Revising the role of the androgen receptor in breast cancer

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Abstract

Breast cancer (BC) is traditionally viewed as an oestrogen-dependent disease in which the androgen receptor (AR) is inhibitory, counteracting the oncogenic activity of oestrogen receptor α (ERα (ESR1)). Most probably as a result of this crosstalk, the AR has prognostic value in ER-positive disease, with AR positivity reported to correlate with a better prognosis. Activation of the AR pathway has been previously used as a therapeutic strategy to treat BC, but its usage declined following the introduction of the anti-oestrogen tamoxifen. More recently, it has been demonstrated that a subset of triple-negative BCs (molecular apocrine) are dependent upon androgen signalling for growth and therapies that inhibit androgen signalling, currently used for the treatment of prostate cancer, e.g. the antiandrogen bicalutamide and the CYP17 inhibitor abiraterone acetate are undergoing clinical trials to investigate their efficacy in this BC subtype. This review summarises the current knowledge of AR activity in BC.

Key Words
- breast cancer
- oestrogen receptor
- androgen receptors
- steroid

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Breast cancer

Breast cancers (BCs) account for one in three newly diagnosed cases of cancer in women and led to 11 600 deaths in 2010 in the UK alone (CRUK 2014). Incidence rates increased by 90% between 1971 and 2010, with the largest increase in women aged 50–69 (ONS 2013). A large proportion of this rise has been attributed to the introduction of BC screening programmes, but other factors such as changes in lifestyle are also likely to have played a role (Parkin *et al.* 2011). The disease is approximately 100 times more common in women than men, with 49 500 and 397 cases respectively diagnosed in 2010. The greatest risk factor associated with the disease after gender is age, but other risk factors such as reproductive and family histories have also been identified.

Oestrogen receptor status and BC subtypes

BCs are a highly heterogeneous disease and gene expression profiling has identified four distinct malignant subtypes termed as basal-like, human epidermal growth factor receptor 2 (HER2)-enriched, luminal A and luminal B cancers (Perou *et al.* 2000, Sørlie *et al.* 2001). This classification is based on the expression of three receptors: oestrogen receptor α (ERα (ESR1)), progesterone receptor (PR (PGR)) and the erythroblastosis oncogene B2 (ErBB2, HER2/NEU), the expression of which are predictive of clinical response and prognosis. Luminal A and luminal B subtypes account for 70% of all BCs and fall into the category of hormone-receptor-positive BCs, luminal A cancers being defined as hormone-receptor-(ERα and PR)-positive and HER2-negative while luminal B cancers are

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both hormone-receptor-positive and HER2-positive. Luminal B tumours, although they show lower expression of oestrogen target genes, are more often of a high grade with a higher Ki67 index and poorer outcome compared with luminal A (Wirapati *et al*. 2008). Conversely, the HER2-enriched subtype is hormone-receptor-negative and has amplification of the oncogene *HER2/NEU*. This subtype accounts for ~20% of cases and is associated with a more aggressive disease and worse prognosis (Ross *et al*. 2009). The remaining 10% of BCs are defined as basal-like or triple-negative BCs (TNBCs), a subtype of BC defined by ER, PR and HER2 negativity. TNBC tumours have a highly varied prognosis and clinical outcome, which is probably a reflection of the number of different subgroups that have been identified through gene expression profiling (Turner *et al*. 2010, Lehmann *et al*. 2011, Turner & Reis-Filho 2013). For example, Lehmann *et al*. (2011) analysed 21 BC datasets and identified six TNBC subtypes that displayed unique gene expression profiles and ontologies: basal-like 1, basal-like 2, immunomodulatory, mesenchymal, mesenchymal stem-like and luminal androgen receptor (AR) subtypes. Interestingly, the luminal AR (molecular apocrine) subtype has been demonstrated to have a gene expression profile resembling that of ERα-positive tumours, and this signalling may be attributable to the AR (Farmer *et al*. 2005, Doane *et al*. 2006).

