REVIEW

Mechanisms linking the renin-angiotensin system, obesity, and breast cancer

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Abstract

Obesity is a complex disease and a global epidemic. It is a risk factor for other chronic diseases including breast cancer, especially in women after menopause. Diverse etiologies underlie the relationship between obesity and breast cancer. Adipose tissue is in part responsible for these interactions. In obesity, adipose tissue undergoes several metabolic dysregulations resulting in the secretion of many pro-inflammatory cytokines, growth factors, and hormones which in turn, can promote tumor microenvironment (TME) formation and cancer progression within the breast tissue. Angiotensin II (Ang II) is a well-known hypertensive hormone produced systemically and locally by the renin-angiotensin system (RAS). Activation of this system in obesity is a potential contributor to local and systemic inflammation in breast adipose tissue. Ang II actions are primarily mediated through binding to its two receptors, type 1 (AT1R) and type 2 (AT2R). RAS inhibitors include angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARBs) which are currently prescribed as safe antihypertensive therapies. Recent studies have explored the potential use of ACE-I and ARBs in breast cancer patients as anti-tumor agents. Therefore, it is vital to understand the role of RAS in breast cancer and identify mechanisms of Ang II and RAS inhibitors in the TME and in obesity and breast cancer crosstalk. In this review, we performed a detailed analysis and discussed mechanisms of Ang II-AT1R interactions in breast cancer with emphasis on obesity-associated breast cancer. We further summarized recent *in vitro*, *in vivo* and human studies that used ACE-I/ARB interventions to improve breast cancer outcomes.

Key Words

- obesity
- breast cancer
- renin-angiotensin system
- adipose tissue inflammation

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Introduction

Breast cancer (BC) is the most common type of cancer among women worldwide (George *et al.* 2013) and the second leading cause of cancer deaths in US women (Suganuma *et al.* 2005). Additionally, one in eight US women have a lifetime risk of developing BC, with approximately 40,920 deaths due to breast cancer in 2018 (Suganuma *et al.* 2005). Obesity is a complex health condition and contributes to 20% of all cancer-related mortality (Pierobon & Frankenfeld 2013, Simpson & Brown 2013). Evidence shows that excessive weight gain, especially in women after menopause, doubles the incidence of BC (DeSantis *et al.* 2014). Interestingly, raising BMI by 5 units increases the risk of receptor-positive BC by 33% in women after menopause (Suzuki *et al.* 2009).

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However, the underlying mechanisms linking obesity and BC are still unclear and require further investigation to identify novel mediators of this interaction, which could pave the way for future BC therapies, especially for women suffering from obesity. In addition to adipocyte-secreted hormones, growth factors and cytokines, another potential contributor to the development of the tumor microenvironment, in part through increased adipocyte secretory activity, is the renin-angiotensin system (RAS). Our laboratory and others have reported that angiotensin II (Ang II), the major bioactive peptide hormone of the RAS pathway increases fatty acid synthesis and inflammation in adipocytes (Kalupahana *et al.* 2012). Thus, RAS, and specifically Ang II, may potentially contribute to the negative metabolic effects of obesity on BC (Vinson *et al.* 2012). RAS inhibitors (angiotensin-converting enzyme inhibitor, ACE-I and angiotensin type I receptor blocker, ARBs), clinically used to treat hypertension, have been proposed as prospective therapeutic agents in managing obesity-associated BC (Pituskin *et al.* 2011). In this review, we dissect the possible mechanism(s) of RAS in obesity and BC crosstalk.

Key modulators of obesity and BC interactions

Human breast tissue is primarily composed of adipose, glandular and connective tissues. Thus, adipose tissue in the breast has a potentially major role in determining BC risk (Pettersson & Tamimi 2012). In obesity, adipose tissue expansion is associated with increased secretion of several pro-inflammatory cytokines, which in turn induce local as well as systemic inflammation (Saely *et al.* 2012). This may subsequently increase BC risk by promoting a toxic microenvironment favorable to cancer cell growth and metastasis.

Various mechanisms have been proposed (Himbert *et al.* 2017) such as (1) increased estrogen production in breast adipocytes due to enhanced aromatase activity, leading to estrogen receptor-positive (ER+) BC development (Bulun *et al.* 2012); (2) secretion of pro-inflammatory adipo-cytokines such as interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and monocyte chemoattractant protein-1 (MCP-1), by hypertrophic obese adipocytes resulting in the development of malignant phenotypes (Lorincz & Sukumar 2006); (3) increased levels of insulin and insulin-like growth factor-1 (IGF-1) in obesity, which are the main influencers behind developing abnormal mitogenic capabilities in epithelial cells (Stephenson & Rose 2003). Below, we briefly discuss some key modulators of obesity and BC interactions.

Role of inflammatory adipo-cytokines

Inflammatory responses are found to contribute to 15–20% of all cancer-related deaths (Balkwill & Mantovani 2001, Balkwill *et al.* 2005). Increased adipose hypertrophy due to obesity is positively correlated with recruitment of inflammatory immune cells to adipose tissue (Monteiro & Azevedo 2010). Metabolic alterations due to obesity facilitate secretion of many pro-inflammatory cytokines like TNFα and IL-6 via Toll-like receptor (TLR)-mediated signaling and nuclear factor kappa B (NF-κB) activation (Zahid *et al.* 2016). Increased TLR and NF-κB interactions have been associated with increasing cancer stemness in BC (Rinkenbaugh & Baldwin 2016). Several cytokines implicated in these inflammatory conditions are discussed below.

IL-6 secreted by adipose-derived stromal cells promote BC cell migration and invasion via a variety of signaling pathways including p38 (mitogen-activated protein kinase kinase, or MAPK), janus kinase (JAK2), and signal transducer and activator of transcription 3 (STAT3) to control cell metabolism and proliferation. IL-6 further promotes prostaglandin E2 (PGE2) production and cyclooxygenase 2 (COX 2) generation in BC cells, thus upregulating cancer cell proliferation, survival and angiogenesis (Walter *et al.* 2009, Himbert *et al.* 2017).

Interleukin (IL)-8 is another major adipo-cytokine produced mainly by macrophages and monocytes where it activates similar inflammatory pathways like IL-6 (Baggiolini *et al.* 1995). Furthermore, IL-8 is involved in chemoattraction and leukocyte recruitment in adipocytes (Himbert *et al.* 2017); thus, it has a direct role in angiogenesis via increased endothelial cell proliferation and survival, and cancer metastasis via induced matrix metalloproteinase expression (Todorović-Raković & Milovanović 2013). Though IL-8 is a marker of ER– BC, it could enhance invasiveness of both ER– and ER+ BC (Todorović-Raković & Milovanović 2013) as it is associated with other pro-inflammatory cytokines like interleukin-32 (IL-32) to induce extracellular matrix (ECM) remodeling and metastases of *in vitro* cancer cells (Catalán *et al.* 2017).

MCP-1, also known as chemokine ligand 2 (CCL2), actively recruits circulating monocytes to the tumor site, which are later differentiated into tumor-associated macrophages (TAM) thereby promoting tumor microenvironment (TME) (Correa *et al.* 2017).

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This, in turn, increases infiltration of immune-suppressive myeloid-derived suppressor cells (MDSCs) and is associated with poor tumor prognosis (Picon-Ruiz *et al.* 2017).

TNFα, a major pro-inflammatory cytokine secreted by obese adipocyte-derived macrophages, can have both growth-promoting and -inhibiting effects on BC cells. In addition, TNFα modulates cancer cell proliferation through activating MAPK 1 and 2 and PI3K/AKT pathways and increases cancer cell sensitivity to chemotherapy and radiotherapy by driving cells out of the dormant G0/G1 phase of growth cycle (Correa *et al.* 2017).

Vascular endothelial growth factor (VEGF) is another well-studied angiogenic growth factor secreted largely by visceral adipose tissue (Fain *et al.* 2004) and expressed by various human cancers including BC (Goel & Mercurio 2013). Increased IL-6 production by obese adipocytes increased *in vivo* VEGF abundance in TME and reduced therapeutic VEGF resistance in obese BC patients (Incio *et al.* 2018). This indicates close connection between VEGF-mediated angiogenesis and obesity-associated inflammation to modulate favorable breast TME development.

Increased secretion and production of cytokines (IL-6, TNFα) and PGE2 by tissues lead to increased transcription of the cytochrome P450 19 aromatase (*CYP19*) gene encoding aromatase (enzyme for accelerated estrogen synthesis by local adipose tissues). In addition, macrophages upregulate aromatase expression via specific mRNA sequences found only in breast tissue, making women with obesity more susceptible to estrogen receptor-positive (ER+) BC (Iyengar *et al.* 2013). This specific type of macrophage crowning is found in ~75% of obese women, indicating inflammation as a mechanistic target linking obesity and ER+ BC (Iyengar *et al.* 2013).

