

Review Article

Androgen receptor as a targeted therapy for breast cancer

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Received April 25, 2012; accepted May 15, 2012; Epub June 28, 2012; Published July 15, 2012

Abstract: Breast cancer occurs at a high frequency in women and, given this fact, a primary focus of breast cancer research has been the study of estrogen receptor α (ER) signaling. However, androgens are known to play a role in normal breast physiology and therefore androgen receptor (AR) signaling is becoming increasingly recognized as an important contributor towards breast carcinogenesis. Moreover, the high frequency of AR expression in breast cancer makes it an attractive therapeutic target, but the ability to exploit AR for therapy has been difficult. Here we review the historical use of androgen/anti-androgen therapies in breast cancer, the challenges of accurately modeling nuclear hormone receptor signaling in vitro, and the presence and prognostic significance of AR in breast cancer.

Keywords: Androgen receptor, MAP kinase, breast cancer, p21, androgens

Introduction

The development of targeted therapies has always been a goal of cancer research. The ideal targeted therapy by definition would be specific for the tumor and not affect other tissues in the body. While there are many examples of effective targeted therapies in a variety of cancers none fully achieve this definition; that is, side effects of medications always occur. Though there may never be a drug that achieves a perfect level of specificity, certainly there is opportunity for new targeted therapies to be as effective as or better than current standards of care. Therefore, the challenge for developing better therapies has recently relied upon the discovery and validation of targets that are mostly or exclusively tumor-specific, including products of gene mutations and/or translocations. An alternative strategy that has been successful for cancer therapy is to develop drugs against targets that are frequently expressed at increased levels in cancerous tissues. Examples include HER2, a member of the epidermal growth factor receptor (EGFR) family, and estrogen receptor α (ER). Both have been successfully exploited as targeted therapies for breast cancer patients [1, 2]. However, many patients are not eligible for these therapies because their tumors lack ex-

pression of these receptors, and/or their tumors become resistant to the therapeutic agent. Thus, there is a continuing need to expand the repertoire of targeted anti-cancer therapies. This review focuses on the androgen receptor (AR) and its future potential as a new generation of endocrine therapies for the treatment of breast cancer.

History of targeting AR for therapy in breast cancer

It has been appreciated now for over a century that hormones play a critical role in breast carcinogenesis [3, 4] and therefore this provides a rationale for their use as anti-cancer therapies. Given the drastically higher prevalence of breast cancer in women compared to men, research has focused on the dominant sex hormone in females, that is, estrogens. However, because male sex hormones also play a role in normal female breast physiology, research has also been conducted in the use of androgens for breast cancer therapy. In principle one might hypothesize that breast cancer may be a result of a hormonal "imbalance" of estrogens to androgens and that this ratio is vastly different between women and men. Thus, empirically and simplistically, exogenous administration of an-

drogens could lead to an effective therapy for the treatment of breast cancer. For the first half of the 20th century, therapies utilizing androgens were mainly reserved for postmenopausal women; treatment for premenopausal patients initially consisted of oophorectomy either surgically by removing the ovaries or chemically by administration of androgens. However, androgen administration was discontinued when physicians became aware that androgens can be converted to estrogens [5]. As demonstrated by the results of experiments with surgical oophorectomy, it was clear that estrogen increased the formation of breast cancers and stimulated most of these malignancies to grow [3, 4]. Despite setbacks in the premenopausal setting, multiple studies in the postmenopausal setting validated the efficacy of androgen therapy [6-8]. Studies showed a disease regression rate of ~20-25% in women treated with androgen therapy which was slightly less effective than the ~25-35% rate demonstrated for women treated with estrogen-based therapy [9, 10].

While androgen therapy had moderate efficacy, the administration of excess androgen had significant negative side effects including increased aggressive behavior and hirsutism [7]. Efforts were made to minimize masculinizing side effects by developing androgen analogs, but similar efforts into developing improved estrogen based therapies were also underway. Eventually, targeting AR as a therapy for breast cancer fell out of favor in the 1970s with the advent of what would later be termed Selective Estrogen Receptor Modulators or SERMs [11]. This new class of drugs, with tamoxifen being the archetype, became the primary treatment modality not simply due to greater efficacy over conventional hormonal therapies but importantly because of a much favorable toxicity profile [10].

