PERIODICUM BIOLOGORUM
VOL. 114, No 4, 511–517, 2012

UDC 57:61
CODEN PDBIAD
ISSN 0031-5362

overview

Hormonal resistance in breast- and prostate cancer

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List of abbrevations:
ER – estrogen receptor
AR – androgen receptor
RTK – receptor tyrosine kinase
EGF – epidermal growth factor
EGFR – epidermal growth factor receptor
SERM – selective estrogen receptor modulator
SERD – selective estrogen receptor downregulator
CRPC – castration resistant prostate cancer

Received January 18, 2013.

Abstract

Breast and prostate cancers are the most common malignant disease in female and male world population, respectively. Both of these tumors are predominantly hormonal-dependent, what is rationale for the widely used endocrine treatment, with specific approach in each of them. Although endocrine treatment is obviously effective and responsible for prolonged progression-free survival and even survival, the problem is that breast and prostate cancers inevitably become "hormone-resistant". The paradigm of treatment has to be changed and today there are some ways to overcome these lack of endocrine responsivness. It is known better today which mechanisms are involved in hormone-resistance, and they are numerous, so the designation of new drugs with key features necessary activity in hormone--resistant tumors. In breast cancer, there are selective estrogen modulators as a way to overcome this problem; there is also a combination of receptor--tyrosine kinase and hormonal treatment documented as active in such cases. On the other hand, abirateron-acetat and enzalutamide as a new androgen--receptor-signalling inhibitors proved that androgen signalling cascade is still active even in a castration-resistant prostate cancer.

INTRODUCTION

Breast- and prostate cancer are two the most common invasive cancers in women and men, respectively. Although these tumors seem to be considerably different due to diverse anatomical and physiological features of the organs where they arise, they share a common feature of "hormonal-dependence". Both of organs require gonadal steroids for their development and tumors arising from them have remarkable underlying biological similarities. Recently, it has been made a great improvement in our understanding of the pathophysiology of breast and prostate cancers which paved the way for new treatment strategies.

The very beginning was George Beatson's treatment of metastatic breast cancer by oopherectomy at the end of 19th century *(1)*. Similarly, castration for the treatment of prostate cancer was such an important advance that it earned Charles Huggins a Nobel Prize in 1966 *(2)*. The sex steroid hormones oestrogen and androgen are key drivers of both breast and prostate cancer. The discovery and characterization of receptors for oestrogen and androgen (that is, oestrogen receptor-α (ERα) and ERâ and androgen receptor (AR)), as well as key enzymes involved in the issues-specific metabolism of steroids led to designing different therapeutic approaches that either inhibit steroid-biosynthesis (gonadal, adrenal, peripheral and intratumoral) or block receptor function (receptor-antagonists) (Table 1) *(3, 4)*. For metastatic disease, hormone therapy has become a standard of care in receptor-positive breast cancer

Table 1

Mechanisms of endocrine resistance.

Resistance pathway	Mechanism
ER expression and activity loss	Mutations
	Gene regulation
	Post-transcriptional modifications (e.g. splice variants, mRNA stability)
	Posttranslational modifications
Trancriptional machinery of ER	Down-regulation of co-repressors
	Over-expression of co-activators
	Increased expression of transcriptional factors
Cross-talk between ER and RTKs	EGF/EGFR
	HER2
	P44/42 MAPK
Cell cycle regulators	Over-expression of positive regulators (e.g.MYC and cyclins E1 and D1)
	Reduced expression of negative regulators (e.g. p21 and p27)
	Reduced expression of pro-apoptotic molecules (e.g.BCL2-interacting killer and caspase-9)

and prostate cancer. The success of current hormone therapies relies on breast and prostate cancer recapitulating the dependence of the parent organ on a specific gonadal steroid for its growth and function. However, although there is initially good response to hormone therapy resulting in inhibition of tumor growth, inevitably these tumors after some time stop responding to hormone therapy and become "hormone-resistant". This is crucial event in evolution of disease which is, with no exception, fatal. Nevertheless, some variations of hormone therapies in breast and prostate cancer might confer additional short-term responses, suggesting that the correct sequencing in breast and prostate cancer is important to improve patient outcomes. The challange is to target steroid receptor signalling pathways that continue to influence tumor growth even after tumor became "hormonal (castration)-resistant".