Furthermore, obesity alters the immune responses against tumor cells. Excessive weight gain modifies the innate immune response, promoting cancer initiation, growth and development by reducing cytotoxicity of natural killer (NK) cells and antigen presentation by dendritic cells (DC) (Himbert *et al.* 2017). As multiple studies reported the role of inflammatory adipo-cytokines in TME formation and breast tumor progression especially under obese condition, dissecting their possible mechanism of action is critical in improving poor cancer outcomes in pre- and post-therapy. Below we summarized the functions of these major adipo-cytokines in BC progression (Fig. 1).

Higher levels of leptin secreted by obese adipocytes induce a pro-inflammatory, pro-angiogenic and pro-mitogenic microenvironment (Newman & Gonzalez-Perez 2014, Himbert *et al.* 2017, Picon-Ruiz *et al.* 2017). Furthermore, leptin is expressed in 75% of tumors and its receptor is expressed in 80% of tumors. Leptin receptor expression is dependent on ER expression and tumor size (Jarde *et al.* 2008). *In vitro* and *in vivo* studies have reported that leptin acts via extracellular signal-regulated kinase (ERK) activation and possibly by estrogen signaling (Dubois *et al.* 2014, Yuan *et al.* 2014). Hence, leptin plays an important role in mediating obesity-associated BC risk (Fig. 1). Leptin increases obesity-associated cancer by multiple pathways: (a) Synergistic interaction of leptin receptors with the IGF-1 receptor (IGF-1R) activates AKT and ERK, which are responsible for obesity-associated BC progression by EGFR transactivation and PI3K/AKT phosphorylation. Both, leptin and IGF-1 are potent mitogens and their interaction significantly increases proliferation, migration and invasion of BC cells (Saxena *et al.* 2008). (b) Leptin induces phosphorylation of insulin receptor substrate (IRS)-1 and IRS-2, which in turn induces AKT activation. (c) Leptin upregulates MMPs, survivin and Notch1. This is in line with other studies where MMP inhibitor, GM6001, and survivin inhibitor, lovastatin, inhibit leptin and IGF-1-mediated EGFR transactivation respectively, in human and mice BC models. This inhibition is followed by reduction in invasiveness and migration of human BC cells (Greco *et al.* 2003, Escobar *et al.* 2004, Saxena *et al.* 2008, Knight *et al.* 2011)

Resistin is a cysteine-rich peptide hormone secreted by adipose tissue (Wang *et al.* 2002), and it can promote tumor progression by stimulating Toll-like receptor 4 (TLR4)/ NF-κB/STAT3 signaling pathway (Wang *et al.* 2017). Moreover, resistin produced by adipose macrophages have similar function as leptin, and high serum resistin levels are associated with increased *in vivo* breast cancer metastasis, tumorigenesis, and higher risk of BC progression especially in postmenopausal women (Wang *et al.* 2017) (Fig. 1).

Visfatin is an enzyme found in visceral adipose tissue and is also known as pre-B-cell colony-enhancing factor 1 (PBEF1) or nicotinamide phosphoribosyl transferase (Nampt) (Samal *et al.* 1994). Visfatin is particularly important in activating Notch1 signaling and inducing epithelial-mesenchymal transition (EMT), cell adhesion, as well as promoting BC cell growth, invasion, and metastasis (Dalamaga *et al.* 2011).

Endotrophin is collagen VI-soluble cleavage product secreted by adipocytes and has multiple roles like EMT stimulation, induction of tumor fibrosis, angiogenesis, and inflammation. However, the exact functions of adipocyte-secreted endotrophin in the obesity-BC association are yet unknown (Dalamaga *et al.* 2011, Lapeire *et al.* 2015).

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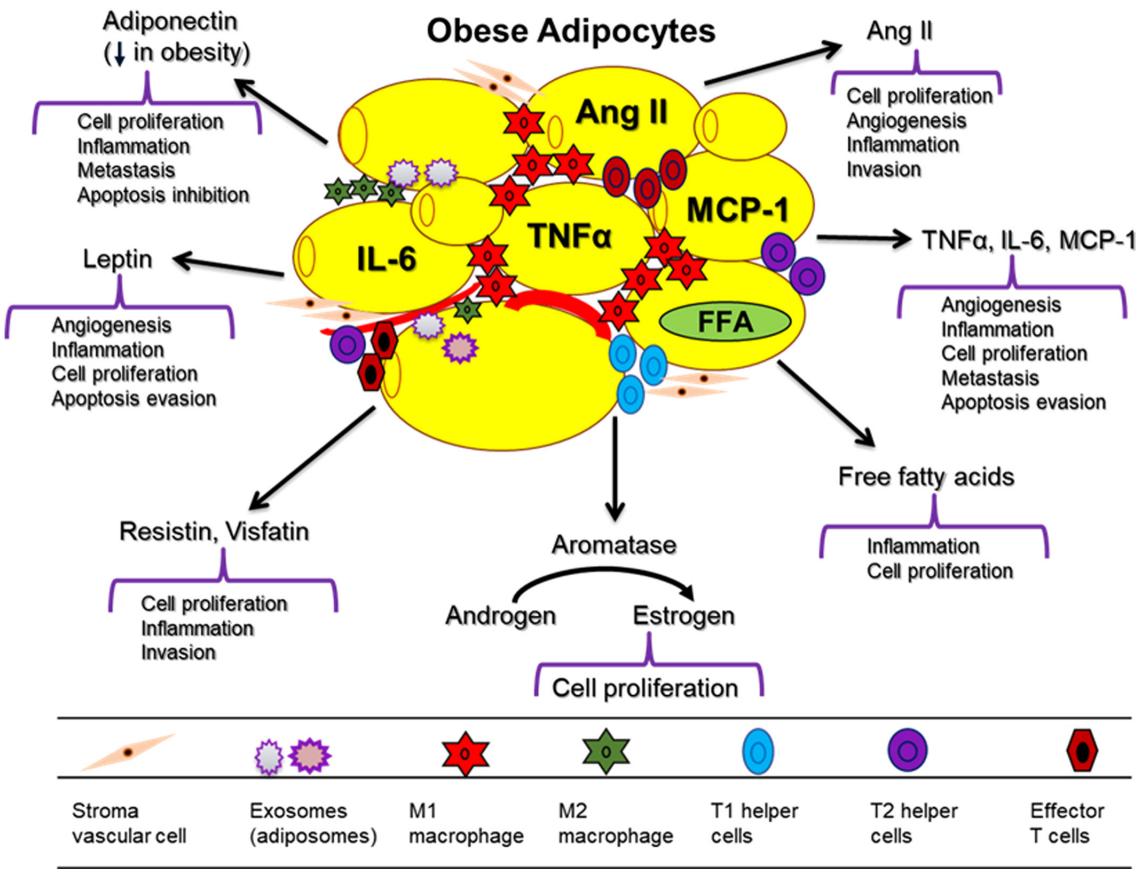

Figure 1
Altered adipose secretory functions contributes to obesity and breast cancer interaction by promoting the tumor microenvironment (TME). Obesity induces secretion of many pro-inflammatory and growth-promoting biomarkers by hypoxic obese adipocytes, which in turn, facilitates tumor cell proliferation, angiogenesis, inflammation and apoptosis evasion in TME. Alteration of immune cell profile such as, increased M1:M2 and T1:T2 ratios, further aids in this process. A full colour version of this figure is available at https://doi.org/10.1530/ERC-19-0314.

Adiponectin, another major adipokine, is a protein hormone and regulates glucose homeostasis and fatty acid oxidation in our body (Diez & Iglesias 2003). Interestingly, adiponectin has an inverse association with BC risk (Himbert *et al.* 2017). *In vitro* studies have reported a protective effect of adiponectin against cancer cell proliferation and metastasis, possibly via stimulation of adenosine monophosphate-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor α (PPARα) signaling and inhibition of MAPK pathway (Arditi *et al.* 2007, Himbert *et al.* 2017). In addition, adiponectin blocks VEGF, B-cell lymphoma (BCL)-2 (anti-apoptotic) expression, as well as increases Bcl2-associated X (BAX), caspase (pro-apoptotic) and the tumor cell-cycle arrest proteins (P53) expression (Divella *et al.* 2016). Adiponectin is responsible for switching macrophages from the M1 to M2 phenotype, thus improving the inflammatory profile (Li *et al.* 2011). By contrast, human BC cells express adiponectin receptors (AdipoR1, R2), which, when present at low concentrations can promote ER+ BC proliferation, but reduce triple-negative breast cancer cell (TNBC) growth in the presence of 17-β estradiol (Dieudonne *et al.* 2006, Pfeiler *et al.* 2008, Austin *et al.* 2018). This can be explained by the downstream signaling crosstalk between adiponectin and estrogen receptors in modulating AMPK and MAPK pathways respectively in TNBC and ER+ BC cells (Gelsomino *et al.* 2019). However, these studies demonstrate the controversial role of adiponectin in breast cancer and a significant mechanistic research gap in identifying adiponectin and estrogen signaling modulation in obesity-BC crosstalk.

