*. 2010, Zhao *et al*. 2010).

The local RAS in the breast

Tissue remodelling and matrix metalloproteinases

In the normal cycle of events in the breast, the ductal system, which begins to develop in puberty, stabilises in the adult but proliferates extensively during pregnancy to enable production of a high level of secretory activity during lactation. After lactation ceases, the ducts undergo apoptotic involution (Fig. 2; Wiseman & Werb 2002, Boutinaud *et al*. 2004, Green & Streuli 2004). Because of the relationship between the stage of the cycle and the incidence of metaplastic change, Villadsen (2005) and Russo *et al*. (2006) postulated that there are at least two types, or a hierarchy, of stem cells. The whole process does not involve the ducts alone, and stromal cells and their products, including growth factors and integrins, are also strongly implicated (Chrenek *et al*. 2001, Pollard 2001, Wiseman & Werb 2002, Barcellos-Hoff & Medina 2005, Zechmann *et al*. 2007). Because of its sites of origin, described below, and the location of its receptors, it is appropriate to consider angiotensin II among these factors and that, perhaps acting through both receptor types, it is instrumental in both proliferative and apoptotic phases of the normal cycle.

The breast cycle (Fig. 2) and its sequence of development and resorption reflect, among other things, synthesis and proteolysis of proteins of the extracellular matrix and the basement membrane, such as collagen, in a balanced manner (Morini *et al*. 2000, Sun *et al*. 2006). Hydrolysis of extracellular matrix proteins is catalysed at the basement membrane by the zinc-dependent matrix metalloproteinases (MMPs) present in stromal and secretory cells of normal and diseased tissue (Werb *et al*. 1996, Lebeau *et al*. 1999, Bodey *et al*. 2001). Accordingly, these enzymes are also involved in the invasive process (Ambili *et al*. 1998, Rudolph-Owen & Matrisian 1998)) and high MMP levels are associated with poor outcomes (Duffy *et al*. 2000). Because epithelial cells depend on the functions of the basement membrane and their constituents, protein breakdown contributes to epithelial dysfunction. In many tissues, angiotensin II plays a key part in such tissue remodelling, and it affects both MMP activity and collagen synthesis (Gack *et al*. 1994, Ford *et al*. 1999, Dzau 2001, Galis & Khatri 2002, Shah *et al*. 2004, Chiu *et al*. 2005, Yang *et al*. 2005, Karakiulakis *et al*. 2007, Kim *et al*. 2007). As MMPs are located in myoepithelial cells, like prorenin (see below), it is clear that locally produced angiotensin II may have such a role in the breast.