Furthermore, common to breast cancer and prostate cancer, hormonal homeostasis is not confined to "classic" hormones – that is, androgens in prostate cancer and oestrogens in breast cancer: oestrogens are also crucial to prostate cancer and androgens to breast cancer development and progression, respectively. There is also a general need to better understand the action and effect of steroid precursors and metabolites, as the levels of these can be altered by hormone therapy, thereby contributing to hormone resistance in breast and prostate cancer. Interestingly, men and women synthesize both androgens and oestrogens, although in different amounts depending on age, and the idea that oestrogens are also important for prostate cancer and androgens for breast cancer has profound implications for developing strategies to treat and prevent both cancers *(5, 6, 7)*. Namely, knowing the different effects of ERs and their antagonists in different tissues, it is to assume that possible therapeutic implications are to arise in near future (Figure 1).

Breast cancer

Approximately 70% of breast cancers express estrogen receptor (ER) and endocrine therapy is probably the most important systemic therapy for hormone receptor positive breast cancer *(8)*. Recent gene expression profile studies have shown high heterogeneity within ER+ breast cancer with the identification of two distinct molecular subtypes characterized by different prognostic and biological features: ER+ luminal A and ER+ luminal B tumors. Luminal A breast cancer is characterized by high expression of ER and classic ER-dependent genes, lower proliferation rate, less aggressive tumor behaviour, and higher responsiveness to endocrine therapy. In contrast, the luminal B subtype is associated with relatively lower expression of ER and ER-related genes, higher proliferation rate, more aggressiveness, and lower endocrine sensitivity *(9)*.

Early therapies included surgical removal of the ovaries, but the synthesis of competitive inhibitors of oestrogen-ER binding during the 1970s led to the first, and to date most successful, targeted cancer therapy: the selective oestrogen receptor modulator (SERM) tamoxifen *(10)*. Adjuvant treatment with tamoxifen almost halves the rate of disease recurrence and reduces the annual breast cancer death rate by one-third, making a significant contribution to the 25–30% decrease in breast cancer mortality in the past two decades *(11),* representing one of the most successful treatment modalities in solid tumors generally. Subsequently, other endocrine therapies have developed that target oestrogen synthesis, such as aromatase inhibitors, or ER signalling, such as other SERMs and "pure" anti-oestrogens *(12, 13)*. One-third of women treated with tamoxifen for 5 years will have recurrent disease within 15 years and so endocrine-resistant disease may represent up to one-quarter of all breast cancers *(12)*.