Obesity is often associated with insulin resistance, resulting in increased levels of insulin and IGF-1. IGF-1 is a growth factor derived from obese adipocytes and its action is mediated via IGF-1R which are often elevated or mutated in different cancers including BC (Picon-Ruiz *et al.* 2017). It is a potent mitogen which increases risk and mortality in obese individuals

(Picon-Ruiz *et al.* 2017). Moreover, binding of insulin and IGF-1 to their respective receptors activates a series of events, including PI3K/AKT/mTOR signaling cascade, which in turn increases the expression of S6 kinases and inhibits eukaryotic translation initiation factor 4e (eIF4e) (Pollak *et al.* 2004). This further increases cell-cycle progression proteins such as cyclin D1 and c-Myc, while reducing apoptosis via suppressed expression of Bax and enhanced expression of Bcl2 (Pollak *et al.* 2004). In addition, insulin and IGF-1 promote estrogen signaling along with aromatase activity, thereby promoting hormone-sensitive BC in individuals with obesity. Apart from this, insulin inhibits hepatic synthesis of sex hormone-binding globulin (SHBG), causing impaired sex hormone (testosterone, dihydrotestosterone, estradiol) binding and transportation. Altogether, it promotes ER+ BC under obese conditions (Iyengar *et al.* 2013).

Another important player is serum estradiol (a steroid hormone), the levels of which are increased in obesity, promoting development of BC will be discussed in detail in later sections of the review.

COX-2 is another major pro-inflammatory enzyme connecting obesity and BC via inflammation. COX-2 overexpression had been found in both invasive and non-invasive human breast carcinomas (Half *et al.* 2002) and COX-2-derived lipid mediator, PGE-2 is found to be positively correlated with obesity and breast inflammation in women (Wang & Dubois 2012). PGE-2 can be secreted from obese adipose macrophages and found to have a role in aromatase upregulation through cAMP-PKA pathway in human breast tissue (Subbaramaiah *et al.* 2012). Moreover, previous studies from our lab and others have reported positive PGE-2 action on adipose lipogenesis, inflammation, and remodeling in obesity (Wortman *et al.* 2009, García-Alonso *et al.* 2016). Taken together, all these associations suggest COX-2 derived PGE-2 role in BC progression by modulating obesity-associated inflammation.

In addition to the above-mentioned adipose-derived factors, browning of white adipose tissue (beige) and brown adipose tissue (BAT) plays a significant role in obesity and BC interactions. Increased uncoupling protein 1 (UCP1) protein and mRNA expression in late-stage and malignant breast tumors indicate higher mammary fat browning in cancer (Wang *et al.* 2014, Han *et al.* 2018). One possible explanation could be higher white adipose tissue (WAT) browning in hypermetabolic cancer patients to compensate for weight loss induced in cancer (Han *et al.* 2018). However, the dynamics of WAT browning in inducing weight loss and improving metabolic health versus increasing WAT atrophy in cancer cachexia needs further investigation to elucidate its conflicting roles in the obesity and BC connection.

The RAS is another major physiological system which has close connection with obesity and inflammation, through altered adipocytokine profiles and dysregulated metabolism (Fig. 1). Interestingly, both WAT and BAT express all the components of RAS including angiotensinogen and Ang-II. Furthermore, studies have reported that UCP-1 induction in response to cold exposure via activation of the sympathetic nervous system increases *in vivo* Ang II expression, which was inhibited upon administration of its receptor blocker, losartan (Pahlavani *et al.* 2017). Increased BAT expression in the mammary gland is specifically associated with upregulated levels of angiogenic, CD31 and metastatic, COX2 *in vivo*. By contrast, COX2 inhibition leads to reduced tumor growth along with reduced level of classic brown (UCP-1) and beige (MYF5) markers in mouse xenograft of MDA-MB-231 triple-negative breast cancer cell (Singh *et al.* 2016). Moreover, our lab reported COX-2-derived PGE-2 upregulation in response to time-dependent Ang II administration *in vitro* suggesting Ang II role in connecting obesity and BC via COX-2 modulation (Kim *et al.* 2002).

Hence, dissecting the relationship between Ang II, adipose tissue types and BC presents an important area of future research as both Ang II and UCP-1-levels are found to be elevated in cancer, especially BC. In the next sections of this review, we will discuss the detailed function of RAS and its key bioactive hormone Ang II in the TME under obese conditions. As multiple studies have reported the importance and the role of adipose-derived factors – like adipokines, cytokines, growth factors, hormones in development of obesity-associated BC – dissection of the underlying pathways is critical, in order for us to understand the mechanisms linking obesity to BC.

Renin-angiotensin system (RAS) and its components

RAS is a well-studied physiological system in our body that has potential to modulate both obesity and BC. It is classically known for its role in blood pressure and fluid balance regulation (Yvan-Charvet & Quignard-Boulange 2011). Recently, it has been found to be expressed in various tissues including liver, kidney, heart, brain, and adrenal glands and have a local role (Yvan-Charvet & Quignard-Boulange 2011). RAS has key roles in inflammation, insulin resistance and obesity development (Engeli *et al.* 2000, Yvan-Charvet & Quignard-Boulange 2011,

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Kalupahana & Moustaid-Moussa 2012). The common precursor of all RAS peptides is angiotensinogen (Agt), which is primarily secreted by the liver. However, under obese conditions, adipocytes secrete large amounts of Agt. Agt is cleaved by renin, an enzyme secreted from the kidneys, to form angiotensin I (Ang I). Ang I is further cleaved to angiotensin II (Ang II) by angiotensin-converting enzyme (ACE) produced in the lungs. Ang II is a major bioactive hormone in the RAS pathway and mediates its effect via binding to two receptors (AT1R, AT2R). AT1R stimulation results in blood pressure elevation, whereas AT2R lowers blood pressure. Ang I and Ang II are further cleaved into Ang (1–9) and Ang (1–7) (Fig. 2) which then binds to Mas receptor to promote vasodilation, growth and fibrosis inhibition (Ferrario *et al.* 2010). Ang II can be cleaved by aminopeptidases to produce Ang III and Ang IV, with Ang IV binding to a newly identified receptor, AT4 (not shown in Fig. 2). However, the exact function of AT4 has not yet been identified (Smith *et al.* 2016) and researchers have reported conflicting effects of Ang IV on vasculature as an antagonist (Slinker *et al.* 1999) and agonist of Ang II (Shostak & Chariot 2015). In obesity, local RAS is activated, and it regulates both adiposity and inflammation (Ramalingam *et al.* 2017). Hence, it has a potential role in developing obesity-associated cancer. Evidence suggests that the combined effects of Ang II and its receptor AT1R significantly increase tumor angiogenesis especially in receptor-negative BC via increasing gene expression of angiogenic growth factors, such as VEGF and hypoxia-inducible transcription factor 2α (HIF-2α) (Herr *et al.* 2008). Meanwhile, Ang II production and/or expression is associated with improvements of breast cancer-related adverse outcomes (Oh *et al.* 2016, Raimondi *et al.* 2016). In addition to that, Ang II and AT1R interaction in obesity is responsible for increased macrophage polarization (shift from anti-inflammatory M2 to pro-inflammatory M1), infiltration and higher M1/M2 ratio which can be altered by ARB administration *in vivo* (Ma *et al.* 2011).

Genes for the RAS pathway (Agt, receptors, renin and ACE enzymes) are expressed in different cancers including BC cells. RAS inhibitors, such as ACE-I (e.g. captopril, enalapril) and/or AT1R blockers or ARBs (e.g. telmisartan, losartan), have been successfully used as antihypertensive agents to prevent pathologies associated with RAS overexpression in many *in vitro*, *in vivo* and clinical studies (de Kloet *et al.* 2011). Interestingly, RAS inhibitors have been used to prevent diabetes (Scheen 2004). Moreover, some of these inhibitors have been used to improve overall cancer survival depending on the cancer type and type of inhibitor used (Sun *et al.* 2017). Given the above-mentioned associations, it is important to understand the potential mechanism of action of RAS in BC, as well as the role of adipose tissue RAS in obesity and associated BC.