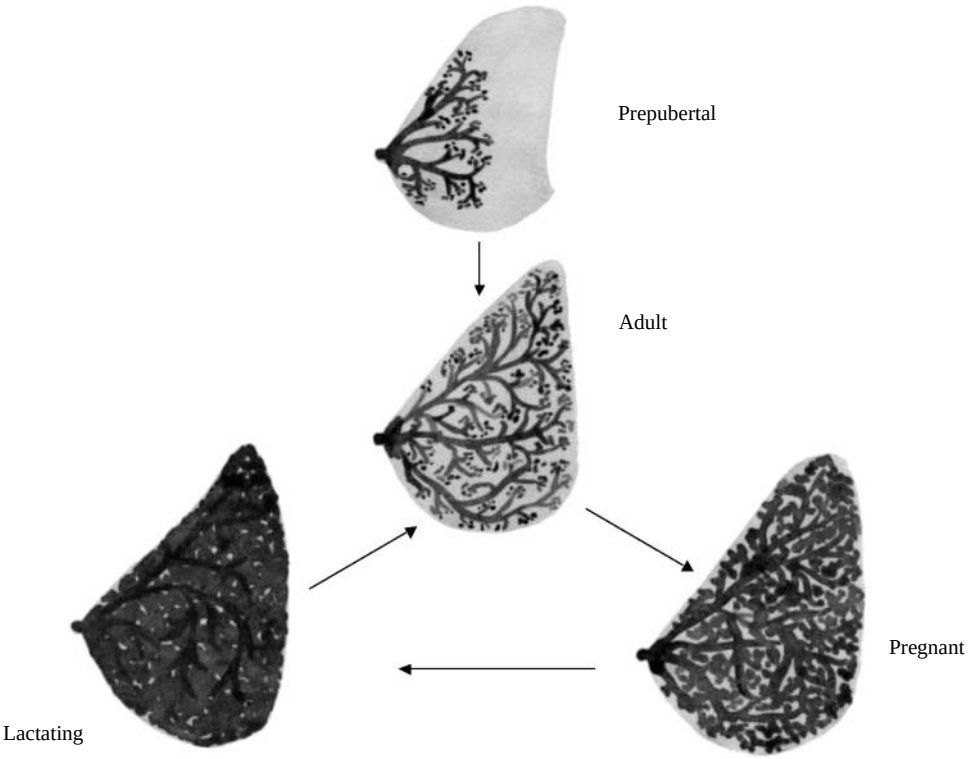

Figure 2 The breast cycle: note particularly extensive duct and gland development during pregnancy and lactation, followed by apoptotic involution when lactation ceases (cf. Wiseman & Werb (2002), Boutinaud *et al.* (2004) and Green & Streuli (2004)). Drawing by Bronwen Vinson. Reproduced from Vinson *et al.* (2007) with kind permission from Springer Science and Business Media.

All the functions of angiotensin II described so far acquire an additional perspective in the light of our understanding of the tissue-based RAS. This is because the significant factor in both normal function and in disease may not be the angiotensin II in the blood, but that which is locally produced, within the tissue.

That many organ systems contain discrete RASs has been well understood for some time: such localised systems have been described in many tissues, including the kidney, liver and adrenal (Phillips *et al*. 1993, Gupta *et al*. 1995, Zimmerman & Dunham 1997, Mulrow 1998, Vinson & Ho 1998, Neo *et al*. 2010), brain, pituitary and reproductive system (Hagemann *et al*. 1994, Ganong 1995, Nielsen *et al*. 1995, Vinson *et al*. 1997, Vila-Porcile & Corvol 1998, McKinley *et al*. 2003, Li *et al*. 2004, Dean *et al*. 2006), pancreas (Tahmasebi *et al*. 1999, Leung & Carlsson 2001, 2005, Lau & Leung 2011), lung (Feng *et al*. 2010) and heart (Okura *et al*. 1992, Bader 2002, Dean *et al*. 2006).

These tissue RASs may be perturbed in cancer. For example, in a mouse model of colorectal cancer metastases, ACE expression was increased (though ACE2 was decreased) in tumour-bearing livers, as well as in the tumours themselves. Tumour volume was reduced by the ACE inhibitor captopril. Liver angiotensinogen was unaffected by the tumours and decreased in captopril treatment, whereas ACE in both liver and tumour tissues was further increased. AT1 receptor expression was elevated by tumour induction and reduced by captopril: MasR, the putative receptor for angiotensin 1–7, was increased by captopril (Neo *et al*. 2010). The possibility that angiotensin III may have a specific role has also been suggested in studies on rats with *N*-methyl nitrosourea-induced breast tumours, in which soluble and membrane-bound aspartyl and glutamyl aminopeptidase activities are increased whereas soluble aminopeptidase N and B activities are decreased, both of which potentially increase angiotensin III production, with reduced angiotensins II and IV (del Pilar Carrera *et al*. 2010).

Localisation of RAS components

In studies on the sites of (pro)renin gene transcription, (pro)renin mRNA was found in most of the breast samples examined, invariably in close proximity to the ductal epithelium but not within the epithelium itself. Prorenin mRNA was abundant in the stroma immediately adjacent to the ducts, in myoepithelial cells in

normal tissue and in early cancer stages but tended to be lost from both sites in more advanced disease, paralleling the partial loss of AT1 receptors (Tahmasebi *et al*. 1998; Fig. 3). Confirmation of these findings, and evidence for other RAS components, was obtained using quantitative RT-PCR and the presence of RNA coding for angiotensinogen, prorenin, ACE and both AT1 and AT2 receptors was demonstrated in normal and diseased breast tissues, supporting the hypothesis that a tissue RAS is present in the breast. As in the *in situ* hybridisation data (Tahmasebi *et al*. 1998), there was significantly less (pro)renin mRNA in carcinoma than in normal tissue, and indeed, ACE and angiotensinogen mRNAs were also reduced in carcinoma compared with normal tissue (Tahmasebi *et al*. 2006). This reflects the earlier finding that AT1 receptors are reduced in advanced tumours.