Management of BC

The most important prognostic and predictive factors in the management of BCs are expression of ERα, PR, HER2 and proliferation markers (e.g. Ki67), and tumour size. A small proportion (~10%) of patients present with non-invasive disease (CRUK 2014). Atypical ductal hyperplasia or ductal carcinoma *in situ* is characterised by the proliferation of malignant epithelial cells confined to the ductal system of the breast, without invasion through the basement membrane into the surrounding stroma (Page *et al*. 1985, Schnitt *et al*. 1988). Surgery followed by radiotherapy is a therapeutic option for *in situ* disease and there has been a shift from radical mastectomy towards minimally invasive procedures (Héquet *et al*. 2011). However, the majority of patients present with invasive BCs. Generally, the therapeutic strategy for invasive BCs is surgery followed by chest wall or breast irradiation. Systemic therapy is also often administered before surgery either in a neoadjuvant setting – for patients with an unfavourable tumour to breast size ratio, aiming to shrink the tumour size and achieve breast-conserving surgery – or after surgery in the adjuvant setting. The therapeutic used is defined by molecular profiling of the tumour on an individual basis, i.e. chemotherapy or a hormonal therapy.

All patients with ERα-positive tumours are candidates for hormone therapy that either antagonises the binding of agonist ligands and/or promotes receptor degradation, through the use of anti-oestrogens, or blocks oestrogen synthesis with aromatase inhibitors (AIs). Two distinct classes of synthetic anti-oestrogens have been developed: selective ER modulators (SERMs) and selective ER down-regulators (SERDs). SERMs are a class of ERα ligands, exemplified by tamoxifen (Nolvadex), that act as either antagonists or agonists depending on tissue context (Jordan 2007), whereas SERDs (e.g. fulvestrant/Faslodex) are a class of steroidal, pure anti-oestrogens. Fulvestrant binds to ERα, induces an inactive conformation, blocking ERα dimerisation and nuclear localisation, and in addition targets ERα for ubiquitination and degradation by the proteasome (Cardoso *et al*. 2013). The use of AIs is generally restricted to postmenopausal women with ER-positive disease. In premenopausal women, oestrogen is predominantly derived from the ovaries, but post menopause oestrogen is mainly produced in the peripheral tissues of the body. AIs are used to reduce oestrogen production within the tumour and in peripheral tissues (Jordan 2007), where the aromatase enzyme converts androstenedione into oestrone and testosterone into oestradiol (E_2). This therapy is not as effective in premenopausal women as a reduction in oestrogen levels activates the hypothalamus–pituitary axis to increase gonadotrophin secretion, thus stimulating the ovaries to increase steroid production.

Patients with ERα-negative disease and HER2 amplification are usually treated with the MAB trastuzumab (Herceptin) either alone or in combination with chemotherapy (Perez *et al*. 2011). HER2, like other members of the ErbB family, is a plasma-membrane-bound receptor tyrosine kinase. HER2 homodimerisation, or heterodimerisation with other members of the family, results in autophosphorylation that subsequently initiates a number of oncogenic signalling pathways such as MAPK and PI3K/Akt. Trastuzumab binds to the extracellular domain of HER2 and inhibits proliferation through multiple mechanisms as well as targeting the cell for destruction via the immune system (Nuti *et al*. 2011). Chemotherapy is also the preferred treatment for TNBCs, although therapies targeting the AR are currently under investigation due to the increasing importance of this receptor in this subtype.

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Steroid receptors

The nuclear receptors comprise one of the largest families of transcription factors, with 48 members presently described in humans (Robinson-Rechavi *et al.* 2003). The steroid receptors form a subfamily, characterised as ligand-dependent, sequence-specific transcription factors (Mangelsdorf *et al.* 1995). Upon ligand binding, the receptors regulate gene expression to control development, homoeostasis and metabolism (Olefsky 2001). Like other nuclear receptors, steroid receptors have a modular structure consisting of an N-terminal activation domain, a central DNA-binding domain and a C-terminal ligand-binding domain (Brooke & Bevan 2009). The steroid receptor family comprises the AR, ER, glucocorticoid receptor (GR), mineralocorticoid receptor (MR) and PR. Two main ER variants have been described, ERα and ERβ, encoded by two separate genes (*ESR1* and *ESR2*). This review will focus on ERα and AR signalling.