Mechanism of RAS action promoting the tumor microenvironment

Various RAS components are overexpressed in BC modulating cancer cell capacities of growth, proliferation,

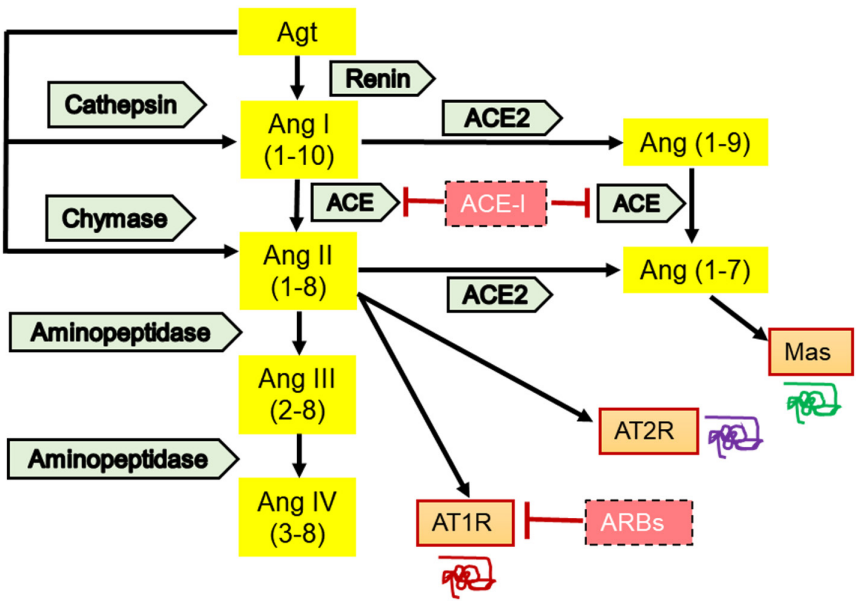

Figure 2
Components of the renin-angiotensin system. Classic RAS pathway initiates when the obligatory peptide precursor of all bioactive RAS components, angiotensinogen (Agt), is cleaved by two enzymes renin and angiotensin-converting enzyme (ACE) to produce angiotensin (Ang) I and Ang II, respectively. Ang II is the main bioactive of the system and exerts its effects via binding to two receptors Ang type I (AT1R) and type 2 (AT2R), promoting either vasoconstriction via AT1R or vasodilation via AT2R. Cathepsin and chymase can also produce Ang I and Ang II from Agt independent of the classic renin-ACE pathway. Ang I and Ang II can be further cleaved into Ang (1-9) and Ang (1-7) to exert their action via Mas receptor, which has functions similar to AT2R. Ang II is again cleaved into Ang III and Ang IV by the action of aminopeptidases. RAS blockade by ACE inhibitors (ACE-I), and AT1R and AT2R blockers (ARBs) is used as antihypertensive therapy and has protective effects against obesity and cancer. A full colour version of this figure is available at https://doi.org/10.1530/ERC-19-0314.

Table 1 Expression of RAS components in human breast tissues and cancer cell lines.

Model	Overexpressed RAS components	References
In vitro and *In vivo*	AT1 receptors (AT1R)	(Rhodes *et al.* 2009)
In vitro	Ang II, ACE, AT1R	(De Paepe *et al.* 2001)
In vitro	Agt, renin, Ang II, ACE, AT1R	(Herr *et al.* 2008)
In vitro	AT1R	(Muscella *et al.* 2002)
In vitro	AT1R	(Inwang *et al.* 1997)
In vitro	Agt, pro-renin, ACE, AT1R	(Tahmasebi *et al.* 2006)

and invasion as summarized in Table 1. While increased AT1R expression is associated with increased pro-tumor functions in both BC and breast epithelial cells, AT2R antagonizes the pro-tumor activity of AT1R by blocking its downstream signaling during BC progression (George *et al.* 2010).

A recent large-scale study comprising 31 gene profiling and 3200 microarray experiments reported that AT1R is overexpressed in 10–20% of BC cohorts especially in ER+, ErbB-2 (HER2)-negative BC and is responsive to estrogen and epidermal growth factor receptor (EGFR) signaling. The study also reported that AT1R and ErbB-2 overexpression were mutually exclusive because of their overlapping downstream pathways of ERK activation (Rhodes *et al.* 2009). Similarly, increased expression of AT1R and ACE has been found in metastatic ovarian adenocarcinoma and prostate cancer compared to benign cancers indicating they might be responsible for transition to invasive tumor in these cases (Suganuma *et al.* 2005, Uemura *et al.* 2006). AT1R overexpression is found in breast hyperplasia (higher irregular shaped breast cells), ductal *in situ* carcinoma (DISC), but were not observed in invasive cancers as the downstream growth-regulating pathways were no longer needed by the invasive carcinoma cells (Uemura *et al.* 2006, Rhodes *et al.* 2009). However, AT2R demonstrates inverse expression patterns to AT1R (i.e., higher AT2R expression was found in invasive BC). This phenomenon can be explained by correlation between AT2R and inducible nitric oxide synthase (iNOS) toward inhibiting vascularization and initiating apoptosis of invasive carcinoma cells. This occurs by inhibiting PI3K/AKT intracellular signal transduction and bypassing the EGFR growth signaling (De Paepe *et al.* 2002). Thus, these studies indicate the involvement of both AT1R and AT2R in the initial stages of cancer development and invasiveness, respectively (George *et al.* 2010).

Another mechanism of AT1R activation includes AT1R interaction with NADPH oxidase to facilitate inflammation and angiogenesis, leading to potential TME restructuring. Other RAS-mediated malignant transformation mechanisms involve processes like cell proliferation due to higher sensitivity to growth-stimulating signals and lowered or insensitivity to growth inhibitory signals, angiogenesis, alteration of apoptosis, increased invasive, metastatic and tissue replicative capacities, and inflammation (Deshayes & Nahmias 2005, Floor *et al.* 2012). These potential mechanisms of RAS action are briefly discussed below.

Cell proliferation and angiogenesis

AT1R is highly overexpressed in TAMs, facilitating macrophage infiltration and VEGF production *in vivo*, thereby promoting inflammation-mediated angiogenic tumor development (Egami *et al.* 2003). EGFR (RTK) transactivation via AT1R induces matrix metalloproteinase (MMP) secretion followed by activation of PI3K/AKT signaling cascade (Deshayes & Nahmias 2005). Additionally, AT1R mediates its proangiogenic effect by increasing both VEGF and VEGF receptor 2 (VEGFR2) expression in endothelial cells, followed by increased expression of angiopoietin-2, a major regulator of angiogenesis via EGFR binding. Similar effects were observed in microvascular endothelial cells. This was confirmed in AT1R-knockout mice, which had reduced tumor growth and angiogenesis compared to wild-type controls (Egami *et al.* 2003). Moreover, treatments with AT1R antagonists reduced tumor size confirming the role of AT1R in cancer progression (Egami *et al.* 2003). In contrast, AT2R inhibits autophosphorylation of EGFR by inducing Src homology region 2 domain, containing tyrosine phosphatase-1 (SHP-1), a tumor-suppressor gene. SHP-1 renders its anti-proliferative effect by inhibiting STAT3 phosphorylation (Song *et al.* 2017) and girdin-dependent tyrosine phosphorylation in PI3K/AKT signaling (Mittal *et al.* 2011). EGFR-induced cell proliferation can be antagonized by AT2R-interacting protein ATIP (another putative tumor suppressor) via increased AT2R transport to cell membrane (Nouet *et al.* 2004). AT2R inhibits AKT and endothelial nitric oxide synthase (e-NOS) phosphorylation and activation by blocking VEGFR2 expression. Thus, AT2R can reduce cell migration and tube formation in human endothelial cells (Deshayes & Nahmias 2005). Furthermore, AT2R-knockout mice had faster growth of stromal cells and increased VEGF production in a murine pancreatic cancer model (Doi *et al.* 2010). Similarly, Mas receptor activation significantly reduced lung tumor growth and

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vessel density, along with decreased VEGF expression in an *in vitro* human lung carcinoma model, possibly by blocking ERK signaling (Gallagher & Tallant 2004). This summarizes the possible opposite roles of AT1R and AT2R in tumor cell proliferation, suggesting that antagonist and agonists of the respective receptors might be associated with beneficial anti-tumor outcomes.