Because of the success of tamoxifen and other ER targeted therapies for the prevention and treatment of breast cancer (e.g. raloxifene, aromatase inhibitors, faslodex) very few clinical trials in the 1970s, 80s, and 90s focused on targeted androgen based therapy. Yet the idea of AR directed therapy for breast cancer was not completely abandoned as documented by a relatively few number of clinical trials during this period [12-14]. Although there are only a scant number of published reports examining the clinical feasibility of targeting AR, much more

work has been done in the laboratory setting. Collectively, these studies helped elucidate the role of AR in breast cancer and the mechanism of action of drugs targeting AR. With this laboratory work as a basis, therapies targeted to AR in breast cancer are re-emerging in the clinic. New clinical trials have been initiated within the last few years using agents directed against AR or against androgen production (see clinicaltrials.gov: NCT00468715, NCT00516542, NCT00755885, NCT00972023). The effectiveness of these androgen based therapies remains to be seen but will become more apparent in subsequent years. Additionally, with more data regarding the presence of AR and the mechanism of action of androgens in breast cancer, researchers have the opportunity to develop more efficacious targeted androgen therapies.

Action of androgens in the breast

Elucidating the effect of nuclear hormones in breast cancer has been a continual challenge. An immense body of work has been undertaken to understand nuclear hormone receptor signaling but these studies have not always provided clarity into how these pathways affect breast carcinogenesis. In this section we review these studies, acknowledge the hurdles that have been encountered, and attempt to provide insight into the results that have been generated over the past few decades.

In part, the lack of understanding of AR signaling as related to breast carcinogenesis is a direct result of the lack of ideal model systems that accurately recapitulate AR biology in human breast epithelial cells. *In vitro* models using cell lines established from primary human breast tumors have been the standard method for analyzing nuclear hormone receptor signaling in breast tissues. However, there are relatively few breast cancer cell lines that express AR as the sole sex hormone receptor, and those that do exist harbor genetic mutations/alterations that could potentially affect AR signaling. For example, the MDA-MB-453 breast cancer cell line is AR positive and ER negative, but also contains homozygous deletion of *TP53*, a homozygous *PTEN* missense mutation, *HER2* amplification and an oncogenic mutation in *PIK3CA* (Sanger COSMIC database) [15, 16].

The use of cancer cell line models has prevailed for years but has not always generated defini-

tive results. A report by Birrell et al. examined the response to androgens in four commonly used breast cancer cell lines [17]. Androgen treatment of one or more of these cell lines has been investigated in numerous reports from a variety of other groups including our own [17-34]. **Table 1** summarizes results from these published reports. The response to androgen treatment in a variety of other breast cancer cell lines also has been detailed by many other groups, but for brevity only the four cell lines investigated by Birrell et al. are included. Often the reports are in agreement with one another in respect to the response seen in a given cell line, but on occasion there are opposing results. This is of concern because irreproducibility obstructs the advancement of these AR ligands into *in vivo* studies or early phase clinical trials. Therefore the cause or causes of these disparate findings is worthy of further consideration.

Numerous experimental variables can be the source of incongruent results. As **Table 1** shows, different methods for assessing cell growth could be an explanation for experimental discrepancy between studies, but this is not likely. A more probable confounding issue is the growth conditions used in a particular assay. Density of cells at time of drug administration can skew observed proliferative or anti-proliferative results (unpublished observations and [23]). Our own unpublished observations and those of others have also shown that a confounding variable in the study of nuclear hormone receptors is serum conditions. Untreated serum can have exogenous and therefore unknown levels of hormones such as estrogen or testosterone. Reduction, though not complete removal, of exogenous growth factors and hormones is possible by treating serum with charcoal-dextran stripping or other methods; this can minimize the influence of exogenous hormones but not completely eliminate it from an experiment. Additionally, in some reports, growth inhibition by AR ligand is only examined in the presence of growth stimulation by another factor (often estrogen) [23, 24, 26, 27, 33]. Using estrogen to supplement cell growth while examining sensitivity to AR ligand can alter results because ER and AR interact within a cell and can modulate the ability of the other to transactivate target genes [35].