Androgen and ER signalling

In women, androgens are produced by the ovaries and adrenal glands and are secreted at a higher level than oestrogen (Burger 2002). The main circulating androgens in premenopausal women are DHEAS, DHEA, androstenedione, testosterone and dihydrotestosterone, with the AR only having high affinity for the latter two. In women, 50% of circulating testosterone is produced by the ovaries and adrenal gland and released directly into the blood. The remaining 50% is synthesised from adrenal androgens in other parts of the body (e.g. adipose tissue; Burger 2002). The aromatase enzyme metabolises testosterone to E_2 and androstenedione to oestrone. Oestrone can also be converted to E_2, a step metabolised by 17β-hydroxysteroid dehydrogenase.

There are a number of similarities between the AR and ERα signalling pathways. In the absence of ligand, both receptors are held in an inactive ligand-binding competent state through association with heat shock protein complexes (Pratt & Toft 1997, Le Romancer *et al.* 2011). Upon ligand binding, the receptors undergo a conformational change that promotes nuclear localisation, dimerisation and DNA binding. Both receptors recruit a range of cofactors, some of which are common to both pathways, and the general transcription machinery to subsequently initiate transcription. Steroid receptors interact with DNA via sequence-specific hormone response elements consisting of an inverted repeat of core recognition sequence separated by 3 bp, and this is exemplified by ER binding to an inverted repeat of 5′-AGGTCA-3′ (Carroll *et al.* 2006). The AR binds to an imperfect inverted repeat of the 5′-AGAACA-3′ core recognition sequence (Beato 1989, Massie *et al.* 2011), but this is not specific for the AR, as the GR, MR and PR also bind to such response elements (Glass 1994). However, response elements specific for the AR have also been identified and consist of direct repeats of the core recognition sequence (Claessens *et al.* 2001).

ERα can also regulate gene transcription without directly binding to response elements. This is achieved through interaction with transcription factors that tether the receptor to DNA (Björnström & Sjöberg 2005). For example, ERα is recruited to the BC susceptibility gene *BRCA1* via interaction with specificity protein1 (SP1) transcription factors and activator protein 1, allowing for oestrogen regulation of a target gene that lacks an oestrogen response element (ERE; Jeffy *et al.* 2005, Hockings *et al.* 2008). In addition to their genomic activity, both AR and ERα are also known to signal at the cell membrane and activate downstream signalling cascades. For example, AR and ERα can form ternary complexes with c-Src and modulator of non-genomic activity of oestrogen receptor (MNAR; Wong *et al.* 2002, Unni *et al.* 2004). Binding of the ligand to either receptor results in activation of c-Src and subsequent activation of various downstream pathways, including MAPK. This non-genomic signalling allows for a more rapid cellular response to stimuli compared with the classical pathway (Falkenstein *et al.* 2000).

AR and ERα crosstalk

Several studies have demonstrated that the AR and ERα inhibit each other's activity and that multiple mechanisms of crosstalk exist between the receptors (Fig. 1). For example, Panet-Raymond *et al.* (2000) showed that, in the presence of E_2, the N-terminus of AR can interact with the ERα LBD and that this interaction is inhibitory to the transcriptional activity of both receptors, demonstrating that direct interaction between the receptors impedes signalling. Electrophoretic mobility shift assays and chromatin immunoprecipitation studies have also demonstrated that the AR can bind to EREs (Peters *et al.* 2009). Transfection of BC cells with the *AR* DNA-binding domain was sufficient to inhibit ERα activity indicating that direct competition for binding sites is also a mechanism of crosstalk between the pathways. Lastly, the transcriptional activities of the AR and ERα are known to be influenced by common cofactors (reviewed in