Apoptosis

Ang II-mediated AT1R activation increases cell survival and inhibits apoptosis during malignant cell formation in two ways: (i) NF-κB activation which activates Bcl-XL and survivin, which then leads to cisplatin (alkylating agent)-induced apoptosis inhibition in pancreatic cancer cells (Amaya *et al.* 2004). (ii) PI3K/AKT signaling activation is followed by downregulation of caspase 9, resulting in doxorubicin (topoisomerase inhibitor)-induced apoptotic inhibition in ER+ BC cells (Zhao *et al.* 2008). AT1R increases survivin expression and suppresses caspase-3-mediated apoptotic activity by PI3K/AKT pathway, which in turn, promotes survival in microvascular endothelial cells in breast tumor microenvironment. Furthermore, activation of PI3K/AKT and Ras/MAPK/ERK signaling pathways are often associated with downregulation of STAT signaling and upregulation of survivin and Bcl-2 expression in BC cells (Aziz & Aziz 2013). In contrast, AT2R overexpression induces apoptotic cell death in prostate and lung cancer cells independent of Ang II stimulation, but dependent upon p38 MAPK and caspases 3 and 8 levels, although the exact mechanism of action of AT2R mediated apoptosis in different cancer cell types needs further investigation (George *et al.* 2010, Pickel *et al.* 2010, Pei *et al.* 2017). All these studies indicate potential anti-apoptotic role of AT1R in obesity-BC crosstalk, while the apoptotic role of AT2R in cancer progression is controversial and needs further investigation.

Inflammation

RAS signaling activation through AT1R promotes downstream activation of several transcription factors like NF-κB, STAT 3 and hypoxia-inducible transcription factor 1α (HIF-1α), followed by induction of various molecules integral to TME (i.e. IL-6, IL-8, MCP-1, macrophage colony stimulating factor (M-CSF), VEGF, tissue inhibitor of metalloproteinase 1 (TIMP1), HIF-1α, and HIF-2α) (Van Uden *et al.* 2008, George *et al.* 2010). In contrast, AT2R inhibits MCP-1 production in smooth muscle cells by stabilizing IKBα via SHP-1 (Deshayes & Nahmias 2005). Apart from this, another key inflammatory molecule generated by RAS is reactive oxygen species (ROS) through AT1R and NADPH oxidase interaction, followed by activation of the MAPK and PI3K/AKT signaling pathways. Hypoxia, excess ROS generation, and oxidative stress result in increased endoplasmic reticulum stress, cell damage or death; which in turn activates several downstream stress recovery pathways (autophagy, anti-inflammatory) and increases growth factor signaling in TME (Gallagher & Tallant 2004). Uemura *et al.* found that Ang II induces ROS production in prostate cancer cells, while AT1R inhibition reduces oxidative stress and free radical production in an *in vitro* model of prostate cancer (Uemura *et al.* 2008). In addition, Ang II/AT1R signaling promotes production and infiltration of TAMs in different tumor models, while RAS inhibitors can restrain tumor growth and TAM response (Pinter & Jain 2017). By contrast, AT2R and its interacting intracellular protein, ATIP, display tumor-suppressor effect (Rodrigues-Ferreira *et al.* 2015). AT2R and its agonists have protective anti-inflammatory effect against obesity and other chronic diseases such as hypertension, cardiac and renal inflammation (Esquitino *et al.* 2015); however, the mechanisms behind its inflammatory role in different cancers need more research. Interestingly, AT2R is overexpressed in different BC subtypes (Rodrigues-Ferreira & Nahmias 2015) and researchers developed novel human invasive *in vitro* BC model to study the AT2R–ATIP interaction independent of AT1R–Ang II activation (Rodrigues-Ferreira *et al.* 2012). However, AT2R–ATIP interaction promoting or preventing in BC needs further illustration given anti-proliferative and anti-metastatic effect of ATIP in different *in vitro* and *in vivo* cancer models (Guimond *et al.* 2013, Rodrigues-Ferreira & Nahmias 2015). This suggests RAS role in promoting cancer-related inflammation in an immunosuppressive microenvironment which could be a possible mechanism of action for BC progression in obesity by adipose Ang II overproduction.

Cell migration, invasion, and metastasis

Accumulating evidence shows that RAS enhances the ability of malignant cells to migrate, invade, and metastasize as well as facilitate TME (George *et al.* 2010). AT1R plays an important role in leukocyte extravasation by increasing expression of endothelial adhesion molecules like E-selectin, P-selectin and vascular cell adhesion molecule-1 (VCAM-1), inducing malignant cell growth, neovascular formation and metastasis (Alvarez *et al.* 2004).

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Furthermore, Ang II-AT1R-mediated activation of PI3K pathway induces invasion and migration of choriocarcinoma (Ishimatsu *et al.* 2006). Interestingly, one contrasting result was found in BC cells treated with Ang II. Barker *et al.* reported that AT1R activation resulted in reduced cell adhesion and invasion in receptor-positive MCF-7 and T47D BC cells, through protein kinase C (PKC)-dependent downregulation of integrin receptor α3β1 expression (Puddefoot *et al.* 2006). One possible explanation could be the competitive action of integrins to activate ERK1/2 via the FAK-SRC-MAPK pathway instead of the Ang II-mediated EGFR phosphorylation pathway. However, other studies reported activation of the epithelial basement membrane receptor, integrin α3β1, which leads to higher induction of MMP-9 and COX-2 in different cell and animal models of BC (Subbaram & Dipersio 2011). Therefore, these contrasting studies suggest the need of further research involving different tumor subtypes under different conditions to dissect the role of Ang II in BC cell migration.

Apart from the aforementioned regulatory functions of RAS, mutations or polymorphisms of RAS components have a significant effect on cancer development and risk modulation. Higher AT1R expression is found in invasive carcinomas (such as ovarian adenocarcinoma) than benign cystadenomas (Suganuma *et al.* 2005). Moreover, AT1R and ACE expression is localized to the tumor in gastric cancer and tumor metastatic ability was influenced by an ACE insertion/deletion (I/D) polymorphism (Röcken *et al.* 2005). ACE-I/D polymorphism and AGTR1 mutation at 5′ end are associated with reduced postmenopausal BC risk (George *et al.* 2010). Hence, modulation of RAS components expression in cancer, particularly BC, is a potential therapeutic approach and novel treatment option which requires further investigation.

Potential mechanisms linking angiotensin with obesity-associated BC

Increased Ang II produced by local adipocytes in breast could be a potential link between obesity and BC. Here, we are proposing several mechanisms which involve modulating multiple factors such as estrogen, growth factor receptors, oxidative stress and inflammation (Simone *et al.* 2016) associated with obesity and BC with or without RAS implication.

Estrogen signaling

Ovaries are the primary producers of estrogen in premenopausal women, while after menopause, adipose tissue including that of breast produces estrogen. High aromatase expression in obese fat cells is a source of high estrogen levels in postmenopausal BC (Simpson & Brown 2013). Estrogen alone or in combination with epidermal growth factor (EGF) induces Ang II–AT1R signaling. This leads to downstream activation of MAPK/RAF/ERK1/ERK2 mediated cell proliferation and survival in both ER-positive and ER-negative human BC cells (Lim *et al.* 2006). In addition, Ang II receptor (AT1R and AT2R) signaling can be modulated by ER expression. For instance, decreased AT1R and increased AT2R expression have been observed in hearts of ovariectomized and/or estrogen-replaced mice to improve responses to ischemia and reperfusion injury (Xue *et al.* 2015). Furthermore, estrogen signaling and its activity are strongly influenced by obesity-associated inflammatory markers (Zahid *et al.* 2016). There are three types of receptors involved in estrogen signaling, ERα, ERβ and G protein-coupled estrogen receptor (GPER). ERα is found to regulate RAS components transcription in an *in vivo* hypertensive model (Tremblay *et al.* 2010), hence, may be associated with other metabolic alterations mediated by RAS pathway. Further, GPER is expressed in all types of breast carcinomas and its deregulated expression is associated with poor cancer outcomes, tumorigenesis and tamoxifen resistance (Catalano *et al.* 2014, Yan *et al.* 2015). GPER exhibits functional and structural properties of G protein-coupled-receptor (GPCR) superfamily members and studies have shown that it plays a role in estrogen-induced carcinogenesis (Simone *et al.* 2016). In addition, both AT1R and GPER are GPCRs and hence might follow a similar pathway to EGFR phosphorylation to induce cancer cell proliferation and mediate an obesity–BC interaction. Estradiol action via GPER signaling promotes protein kinase A (PKA)-dependent cell proliferation, by activation of ERK1/ERK2 and PI3K/AKT pathway. Moreover, GPER is responsible for epithelial cells loss of polarity and cell adhesion properties, followed by mesenchymal stem cell-like adaptations for enhanced metastatic and invasive properties. This ultimately leads to progression of estrogen-induced carcinogenesis and increased MMP-9 expression in the EMT process. Within the TME, GPER can promote new vascular tube formation and inflammation through activation of HIF-1α, PGE2 and IL-6 expression (Samarajeewa *et al.* 2013, Che *et al.* 2014), which are potential targets of Ang II-mediated inflammation and angiogenesis in obesity-associated BC. In lieu, Ang II is a potential agonist of GPCR and known to induce EGFR transactivation (Forrester *et al.* 2016). Based on these findings, it is likely that Ang II is a potential modulator of estrogen signaling via GPER in