Another confounding factor is the use of different ligands. Most studies have used dihydro-

testosterone (DHT, the more potent and non-aromatizable form of testosterone) or R1881 (a non-aromatizable synthetic analogue of testosterone) to minimize the conversion of androgen to estrogen by cells in culture. An important issue to consider is the specificity of these ligands. While all ligands in **Table 1** have been shown to bind to AR, their ability to bind other receptors and cause conflicting responses has also been documented. Medroxyprogesterone acetate (MPA) provides an excellent example of this phenomenon. MPA is a synthetic progestin but it has been shown to bind to AR and results in androgenic signaling [36-38]. Thus, Dauvois et al. include it alongside DHT as an AR ligand in their analyses. The study from Zava and McGuire represents a similar situation. In their study, low doses (10nM) of DHT bind to AR and it is translocated to the nucleus but has no effect on cell proliferation. However, a higher concentration (1 μ M) stimulates proliferation [19]. The conundrum is that while nuclear translocation of AR was seen at this higher concentration so was nuclear translocation of ER. Since ER translocation was not seen at the lower concentration, the observed growth effects may have been mediated by ER rather than AR. Yet another illustrative example is the selective estrogen receptor downregulator, Faslodex (fulvestrant or ICI 182,780). This anti-estrogen clearly binds to ER and downregulates its expression but it has also been shown to have the same effect on AR in cultured cells [39]. Despite the limitations of cell based models, a better understanding of sex hormone signaling in breast cancer can be achieved through implementation of experimentally defined systems. The limitations of cell line models certainly should be considered with care and concern when considering the development of new targeted molecules for the treatment of cancer.

To this end, much effort has been invested into understanding the mechanism of action of AR in human epithelial cells. This includes research on intramolecular interactions within a single AR molecule, intermolecular interactions of AR upon dimerization, cellular localization of AR with and without ligand, protein turnover, and associations with other cellular proteins. It would be impossible to give each of these topics a thorough discussion in the length of this abbreviated review; therefore, we will focus briefly on the interaction of AR with other cellular proteins. In an effort to elucidate AR nuclear hor-

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Table 1. Growth response of breast cancer cell lines to androgen receptor ligand