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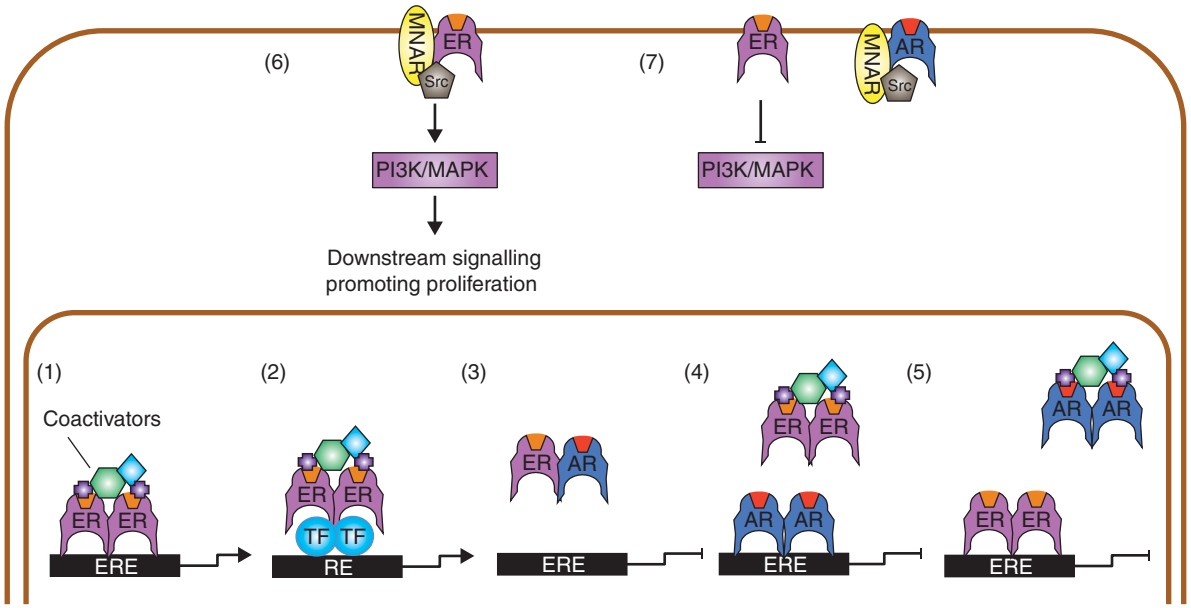

Figure 1

Potential mechanisms of crosstalk between the androgen receptor and oestrogen receptor α pathways. (1) In classical ERα signalling, the ligand-bound receptor binds to specific DNA sequences (oestrogen response elements (EREs)) found in the regulatory regions of target genes, and via the recruitment of a complex of accessory proteins (coactivators) and the general transcription machinery, initiates gene transcription. (2) ERα also regulates gene transcription through interaction with transcription factors that tether the receptor to DNA. (3) The AR and ERα have been found to directly interact and this interaction is inhibitory to the transcriptional activity of both receptors. (4) The AR can bind to EREs and hence there may be competition for DNA occupancy. (5) ERα and AR share common coactivator proteins and hence through sequestration of accessory proteins, the AR may reduce ERα signalling. (6) ERα also has non-genomic actions, with membrane-bound receptors able to regulate protein kinase cascades (e.g. MAPK). (7) The AR has a similar non-genomic activity and competition for accessory proteins (e.g. MNAR), important in this signalling, may inhibit receptor activity.

Risbridger *et al.* (2010)). For example ARA70, a well-known AR cofactor, can also act as an ERα coactivator and competition for such factors is likely to have a bearing on receptor signalling (Lanzino *et al.* 2005). Similarly, as described above, the AR and ERα interact with common partners to regulate signalling pathways at the cell membrane, and hence competition for scaffold proteins such as MNAR (PELP1) may regulate the non-genomic activity of these receptors.