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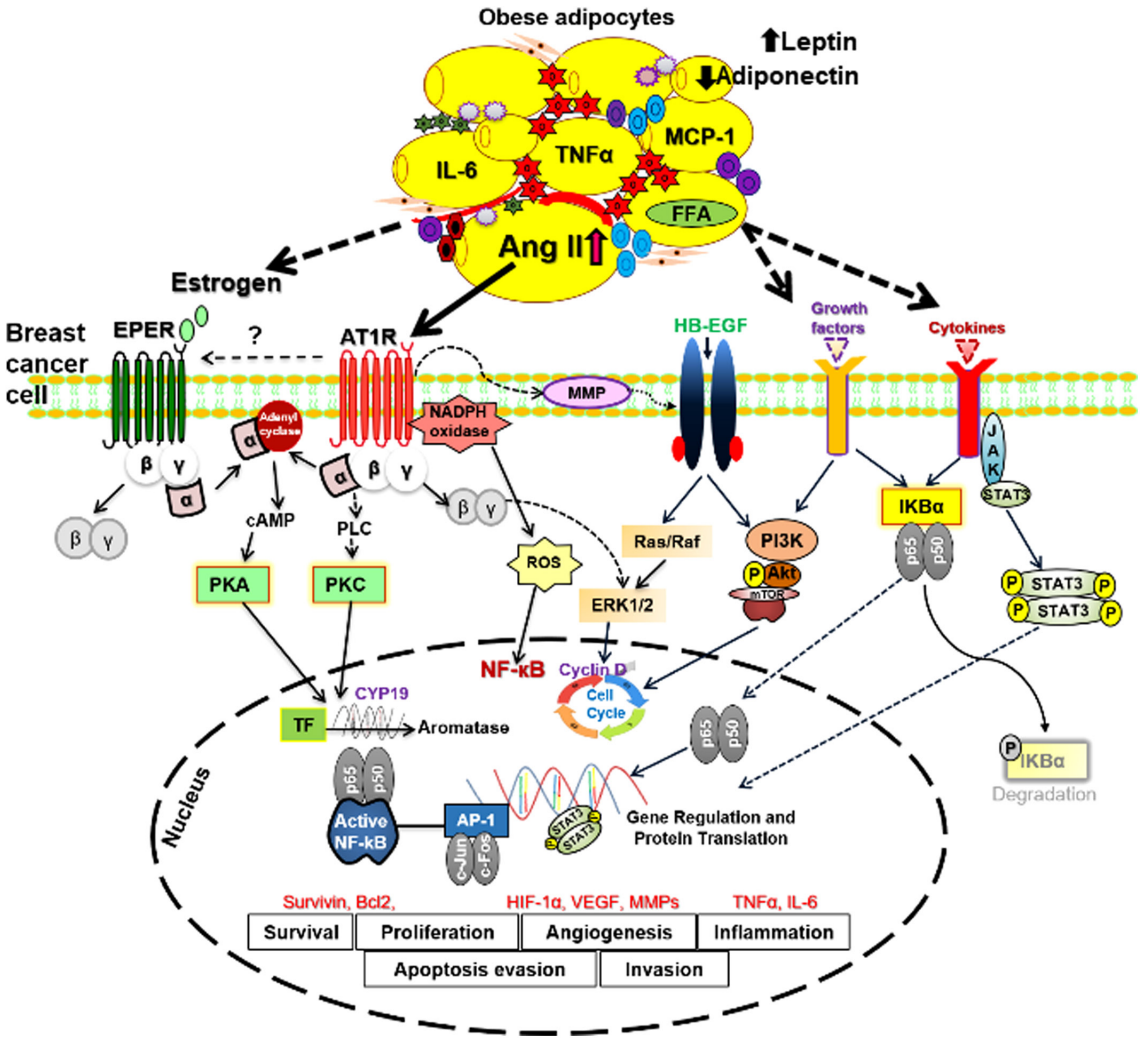

Figure 3

Obesity and breast cancer crosstalk by Ang II and AT1R interaction. In obesity, hypertrophic and hypoxic adipocyte secretes many pro-inflammatory cytokines, adipokines, hormones and growth factors like TNFα, MCP-1, IL-6 and Ang II. Moreover, increased leptin and reduced adiponectin secretion can deteriorate the pro-inflammatory microenvironment. Hence, local adipose RAS is activated and promotes tumor microenvironment (TME) by Ang II-AT1R interaction (classic). AT1R-dependent cleavage of heparin-bound extracellular growth factor (HB-EGF) leads to transactivation EGF receptor (EGFR) and activation of ERK1/ERK2 and PKC. Then, activated EGFR can induce PI3k/AKT pathway and increased protein transcription facilitating cancer cell survival and proliferation (cyclinD1). Obese adipocyte-derived cytokines and growth factors also promote PI3K-AKT pathway, as well as NF-κB pathway via IKK degradation and STAT-3 phosphorylation. Generation of reactive oxygen species (ROS) by AT1R-NADPH oxidase interaction further promotes NF-κB pathway. Obese adipocyte-derived estrogen can bind to its receptor GPER on breast cancer cell and thus increases aromatase expression via transcription factor (TF) regulation by PKA and PKC signaling. However, the effect of Ang II-AT1R on GPER activation in breast cancer requires further illustration. Altogether, obese adipocyte-derived Ang II can promote breast cancer cell survival, proliferation, inflammation, angiogenesis, and invasion by upregulating expression of various pro-tumorigenic genes and proteins through EGFR transactivation and NF-κB inflammation. A full colour version of this figure is available at https://doi.org/10.1530/ERC-19-0314.

obesity-associated BC. However, further investigation is required to identify the role of Ang II in ER signaling during obesity and BC development (Fig. 3).

Altered growth factor receptor signaling

Two major metabolic pathways (PI3K/AKT and JUN/MAPK) are altered in BC. These alterations promote cell proliferation and inhibit cell differentiation or cell-cycle arrest at beginning of tumor initiation. Therefore, tumor-initiating cells are protected from ROS and oxidative stress by switching to PI3K/AKT pathway. This in turn drives increased tumor progression and metastasis (Guille *et al.* 2013). By contrast, obesity is often associated with increased oxidative stress and ROS production which can lead to genetic instability inducing tumor progression by triggering the PI3K/AKT pathway (Seibold *et al.* 2011).

This may be explained by the presence of mutated oxidative stress-related genes in BC (Seibold *et al.* 2011), increased activation of autophagy regulatory pathways such as mTOR/HIF-1α/ NF-κB, inactivation of tumor suppressors such as PTEN and carcinogenic metabolic-phenotypic changes induced by senescent fibroblasts to maintain BC cell growth (Jezierska-Drutel *et al.* 2013). In accordance, PI3Ks are important for cancer progression and can be activated in response to EGFR and GPCR interactions. PI3K receives signals from various growth factors and cytokines and converts them into intracellular messengers by generating phospholipids. This in turn leads to the activation of Akt and other downstream effector pathways (e.g. NF-κB) (Cantley 2002). Furthermore, Ang II-mediated EGFR transactivation is responsible for regulating various downstream signaling pathways such as PI3K/Akt, Ras/Raf/MAPK/ERK, STAT and PKC signaling (Aziz & Aziz 2013, George *et al.* 2013). Aberrant overexpression or mutations of upstream growth factor receptors due to obesity/cancer/agonist (e.g. Ang II) action can cause amplification of EGFR and activation of small GTPase, ras proteins. For example, CSF-1 (colony-stimulating factor-1), which is the upstream receptor of PI3K/Akt is expressed in ~15% of BC tissues, but not in normal breast tissue (Kacinski 1995, Aziz & Aziz 2013).

Leptin is a potent growth factor of BC and its receptors are expressed in both normal and cancerous breast tissues (Somasundar *et al.* 2004). Ang II is responsible for increased leptin synthesis in both *in vitro* (Skurk *et al.* 2005) and *in vivo* (Cassis *et al.* 2004) models of obesity and thus can be correlated with leptin-mediated BC progression. However, the detailed mechanism behind leptin and Ang II interaction in obesity-associated cancer crosstalk remains unclear.