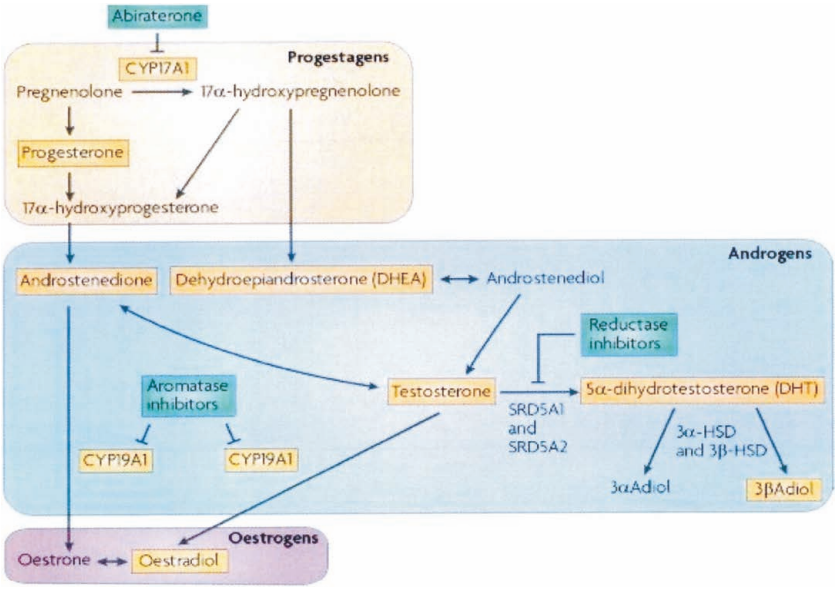

Figure 1. *Common essential pathways of steroid biosynthesis in the breast and prostate. The aromatase (cytochrome P450 19A1 (CYP19A1)) and 5α-reductase (SRD5A1 and SRD5A2) enzymes are essential for oestrogen and androgen signalling through their respective receptors, oestrogen receptor-α (ERα) and ERâ, and androgen receptor (AR) in the breast and prostate. Whereas 5α-reductase type 1 (SRD5A1) is expressed in the breast and increases in breast cancer, 5α-reductase type 2 (SRD5A2) is predominantly expressed in the prostate.*

The primary mechanisms of de novo or intrinsic resistance to tamoxifen is lack of expression or ERα *(14)*. Recently, a second intrinsic mechanism has been documented in which patients carrying inactive alleles of cytochrome P450 (CYP2D6) (approximately 8% of Caucasian women) fail to convert tamoxifen to its active metabolite, endoxifen, and are consequently less responsive to tamoxifen *(15)*. By contrast, there are many mechanisms that have been postulated to account for acquired resistance following prolonged exposure to tamoxifen, some of which may also account for intrinsic resistance in the clinic *(15)*. These data have been obtained from ERá-positive breast cancer cell lines and from variants of these cell lines selected for adaptiation to sustained exposure to anti-oestrogens or withdrawal of oestrogen. Deregulation of various aspects of oestrogen signalling is a common mechanism for resistance, but unrelated mechanisms that provide tumour cells with alternative proliferative and survival stimuli also confer resistance *(15, 16)*.

In recent years several mechanisms of resistance to endocrine therapy have been recognized (Table 1) *(17)*. First of all, any variation in the ER at the gene or protein level contributes to endocrine resistance and to the development of a more aggressive phenotype. ER loss over time in the tumor occurs in approximately 20% of patients treated with endocrine therapy *(18)*. Down-regulation or complete loss of ER may occur at multiple levels and by several mechanisms. ER expression is thought to primarily be controlled by epigenetic and post-transcriptional mechanisms, and not at the genomic level. ER mutations occur in less than 1% of ER+ tumors and only a few point mutations have been identified in human patient samples from a variety of disease states *(17)*. Ot the other hand, a large number of naturally occurring splice variants of both ERα and ERβ have been identified in normal and cancerous tissues. Moreover, regulation of the ER mRNA stability by specific micro RNAs represents a novel mechanism responsible for ER loss *(19, 20)*. ER levels and function are also regulated by post-translational modifications (e.g. phosphorylation, methylation and ubiquitination), which alter interactions of ER with its co-regulators and consequently contribute to endocrine resistance. Furthermore, ER exerts its action on gene expression by associating with a group of regulatory proteins that form the transcription initiation complex. Therefore, changes in the proteins that form this transcription initiation complex with ER greatly influence effectiveness of endocrine therapy. First, expression of ER corepressors and coactivators directly controls the equilibrium between agonist versus antagonist effects of SERMs; second, increased activity of transcriptional factors such as AP-1, SP-1 and NFêB, which are critical for mediating ER signalling int the non-classical nuclear genomic pathway is also associated with endocrine resistance *(21, 22, 23, 24, 25)*.

There are new endocrine therapies, like selective-estrogen receptor-downregulators (SERD), like fulvestrant, for which it was proved to show clinical benefit in HER2--overexpressing metastatic breast cancer-patients (only modest efficacy) *(26)*. Receptor-tyrosine kinases (RTKs) and their downstream signalling pathways can alternatively stimulate cancer growth either in concert with ER signalling or by bypassing it. These pathways can also directly negate or overcome the inhibitory effects of endocrine therapy by modulating ER activity. It has been documented that increased expression of EGFR, HER2