Cell line	AR ligand	Concentration	Growth response	Assay	Grown in	Reference
MDA-MB-453	DHT	1nM	(+)(+)(+)	methylene blue whole cell binding	96-well plate	Birrell et al. 1995
	mibolerone	1nM	(+)(+)(+)	methylene blue whole cell binding	96-well plate	Birrell et al. 1995
	R1881	10nM	(+)(+)(+)	cell count using Vi-cell XR	T25 flask	Garay et al.
MCF-7	DHT	1nM	(+)(+)(+)	methylene blue whole cell binding	96-well plate	Birrell et al. 1995
	mibolerone	1nM	(+)(+)(+)	methylene blue whole cell binding	96-well plate	Birrell et al. 1995
	DHT	0.1nM - 10nM	(-)	cell count using hemacytometer w/trypan blue	24-well plate	Cops et al. 2008
	mibolerone	0.1nM - 10nM	(-)	cell count using hemacytometer w/trypan blue	24-well plate	Cops et al. 2008
	R1881	10nM	(-)(-)(-)	cell count using Vi-cell XR	T25 flask	Garay et al.
	mibolerone	10nM	(-)(-)(-)	cell count using Vi-cell XR	T25 flask	Garay et al.
	DHT	0.1nM - 100nM	(-)(-)(-)	cell count using hemacytometer	6-well plate	Greeve et al. 2004
	DHT	1nM - 1µM	(+)(+)(+)	cell count using hemacytometer	4x-cluster dish	Hackenberg et al. 1988
	DHT	1nM - 100nM	(+)(+)(+)	tritiated thymidine incorporation	24-well plate	Lin et al. 2009
	DHT	100nM	(+)(+)(+)	net protein synthesis	60mm dish	Lippman et al. 1976
	AD	1nM - 10nM	(-)	MTT colorimetric assay	96-well plate	Macedo et al. 2006
	DHT	0.01nM - 1nM	(-)(-)(-)	MTT colorimetric assay	96-well plate	Macedo et al. 2006
	T	100nM	(+)(+)(+)	methylene blue whole cell binding	60mm dish	Maggiolini et al. 1999
	DHT	1nM - 100nM	(-)(-)(-)	MTT colorimetric assay	96-well plate	Ortmann et al. 2002
	T47D	T	1nM - 100nM	(-)(-)(-)	MTT colorimetric assay	96-well plate
DHT		10nM	NR	N/A	N/A	Zava and McGuire 1978
DHT		1µM	(+)(+)(+)	N/A	N/A	Zava and McGuire 1978
DHT		1nM	(-)(-)(-)	methylene blue whole cell binding	96-well plate	Birrell et al. 1995
mibolerone		1nM	(-)(-)(-)	methylene blue whole cell binding	96-well plate	Birrell et al. 1995
DHT		N/A	NR	cell count and tritiated thymidine incorporation	N/A	Chalbos et al. 1982
DHT		0.1nM - 10nM	(-)	cell count using hemacytometer w/trypan blue	24-well plate	Cops et al. 2008
mibolerone		0.1nM - 10nM	(-)(-)(-)	cell count using hemacytometer w/trypan blue	24-well plate	Cops et al. 2008
R1881		10nM	NR	cell count using Vi-cell XR	T25 flask	Garay et al.
DHT		10nM	NR	quantification of total DNA and total protein	T75 flask	Horwitz et al. 1985
T		10nM	NR	quantification of total DNA and total protein	T75 flask	Horwitz et al. 1985
DHT		1nM - 100nM	(-)(-)(-)	MTT colorimetric assay	96-well plate	Ortmann et al. 2002
T		1nM - 100nM	(-)(-)(-)	MTT colorimetric assay	96-well plate	Ortmann et al. 2002
DHT		0.1nM - 1µM	(-)(-)(-)	cell count using Coulter Counter	6-well plate	Reese et al. 1988
ZR-75-1		DHT	10nM - 100nM	(-)	cell count using hemacytometer	T25 flask
	T	10nM - 100nM	(-)	cell count using hemacytometer	T25 flask	Sutherland et al. 1988
	DHT	1nM	(-)(-)(-)	methylene blue whole cell binding	96-well plate	Birrell et al. 1995
	mibolerone	1nM	(-)(-)(-)	methylene blue whole cell binding	96-well plate	Birrell et al. 1995
	DHT	~0.67nM	(-)(-)(-)	tumor volume	athymic mice	Dauvois et al. 1991
	MPA^	300µg/day	(-)(-)(-)	tumor volume	athymic mice	Dauvois et al. 1991
	DHT	1nM	(-)(-)(-)	cell count using Coulter Counter ZM	6-well plate	de Launoit et al. 1991
	R1881	10nM	NR	cell count using Vi-cell XR	T25 flask	Garay et al.
	DHT	10nM - 1µM	(-)(-)(-)	FACS quantification of subdiploid population	N/A	Kandouz et al. 1999
	DHT	0.01nM - 10nM	(-)(-)(-)	cell count using Coulter Counter ZM	24-well plate	Poulin et al. 1988
	T	0.01nM - 10nM	(-)(-)(-)	cell count using Coulter Counter ZM	24-well plate	Poulin et al. 1988

Abbreviations: DHT = dihydrotestosterone, AD = androstenedione, T= testosterone, MPA = medroxyprogesterone acetate. Growth effect is scored weak () or strong (()) based on report by cited authors; NR = no response. ^ MPA is a synthetic progestin but has been shown to bind androgen receptor and have androgenic effects