mRNA coding for prorenin was distributed between myoepithelium and, most extensively in fibroblasts and connective tissue close to the ducts. Conversely, prorenin protein itself was mostly present in myoepithelial cells and absent from the connective tissue. Of course, this distribution could represent differences in mRNA translation between the two cell types, but a rather different picture emerges in cancer. Although the distribution of prorenin and its mRNA in ductal and in lobular carcinoma *in situ* was similar to normal, in more advanced conditions, as the myoepithelium was lost, prorenin protein was only sparsely present in the epithelium, but it was located in fibroblasts. Here, though always present, it appeared to decrease in amount as malignancy advanced (Tahmasebi *et al*. 1998; Fig. 3). Two possibilities present themselves, one is that the prorenin mRNA that is ever present in breast fibroblasts is translated only in cancer. Alternatively, it is always translated, even in normal tissue, but the prorenin formed is normally transported elsewhere, to the myoepithelium or to the epithelium (though this latter is not frequently observed). Whatever the explanation, it is evident that the functions of the breast RAS may be greatly perturbed in cancer. Similar processes may well occur in other types of cancer, for example in the pancreas (Lau & Leung 2011).

There is a difficulty in testing this concept of an entirely localised RAS in any tissue – what can *in situ*

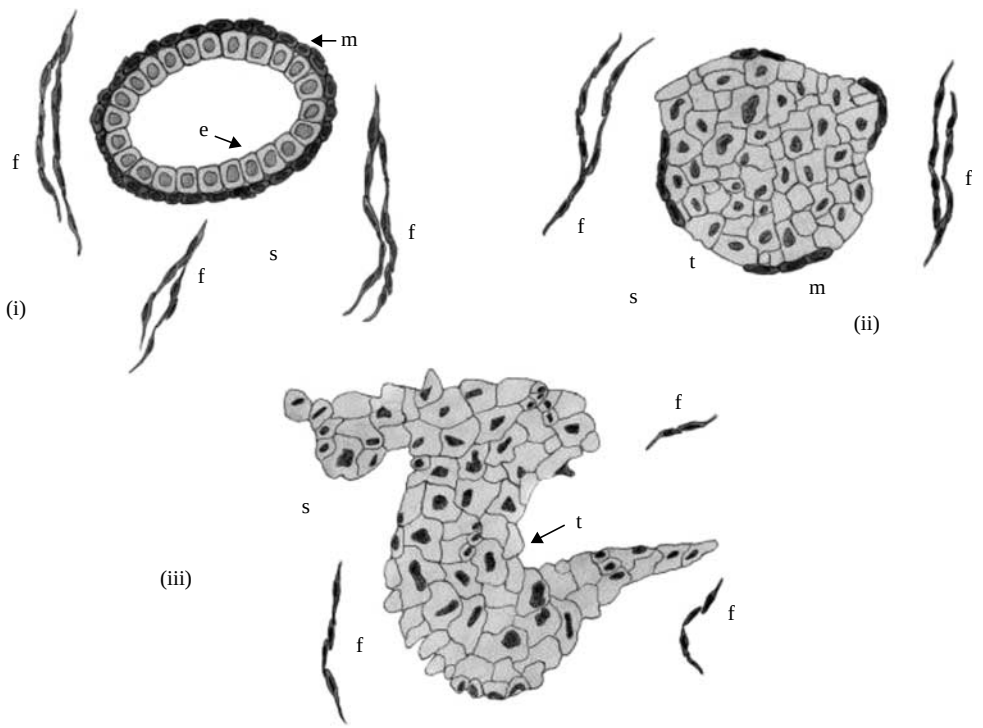

Figure 3 Both angiotensin II receptors and ACE are present in epithelial cells and in cancer cells. Sites of (pro)renin mRNA transcription (dark shading) are shown in (i) normal breast ducts, (ii) intraductal carcinoma *in situ* and (iii) invasive carcinoma. The myoepithelial source of (pro)renin transcription is lost as cancer develops. As in normal tissue this lies in close proximity to the epithelium, the configuration strongly suggests that angiotensin II can be produced at its epithelial site of action. This tightly linked system is lost in cancer, suggesting that the AT1 and AT2 receptor-containing carcinoma eventually becomes deprived of its source of angiotensin II. Adapted from Tahmasebi *et al.* (1998, 2006). e, epithelium; m, myoepithelium; f, fibroblast; t, tumour; s, stroma. Drawing by Bronwen Vinson. Reproduced from Vinson *et al.* (2007) with kind permission from Springer Science and Business Media.

hybridisation or immunocytochemistry reveal about the state of activation of any of the components? Prorenin provides a key example here: the methods used in the papers cited above do not distinguish between the cleaved or activated forms. The primary mechanism for prorenin activation has been considered to be through cleavage by prohormone convertases (Benjannet *et al*. 1992), which may be highly expressed in cancer, including breast tumours, and this is associated with greater oestrogen dependency (Cheng *et al*. 1997, 2001). Of course, prohormone convertases may be involved in tumorigenic processes that do not involve either prorenin or angiotensin II (Siegfried *et al*. 2003, Scamuffa *et al*. 2008). Alternatively, the discovery of a specific prorenin receptor that binds prorenin and activates intracellular signalling pathways while at the same time activating its enzymic activity in the absence of cleavage opens new possibilities (Nguyen & Contrepas 2008, Nguyen 2011). These and related questions of activation of the breast RAS will need to be addressed in future.