and IGF1R in breast cancer cell lines causes tamoxifen resistance. Moreover, cumulative clinical evidence suggests that HER2 and/or EGFR over-expression is associated with a poorer outcome in tamoxifen-treated patients *(27)*. A bidirectional crosstalk between ER and RTK signalling has been demonstrated to cause endocrine resistance. ER, via both its non-nuclear and nuclear activities, can up-regulate growth factor RTK-signaling. Simultaneously, several RTK patways can modulate both genomic and non-genomic activities of ER and its ligand dependency *(28, 29, 30)*. Finally, preclinical and clinical evidence suggest that the activity of both positive regulators impacts tumor sensitivity to endocrine treatment. In particular, over-expression of the positive regulators MYC and cyclin E1 and D1 determines endocrine resistance, either by activating cyclin-dependent kinases critical for G1 phase or by relieving the inhibitory effects of the negative cell cycle regulators p21 and p27 *(24, 31)*. Also, over-expression of anti-apoptotic molecules (e.g. BCL-XL) and reduced expression of pro-apoptotic molecules (e.g. BCL2-interacting killer and caspase 9) can modulate anti-estrogen-mediated apoptosis *(32)*.

As described, preclinical and clinical evidence supports the hypothesis that cancer cells can overcome the inhibitory effects of endocrine therapy either by using RTKs as the dominant survival pathway or by modifying ER activity through bidirectional RTK-ER crosstalk. Targeted therapy against only one pathway likely will result in resistance to therapy due to compensation or cross talk with the other pathway. As an example, expression of all three HER family members (EGFR, HER2 and HER3) have shown to be predictive for early relaps in ER+breast cancer patients receiving tamoxifen as an adjuvant treatment *(33)*. So, the more promising strategy to prevent or overcome endocrine resistance in ER+breast cancer is to combine different targeted treatments to effectively block both ER and RTK signalling. Significant effort has been made to evaluate the efficacy of RTK-targeted therapies in combination with endocrine treatment (for example, phase III trial combining trastuzumab and anastrozole, TAnDEM). Some others, like EGFR-inhibitor geftinib in combination with endocrine treatment, then letrozole plus dual tyrosine kinase inhibitor (EGFR/HER2) lapatinib in HER2+ patients, were also performed *(27)*.

To conclude, the development of resistance to endocrine therapy is the result of complex processes involving multiple mechanisms and escape pathways, and therapeutic blockade of estrogen signalling as the exclusive therapeutic strategy may eventually result in treatment failure. Furtunately, the introduction of new hormonal agents and regimens in the last decades has markedly improved the outcome of ER+ breast cancer patients. Today, the most promising strategy to prevent and/or overcome endocrine resistance might be to combine hormonal agents with drugs targeting several effectors of RTK and stress-related pathways, in the attempt to block all the possible tumor survival escapes. Future clinical trials with appropriate patient selection based on re-biopsy of recurrent lesions, will provide evidence for optimizing individualized therapeutic regimens combining endocrine therapy with one or more pathway-targeted agents to treat ER+ breast cancer in the most effective manner.

Prostate cancer

Androgen deprivation remains the mainstay of therapy for patients with advanced prostate cancer *(34, 35)*. Because androgen may play a role as both a survival factor and a growth factor for prostatic carcinoma cells, interference with the androgen-signaling pathway will generate clinically meaningful remissions in the majority of patients. These remissions are by a reduction in symptoms related to disease, if they exist, and a reduction in the serum PSA level. The majority of circulating androgen is produced by the testicles in the form of testosterone and the remainder is produced by the adrenal glands, which synthesize the so-called adrenal androgens. These adrenal androgens may contribute up to 40% of the androgen detected within prostate. Androgen deprivation is achieved through surgical (orchiectomy) or chemical (gonadotropin-releasing hormone analogues) castration. Estrogens and progestational agents, which are less frequently used, will also reduce androgen levels through nuclear receptor-mediated activity. Antiandrogens (androgen receptor antagonists) or agents that interfere with the adrenal production of androgens, such as ketoconazole and aminogluthetimide, also are used sometimes. Recently, thanks to our improved knowledge of pathophysiology of disease, there are new agents already in use for prostate cancer treatment (Table 1) *(36, 37)*.

In prostate cancer, conventional hormone ablation therapy lowers circulating serum androgen levels. Androgen levels in the prostate remain at non-castrate levels and prostate tumor cells synthesize their own androgens in the castrate setting *(38)*. These finding was extremely important because previously it was thought that there is primarly development of androgen-insensitive tumor clone. Actually, cancer evolves mechanism to excape systemic androgen deprivation while still taking advantage of signalling through AR. This clinical state is therefore more accurately defined as "castrate-resistant" prostate cancer (CRPC) *(39)*.