AR in the breast

In normal breast

At birth, the mammary gland consists of a rudimentary ductal system that continues to grow in proportion to the body until puberty, when expansive growth occurs. At this stage, ERα is the key receptor regulating ductal morphogenesis, as determined by the analysis of mouse knockout models (reviewed by Macias & Hinck (2012)). Interestingly, immunohistochemistry has demonstrated that, in premenopausal women, only 10% of epithelial cells in acini and interlobular ducts stain positive for ERα and it appears that, in response to oestrogen, these cells secrete paracrine factors that stimulate the surrounding ER-negative cells to proliferate. In contrast, a higher percentage (20%) of cells stain positive for the AR (Li *et al.* 2010) and several studies have demonstrated that the AR also plays a role in regulating normal breast development. For example, the *Ar* knockout mouse has reduced ductal branching, decreased lobuloalveolar development and fewer milk-producing alveoli in the mammary gland (Yeh *et al.* 2003). In a separate study, Peters *et al.* (2011) demonstrated that administration of 5α-dihydrotestosterone or the antiandrogen flutamide to female mice altered mammary gland development/morphology, with stimulation of the AR pathway resulting in reduced ductal extension in animals mid-puberty. Similar results were obtained in ovariectomised rhesus monkeys, where testosterone treatment was able to inhibit E_2-induced mammary epithelial proliferation (Zhou *et al.* 2000). It therefore appears that in normal breast, AR activity is able to balance E_2-induced cell proliferation, influencing the correct development of the gland (Yeh *et al.* 2003).

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AR in BC

Although ERα plays a pivotal role in driving BC growth, the most commonly expressed hormone receptor in *in situ*, invasive and metastatic BCs is the AR. The AR is present in up to 90% of primary tumours (Søreide *et al*. 1992, Hall *et al*. 1996, Park *et al*. 2010) and 25% of metastases (Gucalp *et al*. 2013) and appears to play different roles at different stages and in different subtypes of the disease. Although BCs are still classified in clinical practice based on ERα, PR and HER2 expression, as a consequence of a growing body of evidence indicating the importance of AR activity in the absence of oestrogenic signalling, Farmer *et al*. (2005) proposed reclassification of BCs into three broad subtypes based on the presence or absence of ERα and AR: luminal (ERα+ AR+), basal (ERα− AR−) and molecular apocrine (ERα− AR+).

Many *in vitro* studies have investigated the clinical significance of AR expression in BCs with the aim of characterising the effects of androgen signalling upon proliferation. The majority of studies have demonstrated that AR signalling is inhibitory towards BC cell line growth (Zhou *et al*. 2000, Ortmann *et al*. 2002, Dimitrakakis *et al*. 2003, Greeve *et al*. 2004, Macedo *et al*. 2006, Cops *et al*. 2008). However, some studies have found that androgens have a pro-proliferative activity (Birrell *et al*. 1995, Maggiolini *et al*. 1999, Lin *et al*. 2009). The disparity between these studies may be due to the lack of consistency in the methodologies used to assess cell growth (e.g. cell counting, 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide (MTT) colorimetric assay or FACS), conditions used for cell culturing (full or hormone-depleted media), type of androgen (e.g. dihydrotestosterone or testosterone) and dose and time of stimulation (Garay & Park 2012).

AR as a prognostic factor Immunohistochemical studies have demonstrated that AR expression varies between the different subtypes, with a higher positivity in luminal A-like tumours and a lower positivity in TNBCs (Luo *et al*. 2010, Park *et al*. 2010, Loibl *et al*. 2011, Tsang *et al*. 2014). A number of studies have investigated the prognostic potential of AR expression in BCs, with the majority finding the AR to be associated with favourable clinicopathological features. In ERα-positive BCs, AR has been found to correlate with lower grade, reduced lymph node involvement and longer disease-free survival, and this correlation is proportional to the levels of AR expression (Schippinger *et al*. 2006, Søiland *et al*. 2008, Castellano *et al*. 2010, Hu *et al*. 2011, Park *et al*. 2011, Tsang *et al*. 2014). In one study, AR and ERα levels were analysed in 1467 BC tumours from postmenopausal women enrolled in the Nurses' Health Study (Hu *et al*. 2011). Of the 1164 ER-positive tumours, 88% were also positive for AR and AR positivity was associated with a 30% reduction in BC mortality. Similarly, Castellano *et al*. (2010) investigated AR expression in 953 ER-positive tumours and found that AR expression correlates with small tumour size (<2 cm) and reduced lymph node metastasis. Furthermore, AR expression was also demonstrated to be a marker of good prognosis for time to relapse and disease-specific survival (Castellano *et al*. 2010). It has been proposed that the protective effect of the AR in BCs reflects the inhibitory effect of AR on ERα activity demonstrated *in vitro*.