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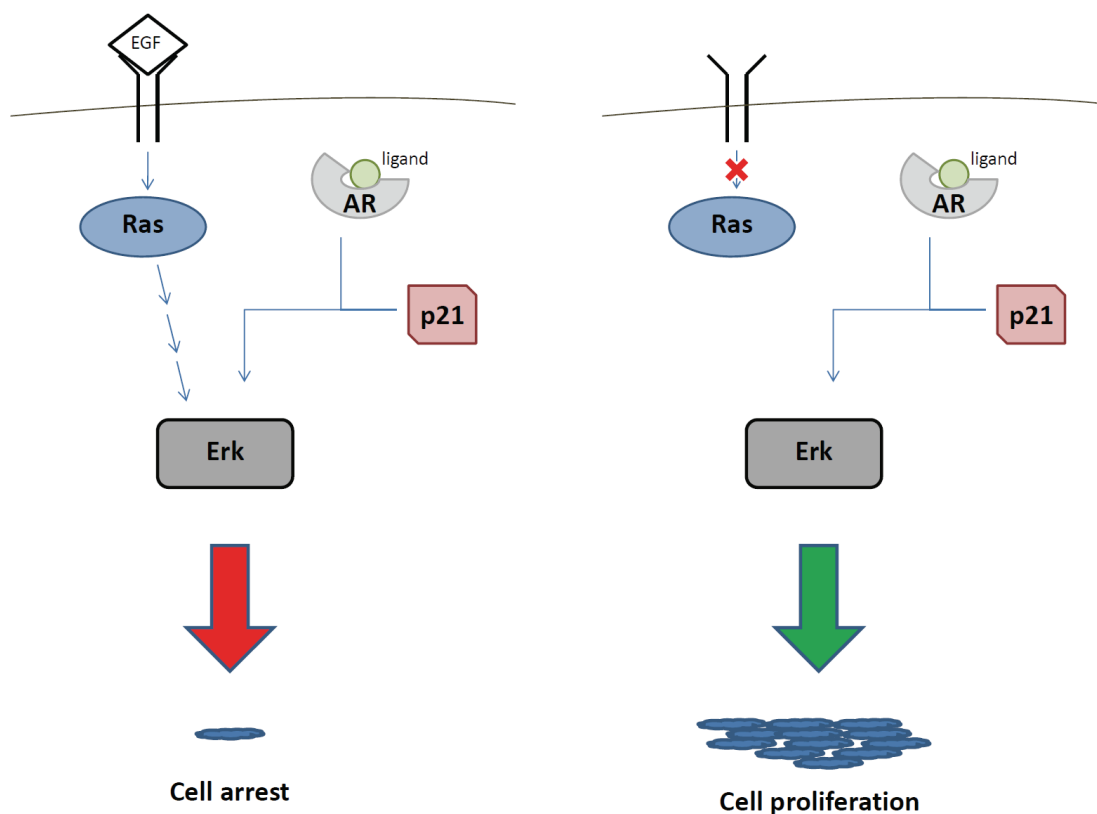


Figure 1. Schematic of signaling crosstalk between androgen receptor and epidermal growth factor receptor pathways. Concurrent signaling via androgen receptor with the epidermal growth factor receptor (left) leads to cell cycle arrest. Signaling via one or the other pathway (right) leads to growth proliferation. p21 is required for AR signaling in either situation.

more signaling in breast epithelial cells, our lab has created a non-tumorigenic breast cell line in which AR is the only expressed steroid hormone receptor [40]. Previously we have uncovered some of the mechanisms of ER signaling by creating a similar *in vitro* system [41, 42]. Utilizing this *in vitro* AR model, we have identified p21 as an important molecule in AR signaling. Similar results have also been reported in prostate and colon cancer cell lines [43]. The role of p21 in breast cancer has been appreciated previously as it is an important regulator of the cell cycle. Numerous other reports have shown that p21 is affected by ER signaling [44-47] and our lab has shown that the presence of functional p21 is necessary for sensitivity to tamoxifen treatment [42]. It is also known that p21 contains a putative androgen response element in its promoter [48]. Experiments using our model demonstrate that p21 is necessary for AR to signal through the MAP kinase path-

way, as measured by ERK phosphorylation [40]. It is unclear, however, whether this is due to a direct or indirect interaction between p21 and AR. What is intriguing and perhaps therapeutically relevant is that the response to AR signaling is dictated by additional MAP kinase activity within the cell. For example, under conditions in which MAP kinase is already being stimulated by epidermal growth factor receptor signaling, additional AR ligand binding with R1881 causes cell cycle arrest. However, in the absence of a MAP kinase pathway activation, the signaling from AR ligand binding with R1881 results in cell proliferation (**Figure 1**). Somewhat ironically, the therapeutic implication is to overload a tumor with growth promoting signals leading to cell cycle arrest. Indeed, recent evidence suggests supraphysiologic doses of androgens may be useful for the treatment of castration resistant prostate cancer and ongoing clinical trials are testing this concept [49]. While more details

of the exact mechanism and other molecules involved in AR and MAP Kinase crosstalk remain to be deciphered, this has provided a starting point to understanding the intricate molecular interactions that result from nuclear hormone receptor signaling.