There are many details better understood in recent years. One of them is certainly the recognition that intratumoral androgen synthesis and activity is biologically relevant and that overexpression of the AR is a consistent feature of prostate cancer progression has led to the development of several new therapeutic approaches. One example is abiraterone acetate, an inhibitor of 17α-hydroxylase and C17,20 lyase (CYP17A1) for the treatment of men with advanced CRPC (). Blockade of CYP17A1 activity by abiraterone suppresses the formation of androstendione, dehydroepiandrosterone (DHEA), testosterone and oestradiol, as well as other metabolites (Figure 1), that my activate promiscuous AR variants in CRPC *(40)*.

There are many mechanisms by which prostate cancer cell may become resistant to hormonal manipulation

Table 2

Historical and contemporary hormonal therapies for prostate cancer.

Drug class	Examples	Mechanisms of action	Key clinical outcomes	Comments
Conventional agents				
Surgery	Castration	Removal of sex steroids	Disease regression; improved symptom control and survival	Surgical approaches now less frequently used
Anti-androgens	Non-steroidal: flutamide, bicalutamide and nilutamide; Steroidal: cyproterone acetate	Blockade of ligand binding to AR	Small benefit when added to hormone ablation	Paradoxical response to anti-androgen withdrawal in around 21% of cases
GnRH agonists	Goserelin, leuprolide, buserelin, nafarelin, histrelin, deslorelin and triptorelin	Reduction in GnRH secretion	Standard of care	initial surge in serum androgen levels may require cover with anti-androgen
GnRH antagonists	Degarelix	Reduction in GnRH secretion	Rapid action, no requirement for antiandrogen	Not widely in use
5-α reductase inhibitors	Finasteride, dutasteride	Inhibition of the conversion of testosterone to dihydrotestosterone	Used for chemoprevention; possible effect on tumour grade at diagnosis	None
Cytochrome P450 inhibition	Ketoconazole and aminoglutethimide	Inhibition of steroid synthesis	Responses rates up to 75%	Infrequently used now
Corticosteroids	Prednisone, prednisolone, dexamethasone and hydrocortisone	Reduction of ACTH secretion and subsequent adrenal steroid production	12% palliative response	Often used as active control in randomized studies
New approacbes				
CYP17A1 inhibitors	Ketoconazole and abiraterone acetate	Reduction in androgen synthesis	Active in CRPC; improved survival	Evidence based on phase III clinical trial
AR signalling inhibitors	MV3100 (enzalutamide)	AR signalling blockade e.g. AR nuclear translocation	Prolonged time to progression and survival	Evidence based on phase III clinical trial

and conventional treatment. Some of these changes involve changes in androgen receptors, the others include extra-receptor changes *(41)*. Androgen receptor-gene amplification (in some 30% of CRPC), leads to androgen--receptor over expression and their activation even in the presence of low dihydrotestosteron-levels *(42)*. Androgen-receptor gene mutations increase number of ligands that may activate AR, which happen in about 10–40% of prostate cancer patients. Another very important mechanism of castration-resistant tumor phenotype is linked with the function of co-activators and co-repressors of nuclear receptors. Namely, there are more than 300 co--regulatory molecules that remodel chromatin structure at nuclear receptor target enhancers and promoters and direct transcription in tissue-specific manner. Cofactor upregulation is believed to be na important mechanism of resistance to hormone therapy in prostate cancers. Some of the best characterized co-regulators in prostate cancer are p160 kDa protein steroid receptor co-activators, which include SRC1 (also known as NCOA1), SRC2 (also known as NCOA2) and SRC3 (also known as NCOA3). In prostate cancer, AR binds to and activates SRC3, which in turn can phosphorylate AR to augment its activity. Another emerging example of a nuclear receptor co-regulator is E6-associated protein (E6AP). When downregulated there is increase in the expression of AR, suggesting a role in maintaining androgen signalling during disease progression *(43)*.