Hence, mitogenic effect of Ang II in obesity-induced BC can be mediated by AT1R-dependent activation of EGFR (ERK) and protein kinases resulting in the upregulation of downstream activators such as AKT, MMP and other growth promoters (Escobar *et al.* 2004).

Activation of the NF-κB inflammatory pathway

Evidence suggests that Ang II is required for activation of NF-κB transcription factors by canonical (IκB-dependent) or non-canonical (IκB-independent) pathways (Zhang *et al.* 2005). Ang II activates NF-κB via NADPH oxidase and AT1R interactions followed by ROS generation. Therefore, NF-κB signaling cascade is a major downstream target by which obesity and BC could crosstalk via modulation of RAS signaling molecules (Fig. 3). However, mechanisms by which Ang II activates NF-κB requires further clarification. One more possible way to activate NF-κB is through AT1R. It activates a series of molecular targets including PKC, EGFR, RTK, ERK1/2 or p38 MAP kinases which leads to the recruitment of adaptor proteins to IKK complex followed by IκB phosphorylation and degradation thereby activating NF-κB (Li & Zhuo 2008). Similarly, Ang II induces phosphorylation of the p65 subunit of NF-κB, activating an alternative RAS/ERK1/2 signaling cascade and ribosomal S6 kinase (S6K), a downstream effector (Zhang *et al.* 2005). Both canonical and non-canonical pathways mediated via Ang II can induce NF-κB activation.

In cancer development and progression, NF-κB promotes tumor initiation, proliferation, apoptosis inhibition, angiogenesis, chemoresistance, and metastasis (Wu & Kral 2005). Furthermore, growth factors promote NF-κB activation through ErbB family stimulation. Studies have shown that EGF triggers NF-κB activation in an IKK-dependent manner (IκB degradation) in BC cells (Biswas *et al.* 2000). On the other hand, NF-κB and EGFR crosstalk promotes cancer progression by blocking EGFR inhibitors. TNFα produced by TAMs activates NF-κB in glioblastoma cells and provides resistance against EGFR inhibitors. TAMs sense dying cells through TLRs and activate NF-κB and ERK1/2 signaling cascade, which in turn establishes a positive loop of NF-κB activation by promoting the expression of pro-inflammatory cytokines like TNFα (Shostak & Chariot 2015). These results indicate NF-κB as a possible middle link in Ang II-induced, inflammation-mediated, obesity and BC crosstalk.

The role of RAS inhibitors in BC treatment

RAS inhibitors (ACE-I) and AT1R blockers (ARBs) are clinically used as antihypertensive drugs without any major side effects. They are currently under evaluation for safety in cancer patients including BC (Rodrigues-Ferreira & Nahmias 2015). Some common antihypertensives such as ACE-I, which include captopril, enalapril, lisinopril and so forth, and ARBs, which include telmisartan, losartan, candesartan and so forth, are often used in combination to achieve a maximal effect (Komine *et al.* 2002). A recent *in vitro* study found that RAS inhibitors do not alter the cytotoxic effect of chemotherapeutic agents. Rather, their efficacy is enhanced when used in combination with chemotherapeutic BC drugs (Smith *et al.* 2016). Corroborating with this, multiple studies have reported that Ang II has detrimental effects on breast tumor outcomes such as angiogenesis and survival

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Table 2 Summary of studies reviewing the role of ACE-I/ARBs on different models of breast cancer research.

Study	Treatment	Model	Major findings	References
Antihypertensive drug use and breast cancer risk: A meta-analysis of observational studies	Antihypertensive medication including ACE-I/ARB	Human	Significantly reduced breast cancer risk (RR = 0.80) with 10 years or more ACE-I/ARB use	(Ni *et al*. 2017)
Use of beta-blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers and breast cancer survival: Systematic review and meta-analysis	RAS inhibitors (ACE-I/ARBs)	Human	No association with ACE-I or ARB use with overall breast cancer survival	(Raimondi *et al*. 2016)
The association between angiotensin receptor blocker use and breast cancer characteristics	ARBs	Human: a retrospective cohort study	Higher incidence of invasive lobular breast carcinoma ($P = 0.009$) and worse cancer-specific survival ($P = 0.024$)	(Goldvaser *et al*. 2016)
Antihypertensive medication use and incident breast cancer in women	Antihypertensive medication use including ACE-I	Human: Longitudinal cohort	ACE-I lower breast cancer risk in a subpopulation with long-term consistent use compared to never users	(Devore *et al*. 2015)
Drugs affecting the renin-angiotensin system and survival from cancer: a population-based study of breast, colorectal and prostate cancer patient cohorts	ACE-I and/or ARB	Human: observational case–control study	No association observed between breast cancer-specific mortality and ACE-I/ARB use	(Cardwell *et al*. 2014)
Use of ACE inhibitors and angiotensin receptor blockers and primary breast cancer outcomes	ACE-I and ARB	Human	No difference in survival outcomes while ARB use improved relapse-free survival (RFS)	(Chae *et al*. 2013)
Protective effect of Perindopril on tumor progression and angiogenesis in animal model of breast cancer	ACE-I (Perindopril: 2 mg/kg/day)	*In vivo*: BALB/c mice implanted with MDA-MB-231 breast cancer cells to generate mouse xenograft model and 60 mg/kg DMBA administered orally to induce breast cancer	Significant reduction in angiogenic, VEGF and inflammatory, c-reactive protein (CRP) levels, followed by increased anti-oxidant parameters (GSH, SOD) found in diseased animal with ACE-I treatment compared to diseased control group; significantly reduced tumor growth found in mouse xenograft model due to ACE-I treatment	(Patel and Nakka, 2017)
The role of captopril and losartan in prevention and regression of tamoxifen -induced resistance of breast cancer cell line MCF7	ACE-I (captopril) and the combination of ACE-I and ARB (captopril plus losartan)	*In vitro:* MCF-7 breast cancer cell line	Combination therapy with captopril and losartan with tamoxifen significantly prevented drug resistance of MCF-7 cells	(Namazi *et al*. 2014)
Angiotensin II type 1 receptor antagonists inhibit cell proliferation and angiogenesis in breast cancer	Ang II doses: (1 to 10,000 nmol/L), ARBs: Losartan (0.01, 0.1, 10, 100 micro mol/L), *In vivo* dose: Candesartan (5 or 10 mg/kg body weight)	*In vitro:* MCF-7 and MDA-MB-231 *In vivo*: BALB/c Female nude mice injected with AT1R over-expressing breast cancer cells	Ang II promoted cell proliferation in MCF-7 breast cancer cells and Losartan reduced adverse Ang II effect on MCF-7 Candesartan significantly inhibited tumor growth and angiogenesis in mice xenograft model	(Chen *et al*. 2013)

(Continued)

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Table 2 Continued.

Study	Treatment	Model	Major findings	References
Inhibition of the renin-angiotensin system downregulates tissue factor and vascular endothelial growth factor (VEGF) in human breast carcinoma cells	ACE-I (Captopril, Enalapril 10 ug/mL), and ARB (Losartan, 10 ug/mL)	*In vitro:* MDA-MB-231 and MCF-7	Blockade of RAS by ACE inhibitors and AT1R blocker inhibited angiogenic VEGF expression in highly metastatic MDA-MB-231 breast cancer cell line	(Napoleone *et al.* 2012)
Angiotensin II receptor type 1 blockers suppress the cell proliferation effects of angiotensin II in breast cancer cells by inhibiting AT1R signaling	AT1R blocker, irbesartan	*In vitro:* MCF-7	AT1R blockade inhibited Ang II effects on cell proliferation, cell-cycle development as well as downstream AT1R signaling events, including activation of MAPK and NF-κB pathway	(Du *et al.* 2012)

(Tahmasebi *et al.* 2006, Herr *et al.* 2008, Xi *et al.* 2011, Oh *et al.* 2016). Additionally, blockade of RAS signaling contributes to the improvement of those adverse effects (Namazi *et al.* 2014, Raimondi *et al.* 2016, Smith *et al.* 2016) (Table 2). Another study reported that mice treated with the ACE-I (captopril) followed by radiation in induced mammary carcinoma had suppressed tumorigenesis than mice treated with either captopril or irradiation compared to control (Cho *et al.* 2016). Similar chemopreventive effects of ACE-I are found in combination with branched-chain amino acid in an *in vivo* model of hepatocellular carcinoma, along with suppressed VEGF-mediated neovascularization as confirmed by *in vivo* and *in vitro* studies (Yoshiji *et al.* 2010). However, more detailed research is warranted to assess the protective effects of RAS inhibitors in BC prevention.