Like the AT1 receptor, ACE is present in the secretory epithelium of the normal breast and also in diseased breast tissue (Tahmasebi *et al*. 2006), suggesting that angiotensin II may be formed directly in the cells on which it acts. However, in cancer, the overall loss and changes in the distribution of prorenin described above may mean that as the disease progresses, neither substrate for the enzyme nor ligand for the receptor remains available. Malignancy is thus correlated with the deregulation of RAS function.

These findings and this proposed mechanism have considerable resonance with other authors' concepts of the role of the stromal and myoepithelial interaction with the secretory epithelium and with cancer. Kalluri & Weinberg (2009) have proposed that one class of epithelial–mesenchymal transformations (EMTs), which they call type 3 EMT (to distinguish from implantation and wound-healing forms, types 1 and 2), is characteristic of the transformation of polarised and highly differentiated epithelial cells into mesenchymal cells. Such cells secrete extracellular matrix components and are highly mobile and invasive, though there is a reverse transformation (MET) at sites of metastatic colonisation (Kalluri 2009, Kalluri & Weinberg 2009). EMTs, of whatever type, are initiated as the epithelial cells that invade through the basement membrane. A number of factors are thought to be involved, including insulin-like growth factor, transforming growth factor β, platelet-derived growth factor, integrins and the signalling pathways they evoke, with all of which AT1 and AT2 receptors may interact.

So what retains epithelia in their normal functional state? Here, the focus is on myoepithelial cells. These too are now known to be important in cancer progression. First rather overlooked, as they only infrequently produce tumours, they are now thought to be natural tumour suppressors because of their role in maintaining epithelial cell polarity and cell cycle progression and inhibiting cell migration and invasion (Lakhani & O'Hare 2001, Polyak & Hu 2005). This has been postulated to be due to the secretion of proteinase and angiogenic inhibitors (Barsky & Karlin 2005). Additionally, as well as inflammatory cells, fibroblasts have also been thought to be the source of factors affecting tumour development (Tlsty & Coussens 2006). These concepts received direct experimental support when MCF7 breast cancer cells were grown *in vitro* in an environment of extracellular matrices of type 1 collagen, or reconstituted basement membrane proteins, together with human fibroblasts. Surviving cells in the presence of collagen organised into clusters, while the further addition of basement membrane proteins induced MCF7 cell polarisation and the formation of lumina, and the presence of fibroblasts induced the formation of elongated structures (Krause *et al*. 2010). Furthermore, differences in gene expression between core biopsies of breast tumours with varying degrees of stromal content were taken to indicate the influence of the stroma (Cleator *et al*. 2006). So the stromal and myoepithelial localisation of RAS components strongly suggests that angiotensin II may have an important, possibly crucial role in this context.