Another very important issue is the role of tumor microenvironment in disease progression. It is known today, that tumor microenvironment is implicated in the

transition from preinvasive to invasive growth and is regarded as a crucial participant in tumorigenesis, promoting a more aggressive phenotype *(44)*. Stroma primarily evolves from smooth muscle in normal prostate tissue, and prostate cancer tumor stroma shows conservation of fibroblast or myofibroblast phenotype. Quantitative changes in tumor stromal markers, including loss of AF in the stroma, are significant predictors of prostate cancer recurrence, independent of Gleason score and prostate-specific (PSA) levels *(45, 46)*. Molecular characterization of cancer-associated fibroblasts has defined aberrant intra-tumoral cell-cell signalling factors. Several developmental signalling pathways were implicated, including Wnt, transforming growth factor-β (TGF-β), bone morphogenetic protein (BMP) and fibroblast growth factor (FGF).

The stromal-mediated action of sex steroids that direct differentiation of the epithelia has important implications for the prostate cancer. Tumor-initiating (cancer "stem") cells in prostate cancer do not express AR, but stromal fibroblasts do. The tumor initiating cells therefore remain responsive to hormones through stromal-epithelial signalling. Therefore, stroma is obvious therapeutic target. For future, it is essential to identify and block the stromal as well as epithelial cofactors required for transcriptional activation of AR signlling to ensure that the hormone response is completely abrogated in the tumor and to eliminate potential mechanisms of resistance to hormone therapy *(47, 48)*.

The immune response is also modified by steroid hormones. In prostate cancer, androgen deprivation initially causes immune responses that are antitumorigenic, but with the development of CRPC the immune response is modified, thereby providing a permissive environment for tumour growth. A possible link between immunity and prostate cancer has been found by increased expression of inflammatory molecules by metastatic behaviour in prostate cancer. Some cytokines, such as IL-6, also mediate autocrine effects, possibly linked to the enhanced proliferation of progenitor cells *(49)*.

In conclusion, many mechanisms of hormonal resistance are better understood and this knowledge has already made possible to design new treatments which are very promising. Castration-resistance is a phenotype that is achieved after many changes in AR-signalling cascade as well as in tumor stroma and immune system.