AR expression in breast cancer and its prognostic value

As mentioned above, the presence of AR expression in breast cancer has always been appreciated but the ability to utilize this information effectively for therapy remains elusive. Although androgen therapy lost its status as a modality for managing breast cancer in the 1970s, laboratory investigation into the presence of AR in breast cancer continued and through the years began to gather momentum [50-52]. Aided by new, more sensitive methods to detect AR, studies demonstrated that AR, somewhat paradoxically, is the most commonly expressed nuclear hormone receptor in breast cancer [52-56]. Despite this fact, AR levels are not routinely assessed because they have not been shown to predict responses to currently used therapies. In contrast, assays for ER and progesterone receptor (PR) are performed routinely and have been shown to predict for response to currently approved endocrine therapies.

The success of ER/PR and HER2 targeted therapies has shifted interest in AR to those breast cancers that lack ER/PR and/or HER2 expression, so called triple negative disease. In addition, AR targeted therapies may also be important for breast cancers that have developed resistance to current hormone and HER2 directed therapies. Interestingly, AR is expressed in the majority of ER negative breast cancers with apocrine differentiation [57]. These tumors often have amplification of HER2 making them amenable to HER2 targeted therapies such as trastuzumab [1, 58]. Recent work detailing the gene expression of triple negative breast cancers supports these findings [59]. However, it has also been shown both *in vitro* and *in vivo* that combinatorial therapy targeting both the MAP kinase pathway and AR is an effective means of reducing tumor cell viability and tumor burden [60]. Whether used as a singular modality or in combination with other systemic agents, AR directed therapies could be a valuable treatment for a large proportion of breast cancers.

Perhaps the most cogent argument for targeting

AR is that approximately 10-35% of tumors without ER/PR expression or HER2 amplification (triple negative tumors) express AR [61, 62]. A study by Moinfar et al. examined sex hormone receptor status as well as HER2 amplification in various grades of carcinoma in situ and invasive cancer [63]. They found an inverse correlation between histopathological grade and the expression of all sex hormone receptors in breast tumors. As tumor grade progressed from 1 to 3, AR expression decreased from 95% to 76% in DCIS and 88% to 47% in invasive carcinoma. In the same analysis, ER expression decreased from 100% to 8% in DCIS and to 9.5% in invasive carcinoma, with increasing tumor grade. These findings have been validated by another independent report [54]. In addition, it has been shown that, albeit at a low percentage (25%), AR is the sole sex hormone receptor expressed in distant breast cancer metastases [52]. As stated, although AR expression decreases with higher tumor grade, the levels of expression remain significantly higher than ER, making AR a potentially valuable target for new therapies.

Interestingly, in the study by Moinfar et al., HER2 expression increases as tumor grade increases – 0% in grade 1 to 84% and 42% in grade 3 DCIS and invasive carcinoma respectively [63]. It is well known that this heightened HER2 expression is often a result of gene amplification [64], but gene amplification of other important mediators of breast carcinogenesis, such as nuclear hormone receptors, is less well-documented. Recently our lab examined the possibility of AR amplification as a possible etiologic factor of breast cancer as has been implied with ER amplification [65]. Examination of a tissue microarray consisting of multiple cores from 18 separate samples showed no amplification of AR [40, 66]. Replicates of these samples were similarly analyzed for AR expression; 62% of samples (21 of 34) had high levels of AR expression. Therefore, AR is overexpressed in the majority of breast tumors but its overexpression is not a result of gene amplification as is commonly seen with HER2. Consistent with this finding, recent reports did not find a high rate of ER amplification in breast cancers in contrast to the original report from Holst et al. [67-71]. Regardless, the frequency of AR expression in primary breast cancer samples justifies its consideration as a potential therapeutic target.