Implications for therapy

One way in which beneficial advances have been made despite initially discouraging data has been to identify subsets of patients who may benefit where others may not. A key example here is in the identification of a subgroup of breast tumours that overexpress the ERBB2 (HER2) tyrosine kinase receptor and are thus sensitive to the monoclonal antibody trastuzumab (Nahta *et al*. 2006, Nahta & Esteva 2007). More and more it becomes clear that patient profiling in this way yields benefit, and this may well be true for the RAS in breast. It is known that a significant subset of breast tumours overexpress the AT1 receptor, and although there are various mechanisms for this, one way may be that AT1 receptor expression is directly controlled by ER, leading to a subset of ER-positive, ERBB2-negative tumours that overexpress AT1 receptor (Ateeq *et al*. 2009, Rhodes *et al*. 2009).

Because of the possibility of both beneficial and disadvantageous effects of AT1 receptor inhibition, it is worth exploring whether means exist to selectively inhibit individual signalling events. This possibility has been discussed in a recent review, in which the signalling roles of individual domains of the receptor were explored, though the possibility that the extracellular N-terminal domain might be involved was not considered (Aplin *et al*. 2009). There may, however, be good reasons to consider the N-terminus in this light because there appear to be ligand binding or signalling determinants in this region (Hjorth *et al*. 1994, Oliveira *et al*. 2007), and a particular role for Arg23 has been identified (Santos *et al*. 2004).

In this respect, the activity of monoclonal antibody 6313/G2 directed against a sequence in the N-terminal domain of the AT1 receptor has provided further information, as it appears to enhance some signalling pathways while inhibiting others. Though not affecting angiotensin II binding to the receptor (Barker *et al*. 1993) the antibody directly stimulates aldosterone secretion via the IP3 pathway in rat glomerulosa cells *in vitro*, though it also blocks PKC activation, apparently by interrupting receptor internalization (Kapas *et al*. 1994, Vinson *et al*. 1994). In other studies on rat vascular smooth muscle cells, basal and angiotensin-stimulated tritiated thymidine incorporation into rat arterial smooth muscle cells was inhibited by 6313/G2, inducing a transient increase in intracellular calcium in cultured rat arterial smooth muscle cells, but reducing PKC and MAPK signal transduction (Xiao *et al*. 2008). A short-chain fragment variable of this antibody also blocked AT1 receptor-mediated caspase-3/7 inhibition in breast cancer cells and dose dependently gave significant tumour regression in breast cell xenografts *in vivo*. These data support the view that differential inhibition of angiotensin II-stimulated signalling pathways may be achieved in this way (Redondo-Muller *et al*. 2008).

Conclusions

There can now be no doubt that the RAS is involved both in the normal physiology (and perhaps development) of the breast and in the ontogeny of breast carcinoma, and possibly other cancers. There is strong evidence that blocking the pathways of AT1 receptor-mediated angiotensin signalling can have beneficial effects. However, in view of the multiple actions of angiotensin II on breast cancer cells, some of which themselves may be considered to be beneficial, this is not without potential cost. In identifying the AT1 receptor as a new target for breast cancer therapy, development of agents that more precisely discriminate between individual signalling pathways is an important goal. The monoclonal antibody 6313/G2 and its recombinant counterpart demonstrate that this kind of approach may be entirely feasible.

Declaration of interest

Queen Mary, University of London owns IP related to antibodies against the AT1 receptor, currently licensed to Oncobiopharm Ltd.

Funding

This review did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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Received in final form 10 December 2011
Accepted 15 December 2011
Made available online as an Accepted Preprint
16 December 2011