REFERENCES

1. BEATSON G T 1926 Treatment of Cancer by Oophorectomy. *Br Med J* 2: 1195.
2. HUGGINS C 1967 Endocrine-induced regression of cancers. *Cancer Res* 27: 1925–1930.
3. PEROU C M, SORLIE T, EISEN M B, VAN DEN RIJN M 2000 Molecular portraits of human breast tumours. *Nature 406(6797):* 747–52
4. CLARK G M, OSBORNE C K, McGUIRE W L 1984 Correlations between estrogen receptor, progesterone receptor, and patient characteristics in human breast cancer. *J Clin Oncol 2(10):* 1102–9
5. RICKE W A 2008 Prostatic hormonal carcinogenesis is mediated by *in situ* estrogen production and estrogen receptor alpha signaling. *FASEB J* 22: 1512–1520
6. McPHERSON S J 2007 Essential role for estrogen receptor beta in stromal-epithelial regulation of prostatic hyperplasia. *Endocrinology 148:* 566–574
7. ELLEM S J, RISBRIDGER G P 2007. Treating prostate cancer: a rationale for targeting local oestrogens. *Nature Rev Cancer 7:* 621–627
8. OSBORNE C K, SCHIFF R, FUQUA S A, SHOU 2001 J. Estrogen receptor: current understanding of its activation and modulation. *Clin Cancer Res 7(12 Suppl):* 4338s4342s:discussion 4411s4412s.
9. JENSEN E V, JORDAN V C 2003 The estrogen receptor: a model for molecular medicine. *Clin Cancer Res 9:* 1980–1989
10. OSBORNE C K 1998 Tamoxifen in the treatment of breast cancer 1998 *N Engl J Med 339(22):* 1609–18
11. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 2005 Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet 365:* 1687–1717
12. MacGREGOR J I, JORDAN V C 1998 Basic guide to the mechanisms of antiestrogen action. *Pharmacol Rev 50:* 151–196
13. JOHNSTON S R, DOWSETT M 2003 Aromatase inhibitors for breast cancer: lessons from the laboratory. *Nature Rev Cancer 3:* 821–831
14. HOPP T A, WEISS H L, PARRA I S, CUI Y, OSBORNE C K, FUQUA S A 2004 Low levels of estrogen receptor beta protein predict resistance to tamoxifen therapy in breast cancer. *Clin Cancer Res 10(22):* 7490–9
15. CHUNG Y L, SHEU M L, YANG S C, LIN C H, YEN S H 2002 Resistance to tamoxifen-inducedapoptosis is associated with direct interaction between Her2/neu and cell membrane estrogen receptor in breast cancer. *Int J Cancer 97(3):* 306–12
16. KAHLERT S, NUEDLING S, van EICKELS M, VETTER H, MEYER R, GROHE C 2000 Estrogen receptor alpha rapidly activates the IGF-1 receptor pathway. J Biol Chem *275(24):* 18447–18453
17. HERYNK M H, FUQUA S A 2004 Estrogen receptor mutations in human disease. *Endocr Rev 25(6):* 869–98
18. IWASE H, GREENMAN J M, BARNES D M, BOBROW L, HODGSON S, MATHEW C G 1995 Loss of heterozygosity of the oestrogen receptor gene in breast cancer. *Br J Cancer 71(3):* 448–50
19. ADAMS B D, FURNEAUX H, WHITE B A 2007 The micro--ribonucleic acid (miRNA) miR-206 targets the human estrogen receptor-alpha (ERalpha) and represses ER-alpha messenger RNA and protein expression in breast cancer cell lines. *Mol Endocrinol 21(5):* 1132–47
20. LAVINSKY R M, JEPSEN K, HEINZEL T, TORCHIA J, MULLEN T M, SCHIFF R 1998 Diverse signaling pathways modulate nuclear receptor recruitment of N-CoR and SMR complexes. *Proc Natl Acad Sci U S A 95(6):* 2920–5
21. ZHOU Y, YAU C, GRAY J W, CHEW K, DAIRKEE S H, MOORE D H 2007 Enhanced NF kappa B and AP-1 transcriptional activity associated with antiestrogen resistant breast cancer. *BMC Cancer 7:* 59
22. SCHIFF R, REDDY P, AHOTUPA M 2000 Oxidative stress and AP-1 activity in tamoxifen-resistant breast tumors in vivo. *J Natl Cancer Inst 92(23):* 1926–34
23. CHU I M, HENGST L, SLINGERLAND J M 2008 The Cdk inhibitor p27 in human cancer: prognostic potential and relevance to anticancer therapy. *Nat Rev Cancer 8(4):* 253–67
24. PEREZ-TENORIO G, BERGLUND F, ESGUERRA MERCA A 2006 Cytoplasmic p21WAF1/CIP1 correlates with Akt activation and poor response to tamoxifen in breast cancer. *Int J Oncol 28(5):* 1031–42
25. BUTT A J, McNEIL C M, MUSGROVE E A, SUTHERLAND R L 2005 Downstream targets of growth factor and oestrogen signalling and endocrine resistance: the potential roles of c-Myc, cyclin D1 and cyclin E. *Endocr Relat Cancer 12 (Suppl 1):* s47–59
26. ROBERTSON J F, STEGER G G, NEVEN P, BARNI S, GIESEKING F, NOLE F 2010 Activity of fulvestrant in HER2-overexpressing advanced breast cancer. *Ann Oncol 21(6):* 1246–53
27. KAUFMAN B, MACKEY J R, CLEMENS M R, BAPSY P P, VAID A, WARDLEY A 2009 Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone recep-

tor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study. *J Clin Oncol 27(33):* 5529–37