Although the ability to target AR for breast cancer therapy has yet to be effectively deployed,

many studies have looked at the utility of AR in breast cancer as a prognostic or predictive marker in breast cancer. AR expression has been linked favorably to response to the synthetic progesterone analogue MPA, with high levels of AR expression predicting for remission of tumors treated with MPA [72, 73]. Whether this is a result of the drug acting directly through AR is unclear, however. In another report by Rakha et al., AR was shown to be the most valuable prognostic factor when compared to a number of other markers including ER, PR, HER2, EGFR, and p53. Expression of AR in lymph-node positive tumors was prognostic for a better disease-free interval and overall survival, and loss of AR expression correlated closely with higher tumor grade, higher recurrence, and metastases [74]. Agoff et al. also found that expression of AR correlated with longer time to relapse of disease [75]. These studies focused on triple negative breast cancers, but the same correlation was found when ER positive tumors were examined. Castellano et al. determined in an ER positive cohort of patients that AR positivity was a prognostic marker for longer time to relapse and disease specific survival [76]. Collectively, these recent studies continue to support data from more historic reports demonstrating that AR expression in tumors correlates with good prognosis [51].

Because of the potential prognostic importance of AR, there also has been a desire to identify more assessable surrogate biomarkers for AR expression in breast cancer. For example, prostate specific antigen (PSA) is a well-known androgen-responsive gene and detection in the blood is used as a biomarker for prostate cancer. Secretion of PSA by breast cells, either benign or malignant, has been evaluated [77]. Also, correlation of PSA levels with breast cancer risk has been determined using feasible bioassays on samples collected via minimally invasive procedures such as collection of nipple aspirate fluid [78] or patient serum [79]. In the latter study, there is an association between higher detectable levels of secreted PSA and histological grade of the breast tumor. However, other reports present conflicting data about this association [80, 81]. Further studies are warranted before the routine use of PSA as reliable marker for breast cancer detection can be implemented.

While useful as a prognostic factor, AR lacks a

causative association between its expression and carcinogenesis. This has led researchers to explore the correlation of other factors in breast carcinogenesis with AR. One report did find a non-significant increase in breast cancer incidence in women taking a testosterone patch for increased libido over control patients, but the study lacked conclusive evidence to link increased androgens with breast cancer risk [82]. A series of studies tried to determine a causative role of AR in breast tumorigenesis involving the BRCA1 and BRCA2 tumor suppressor genes. BRCA genes require inactivation of both alleles for a phenotypic effect. In individuals with a germline mutation of one allele, other genes can modify the susceptibility of the second wild type BRCA allele to inactivation, rendering it more permissive to alterations that lead to its loss or silencing. In the case of AR, the length of a trinucleotide repeat (CAG) in the N-terminus of the gene has been linked to increased risk of developing breast cancer in BRCA mutation carriers; AR therefore may have a role in breast carcinogenesis in these kindreds [83]. This initial report was bolstered by a subsequent discovery that BRCA1 enhances AR activity by binding to the activation function domain in the N-terminal portion of the protein [84]. However, the validity of this hypothesis has been challenged [85-87]. As another example, Gonzalez-Angulo et al. explored the relationship in breast cancer between AR levels and mutations in the PI3-kinase alpha catalytic subunit, PIK3CA. They found AR tends to be more highly expressed in cancers with a particular PIK3CA mutation in the kinase domain of the protein [88], a finding further supported by recent studies by Pietenpol and colleagues [59]. Importantly, this correlation also holds in the subset of cancers that are negative for expression of ER and PR. This information leads to the intriguing idea of coupling androgen-based therapy with therapies targeting other important pathways.

Conclusion

Molecular analysis of tumors is becoming more detailed allowing therapies to become tailored to individual tumor types from patient to patient. Thus, it is becoming clear that no single treatment will be the panacea for cancer; so, if multi-faceted treatment is to be successful, it is necessary to utilize as many targets for therapy as logistically possible. AR is an excellent target for therapy because it has been shown historically to be an effective target for prostate can-

cer treatment and is commonly expressed in the majority of breast cancers. A clear and comprehensive understanding of the mechanism of AR signaling in the breast has yet to be revealed, but with continued laboratory efforts there is hope that soon we will have viable breast cancer therapies that exploit AR signaling.

Acknowledgments

Grant Support: The Avon Foundation (B.H.P.), NIH CA109274 (J.P.Garay is a recipient of a Research Supplement to Promote Diversity in Health-Related Research, B.H.P.).

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