In vitro and in vivo studies investigating the protective role of ACE-I/ARBs

ACE-I, captopril has anti-tumor and anti-angiogenic activity by inhibiting MMP-2 and MMP-9, which are responsible for matrix degradation and cell invasion, in a mouse model for Lewis lung cell carcinoma (Prontera *et al.* 1999). Furthermore, the sulfhydryl group in captopril is capable of chelating zinc ions, further reducing MMP activity. This was shown in a study where captopril administration resulted in reduction of tumor size in a mouse xenograft model of human renal carcinoma (Hii *et al.* 1998). Another study investigated the effect of ACE-I, perindopril on tumor progression and angiogenesis in a mouse xenograft model of triple negative BC. Patel *et al.* found that perindopril when treated with 2 mg/kg body weight per day significantly reduced tumor volume and VEGF levels, demonstrating a protective anti-inflammatory and anti-proliferative effect on TNBC (Patel & Nakka 2017). Captopril was found to be cytotoxic to ER/PR negative human mammary ductal carcinoma cell line in the presence of copper salts (Small *et al.* 1999). Furthermore, ARBs were associated with downregulating cancer cell proliferation, angiogenesis and inflammation by inhibiting transactivation of ERK1/ERK2, VEGF and NK-κB (Deshayes & Nahmias 2005). Kurosaka *et al.* reported that male AT1R knockout mice injected with Lewis lung cancer cells have delayed wound healing and angiogenic response (Kurosaka *et al.* 2009). This is consistent with other studies showing reduced AT1R expression on cell surface and in the cytoplasm of breast carcinoma cells upon AT1R knockout (Inwang *et al.* 1997, Tahmasebi *et al.* 2006). Corroborating with the previous results, overexpression of AT1R increased tumor growth and angiogenesis in a mouse xenograft model of ER+ BC. As expected, losartan (ARB) reversed tumor-promoting effects in both *in vitro* and *in vivo* model of BC (Oh *et al.* 2016). Similar results were found with ARB, candesartan using a nude mouse model of mammary carcinoma (Chen *et al.* 2013). Researchers also observed that in MCF-7 BC cells, captopril along with losartan reduced resistance to tamoxifen, both individually and in combination (Namazi *et al.* 2014). Additionally, losartan and captopril are associated with around 35% reduction of tissue factor, TF (metastatic potential) mRNA expression in metastatic MDA-MB-231 BC cells accompanied by a significant reduction in VEGF-associated neovascularization (Napoleone *et al.* 2012). In summary, Ang II has potential carcinogenic effect, especially when activated in breast adipocytes and mediates most of its inflammatory, angiogenic and tumor-promoting activities via binding to AT1R receptor. Therefore, inhibiting Ang II production and Ang II interaction with AT1R using ACE-I and ARB

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could lead to promising therapeutic approaches in BC treatment.

Human studies reviewing the protective role of ACE-I/ARBs in BC treatment

Although several *in vivo* and *in vitro* studies report protective effects of RAS inhibitors, results are inconsistent in clinical studies with human. Human studies reported mixed results on ACE-I and ARB use in improving overall BC outcomes (Table 2). While RAS inhibitors are used widely as antihypertensive drugs, their role as anti-cancer agent is not yet fully understood. ACE-I and ARBs have been found to demonstrate anti-inflammatory and pro-apoptotic activities in several preclinical studies of BC (Deshayes & Nahmias 2005, Rosenthal & Gavras 2009, George *et al.* 2010). However, clinical studies do not fully support these findings (Raimondi *et al.* 2016). A recent retrospective cohort study with 671 BC patients reported inconsistent effects of ARBs on cancer prevalence and cancer-specific survival after 5-year follow-up. Here, only 7% of the total patients were using ARB and interestingly, though ARB-treated patients had a trend toward larger tumor size, the mean Ki-67-mediated BC aggressiveness was lower among ARB-treated patients. This conflicting data is possibly due to inclusion of both premenopausal and postmenopausal BC patients, inclusion of only ER-positive and EGFR-negative BC cases, and <10-year follow-up period of drug effects. The authors acknowledged that it was a single-center study which may be subjected to unknown bias and the findings cannot be generalized to overall population as ARB usage was studied only in patients with specific type of BC (Goldvaser *et al.* 2016). However, a recent meta-analyses of 21 observational studies reported a significantly reduced risk of BC with 10 or more years of ACE-I/ARB usage (Ni *et al.* 2017). Hence, the conflicting results of two studies mentioned above might be due to their (i) methods of data collection like retrospective in former versus prospective in later, (ii) follow-up time like >10 years in later versus <10 years in the former study, (iii) categorization of BC patients like ER+/EGFR− in the former versus all types of BC inclusion in the later, among all. All these variables could essentially skew the final findings of the studies mentioned earlier. Additionally, some studies reported possible RAS inhibitor-associated increases in different cancer risk and recurrence (Bangalore et al. 2011, Ganz *et al.* 2011). Sun *et al.* addressed these contradictory effects of RAS inhibitors on different cancer trials as being due to variability in drug doses, the type, and progressive stage of particular cancers (Sun *et al.* 2017). Other researchers have reported interesting roles of drug interactions among RAS inhibitors and COX-2 inhibitors. As prostaglandins and Ang II share common downstream effectors, such as the PI3K/AKT pathway (Barnes *et al.* 2007, Zhao *et al.* 2010), they can individually, or in combination (additively or synergistically), affect BC progression. Lee *et al.* reported beneficial effects of ACE-I in enhancing anti-tumor effects of both non-steroidal anti-inflammatory drugs (NSAID) and non-NSAIDs (Lee *et al.* 2012). By contrast, Holmes *et al.* reported that aspirin use is associated with a 50% reduced risk of cancer deaths, while ACE-I alone did not alter the risk of BC deaths in 4661 women between 30 and 55 years included in the Nurses' Health Study (NHS) with Stage I-III invasive BC. Interestingly, risk estimates for cancer deaths and recurrence were lowered significantly with a combination of aspirin and ACE-I (similar to aspirin alone), in a multivariate model of BC deaths and medication use. These findings indicate potent effects of aspirin, and its ability to override the null effects of ACE-I with BC deaths and recurrence (Holmes *et al.* 2013). Major limitations of these findings include retrospective nature of these studies, lack of follow-up studies, self-reported medication data, lack of adherence to drug usage, and inconsistent data on obesity status, smoking, family and hereditary history. Another combination was tested by Chae *et al.* who investigated individual and combined effects of ACE-I, ARBs and the cardioprotective drug, Statin, in reducing BC recurrence. They reported that ACE-I/ARB treatments significantly reduced BC recurrence in patients after a 4-year minimum follow-up, though there was no impact on overall cancer survival (Chae *et al.* 2011). Another study found favorable effects of ARB use on relapse-free BC survival (RFS) in patients undergoing neoadjuvant chemotherapy (Chae *et al.* 2013). Researchers found no association of ARB/ACE-I use with overall and site-specific cancer risk from 15 combined trials of 138,769 participants with higher cardiovascular disease risk (ARB Trialists Collaboration, 2011). The only limitation of such observational studies is failure to follow-up patients for a long period of time. To summarize, the results from human studies indicate the need for more mechanistic studies involving cell, animal, and human models to identify and target the key variables responsible for BC cell growth, proliferation and metastasis.

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Conclusions and future directions

In this review, we have specifically focused on the potential mechanisms linking obesity, RAS and BC. The RAS is a possible link between obesity and BC interaction, as components of RAS are overexpressed in both obese and malignant cells, helping in the process of cell proliferation and growth. Activation of inflammatory pathways like NF-κB via Ang II and AT1R modulation have a major role in obesity-linked BC progression. Despite different adipokines, hormones and growth factors, adipocyte-derived Ang II can mediate its effect by BAT activation or WAT browning, which requires further research to understand RAS-mediated BAT action in obesity and BC crosstalk. Another potential research area is adipose-macrophage interaction in BC. Ang II is responsible for macrophage polarization and infiltration in both obesity and different tumor models. However, their mechanistic interaction is beyond the scope of this review.

In conclusion, obesity is a critical risk factor for developing BC especially in women after menopause. Obesity induces Ang II secretion, thereby promoting toxic tumor microenvironment. Overexpression of Ang II and its receptor AT1R is associated with many tumors, and activities like cell proliferation, angiogenesis, and inflammation. Hence, drugs blocking Ang II and AT1R interaction are of specific importance in altering adverse tumor outcomes. Although clinical and preclinical human studies report contradictory effects of ACE-I/ARB in BC, results available from cell and animal studies provide evidence of their beneficial effect on a mechanistic level. Given ongoing clinical use of RAS inhibitors, their feasibility and established safety as antihypertensives with minimum side effects, more in-depth investigations are warranted.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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