28. MILLER T W, PEREZ-TORRES M, NARASSANA A, GUIX M, STAL O, PEREZ-TENORIO G 2009 Loss of Phosphatase and Tensin homologue deleted on chromosome 10 engages ErbB3 and insulin-like growth factor-I receptor signaling to promote antiestrogen resistance in breast cancer. *Cancer Res 69(10):* 4192–201
29. deGRAFFENRIED L A, FRIEDRICHS W E, RUSSELL D H, DONZIS E J, MIDDLETON A K, SILVA J M 2004 Inhibition of mTOR activity restores tamoxifen response in breast cancer cells with aberrant Akt activity. *Clin Cancer Res 10(23):* 8059–67
30. DeGRAFFENRIED L A, FRIEDRICHS W E, FULCHER L, FERNANDES G, SILVA J M, PERALBA J M 2003 Eicosapentaenoic acid restores tamoxifen sensitivity in breast cancer cells with high Akt activity. *Ann Oncol 14(7):* 1051–6
31. BUTT A J, McNEIL C M, MUSGROVE E A, SUTHERLAND R L 2005 Downstream targets of growth factor and oestrogen signalling and endocrine resistance: the potential roles of c-Myc, cyclin D1 and cyclin E. *Endocr Relat Cancer 12(Suppl 1):* S47–59
32. KUMAR R, MANDAL M, LIPTON A, HARVEY H, THOMPSON C B 1996 Overexpression of HER2 modulates bcl-2, bcl-XL, and tamoxifen-induced apoptosis in human MCF-7 breast cancer cells. *Clin Cancer Res 2(7):* 1215–9
33. ARPINO G, WIECHMANN L, OSBORNE C K, SCHIFF R 2008. Crosstalk between the estrogen receptor and the HER tyrosine kinase receptor family: molecular mechanism and clinical implications for endocrine therapy resistance. *Endocr Rev 29:* 217–233
34. MOHLER J L 2004 The androgen axis in recurrent prostate cancer. *Clin Cancer Res 10:* 440–448
35. TITUS, M A, SCHELL M J, LIH F B, TOMER K B, MOHLER J L 2005 Testosterone and dihydrotestosterone tissue levels in recurrent prostate cancer. *Clin Cancer Res 11:* 4653–4657
36. TRAN C 2009 Development of a second-generation antiandrogen for treatment of advanced prostate cancer. *Science 324:* 787–790
37. NAKABAYASHI M, WERNER L, OH W K, REGAN M M, KANTOFF P W, TAPLIN M E 2011 Secondary Hormonal Therapy in Men with Castration Resistant Prostate Cancer. *Clin Genitour Canc 9(2):* 95–103
38. LOCKE J A 2008 Androgen levels increase by intratumoral de novo steroidogenesis during progression of castration-resistant prostate cancer. *Cancer Res 68:* 6407–6415
39. CELESTIA S, HIGANO 2012. New treatment options in castration--resistant prostate cancer. *Cancer Treatment Reviews 38(5):* 3340–345
40. ANG J E, OLMOS D & de BONO J S 2007 CYP17 blockade by abiraterone: further evidence for frequent continued hormone-dependence in castration-resistant prostate cancer. *Br J Cancer 100:* 671–675
41. ELAHE A, MOSTAGEL, MONTGOMERY B, NELSON P S 2009. Castration-resistant prostate cancer. Targeting androgen metabolic pathway in recurrent disease. Urologic Oncology. *Seminars and Original Investigations 27(3):* 251–257
42. SEIDENFELD J 2000 Single-therapy androgen suppression in men with advanced prostate cancer: a systematic review and meta-analysis. *Ann Intern Med 132:* 566–577
43. ZHOU H J 2005 SRC-3 is required for prostate cancer cell proliferation and survival. *Cancer Res 65:* 7976–7983
44. TAYLOR R A, RISBRIDGER G P 2008 Prostatic tumor stroma: a key player in cancer progression. *Curr Cancer Drug Targets 8:* 490–497
45. HENSHALL S M 2001 Altered expression of androgen receptor in the malignant epithelium and adjacent stroma is associated with early relapse in prostate cancer. *Cancer Res 61:* 423– 427
46. CUNHA G R 2008 Mesenchymal-epithelial interactions: past, present, and future. *Differentiation 76:* 578–586
47. DAVIS I D, DESAI J 2008 Clinical use of therapies targeting tumor vasculature and stroma. *Curr Cancer Drug Targets 8:* 498–508
48. SARTOR A O 2008 Antiandrogen withdrawal in castrate-refractory prostate cancer: a Southwest Oncology Group trial (SWOG 9426). *Cancer 112:* 2393–2400
49. HURWITZ A A, YANOVER P, MARKOWITZ M, ALLISON J P, KWON E D 2003 Prostate cancer: advances in immunotherapy. *BioDrugs 17:* 131–8