AR and HER2 expression have been found to correlate in BCs (Micello *et al*. 2010, Niemeier *et al*. 2010, Park *et al*. 2010). For example, Micello *et al*. (2010) found that 77% of HER2-positive tumours were AR-positive compared with 30% in the HER2-negative group. Importantly, the improved survival associated with the AR in ERα-positive tumours was only identified in HER2-positive disease while no significant difference in overall and disease-free survival was detected in HER2-negative luminal B BCs (Tsang *et al*. 2014). Previous studies have investigated the relationship between the AR and HER2 pathways and have demonstrated that hyper-activation of HER2 enhances AR activity and that AR directly upregulates *HER2* gene expression in a positive feedback loop (Naderi & Hughes-Davies 2008, Chia *et al*. 2011).

The AR is expressed in 10–43% of TNBCs (McGhan *et al*. 2014), but the prognostic value of the AR in this subtype remains unclear, with some studies indicating an increased mortality (Hu *et al*. 2011), some showing no influence of AR expression (Mrklić *et al*. 2013) and some indicating a better prognosis (Robinson *et al*. 2011, He *et al*. 2012, Sutton *et al*. 2012, Tang *et al*. 2012). For example, Hu *et al*. (2011) analysed AR expression in 211 TNBC cases and found that patients with AR-positive tumours had an 83% increase in overall mortality compared with the AR-negative group; furthermore, McGhan *et al*. (2014) found AR expression to correlate with higher tumour stage and an increase in lymph node metastases. In contrast, several studies have found AR-positive TNBC patients to have a reduced proportion of lymph node metastases (Rakha *et al*. 2007, Luo *et al*. 2010, He *et al*. 2012), increased overall survival (Luo *et al*. 2010, He *et al*. 2012), lower tumour burden and favourable differentiation (Park *et al*. 2010). It is unclear as to why contradictory results have been obtained in these studies,

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but this may in part be due to the variability in antibodies used and the different scoring systems (e.g. *H* score or % positivity) and cutoffs (>0 up to ≥10%) used to define AR positivity (McGhan *et al*. 2014).

Immunohistochemical detection of the AR could be a useful indicator of better prognosis and improved survival rate, particularly in ER-positive disease. Downstream targets of the AR may also be useful biomarkers for BCs, as they can be used as a measure of receptor activity. Prostate-specific antigen (PSA) is an androgen-responsive gene, serum levels of the protein product of which are used as a biomarker for the management of prostate cancer. Although generally regarded as a prostate-specific gene, low PSA expression has also been found in mammary epithelia and PSA levels have also been correlated with BCs, with PSA expression associated with early disease stage, low grade, small tumour size, ER-positive disease, reduced risk of relapse and longer survival (Yu *et al*. 1995, Mohajeri *et al*. 2011). The current tests lack the sensitivity to measure the low levels of PSA in the sera of women, however, new ultrasensitive tests are under development (Chang *et al*. 2011). Although AR and PSA expression are not routinely assessed in patients, if therapies targeting the androgen pathway are approved for clinical use for the treatment of BC, such assays will be crucial in identifying those patients most likely to benefit.

AR in molecular apocrine disease TNBC expressing AR is clinically defined as 'molecular apocrine' (Farmer *et al*. 2005). This subtype has been extensively studied *in vitro*, predominantly using the MDA-MB-453 cell line (e.g. Doane *et al*. (2006) and Robinson *et al*. (2011)). Increased androgen signalling has also been confirmed in other TNBC cell lines (e.g. GSE-10890 and E-TABM-157) and the dependence of these cell lines on AR activity for growth has been demonstrated by targeting AR with siRNA, or treatment with the antiandrogen bicalutamide (Lehmann *et al*. 2011, Robinson *et al*. 2011). Robinson *et al*. (2011) clarified the role that AR plays in ERα-negative BCs by performing chromatin immunoprecipitation (ChIP)-sequencing to map AR-binding events in the MDA-MB-453 genome. The group were able to show that, in the absence of ERα, more than half of AR-binding events in the genome map in a similar pattern to that of ERα in ER-positive cells, promoting the expression of ERα target genes. In this context the AR is capable of, at least in part, mimicking ERα in a transcriptionally active manner, stimulating an expression pattern more similar to that of ERα in MCF7 cells than the profile reported for the AR in the LNCaP prostate cancer cell line. The pioneer factor FoxA1 appears to be critical in directing the AR to target genes (Robinson *et al*. 2011). This indicates that, in ERα-negative disease, the AR can drive tumour progression and therefore represents a therapeutic target for this subtype of BC.

AR as a therapeutic target Targeting the AR and/or androgen synthesis is the mainstay of prostate cancer therapy, as well as long-established therapeutic antiandrogens, such as bicalutamide, new therapeutics have been developed recently with the aim of overcoming drug resistance in this malignancy. Examples include abiraterone acetate, an inhibitor of androgen biosynthesis, and the second-generation antiandrogen enzalutamide (Attard *et al*. 2005, Tran *et al*. 2009). In women, antiandrogens are currently administered to treat various medical conditions attributed to aberrations in the androgen pathway (e.g. amenorrhoea, androgenic alopecia and hirsutism), and they have also been trialled for the treatment of ovarian cancer (reviewed in Karrer-Voegeli *et al*. (2009) and Papadatos-Pastos *et al*. (2011)). Similarly, the AR is also now considered as a therapeutic target for the treatment of BC, with methods to activate the receptor as a potential option for ERα-positive disease, and inhibition of the receptor as an option for molecular apocrine disease.

Androgen supplementation therapy does have antiproliferative activity in BC patients, but it is associated with negative side effects (e.g. increased aggressive behaviour and excessive hair growth). This, as well as the demonstration that androgens can be converted to E_2 and the introduction of tamoxifen, led to androgen therapy losing popularity in the 1970s (Garay & Park 2012). However, due to the demonstration of an oncogenic role for the AR in molecular apocrine diseases, clinical trials are underway/planned to assess the potential of inhibiting androgen signalling for the treatment of this subtype. For example, Gucalp *et al*. (2013) performed a single-arm phase II study to investigate the efficacy of the antiandrogen bicalutamide in patients with AR-positive immunohistochemistry (IHC) ≥10%, ER- and PR-negative metastatic BCs. A total of 26 participants received 150 mg bicalutamide daily until disease progression. The therapy was in general well tolerated and 19% of the patients showed a 6-month clinical benefit rate (Gucalp *et al*. 2013). This therefore demonstrates that inhibiting the AR is a promising therapeutic strategy for a subset of patients. Further clinical trials are also planned to investigate the efficacy of the antiandrogen Enzalutamide (clinicaltrials.gov: NCT01889238) and the newly developed CYP17 inhibitors abiraterone acetate (NCT00755885) and orteronel (NCT01990209), for the treatment of molecular

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apocrine disease, although it will be several years before the results of these studies are published.

Conclusions

A key aim of cancer research is to identify targeted therapies to allow for personalised and tailored therapeutic regimes, and biomarkers for patient stratification to improve therapy efficacy. The AR is a key regulator of BC growth, as a crosstalk inhibitor of oestrogen signalling in ER-positive disease and as an oncogenic driver of tumour growth in molecular apocrine disease and therefore represents a useful marker and therapeutic target for the management of BCs. As a result of recent advances in the field, further clinical trials targeting this pathway are planned for the near future. Should promising initial results be upheld and expanded, this will represent a breakthrough for a subset of patients who currently have limited disease management options.

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

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