The changing roles of steroid nuclear receptors with prostate cancer progression

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Abstract

Estrogens were once used for the treatment of prostate cancer (PC). They may still be used in various parts of the world to that effect. Recent developments in the understanding of a role for estrogen receptor $\beta$ (ER$\beta$) in the development and progression of this disease resurrect the discussion on the intertwined roles of ER$\beta$ and the androgen receptor (AR) in promoting PC. A new article by Zellweger et al. in Endocrine-Related Cancer investigates the expression and assesses the activity of ER$\alpha$ and ER$\beta$ as well as the AR, in addition to a phosphorylated form of AR in hormone-naïve and castration-resistant PC.

Key Words
- estrogen receptor $\beta$
- androgen receptor
- serine 210 phosphorylation
- prostate cancer
- hormone-naïve

Estrogens were used until the 1950s as the primary medical treatment for prostate cancer (PC); however, their use was associated with increased cardiovascular toxicity and other debilitating side effects, such as breast enlargement and breast tenderness; hence, when LH-releasing hormone (LHRH) agonists were discovered to lower testosterone levels, oral estrogen therapy was all but abandoned as a treatment option for PC (Oh 2002). Recent understanding of the role of estrogen receptor $\beta$ (ER$\beta$) in PC explains how estrogens may have worked against PC development – ER$\beta$ is activated by 17$\beta$-estradiol as well as other ligands, including phytoestrogens derived from soy products such as genistein and equol that are known to inhibit the growth of PC cells (Minutolo et al. 2011). ER$\beta$ has anti-proliferative effects in PC cells (Pravettoni et al. 2007), and its expression is lost in PC (Horvath et al. 2001, Bardin et al. 2004).

In the June 2013 issue of Endocrine-Related Cancer, Zellweger et al. (2013) go one step further and shows what happens to ER$\beta$ as hormone-naïve PC (HNPC) progresses to castration-resistant PC (CRPC). They are able to demonstrate the effects in CRPC because they have access to CRPC tissue that most researchers in the USA do not. In the USA, the standard of care for PC is prostatectomy. Patients who demonstrate recurrence after surgical removal of the prostate are treated with LHRH agonists, and therefore, men with PC who develop CRPC do not have prostates that may be analyzed. On the other hand, Zellweger’s patients were treated with LHRH agonists and by orchiectomy when initially diagnosed for PC – when they became refractory to this therapy, and developed additional symptoms, they were treated by transurethral resection of the prostate – probably because they experienced urinary obstruction. That is how they were able to collect about 100 CRPC specimens in addition to a similar number of patients with HNPC.

In this article, Zellweger et al. first show that ER$\beta$ levels are suppressed in PC compared with tissues from patients with benign prostatic hyperplasia (BPH) in support of previously published reports (Horvath et al. 2001, Bardin et al. 2004). They go on to show that ER$\beta$ is downregulated in CRPC cells compared with hormone-naïve cells. They also demonstrate that ER$\beta$ is activated in CRPC cells, and its activation is associated with increased expression of genes that are known to be regulated by ER$\beta$. These findings suggest that ER$\beta$ may play a role in the development and progression of CRPC.
et al. 2004), and then go on to make the provocative observation that ERβ levels correlate with survival in HNPC but not in CRPC (Zellweger et al. 2013). Strikingly, ERz, which plays such a prominent role in breast cancer development and progression, does not seem to change much – or even be expressed at substantial levels – in PC. The observation of ERβ correlating with survival in HNPC is contradictory to accepted doctrines: ERβ is supposed to protect against PC (Pravettoni et al. 2007). So the observation of an initial decrease in ERβ in PC is understandable – if it protects against PC, this receptor needs to be downregulated in order for PC to develop. But why should higher levels of ERβ correspond to lower survival in HNPC?

The answer may be found in the article by Zellweger et al. as well. The authors show a correlation between ERβ levels and androgen receptor (AR) phosphorylation at serine 210 (S210), in both HNPC and CRPC (Zellweger et al. 2013). Zellweger et al. then demonstrate that pAR(S210) levels are decreased in HNPC (score: 38.9) compared with BPH (score: 79.2). In addition, they also show that pAR(S210), similar to ERβ levels, correspond to lower survival in HNPC but not in CRPC. Therefore, although Zellweger’s data could not conclusively prove it, it is imaginable that the effects of ERβ in HNPC are mediated by pAR(S210). The pathway that mediates the link between pAR(S210) and ERβ in HNPC, if it exists at all, is not currently known.

But why would AR(S210) phosphorylation alter as it does? The answer is not currently known, but we can speculate! This is the site on the AR that was first shown to be phosphorylated by Akt, which is known to promote survival (Lin et al. 2001). Now, we and others previously showed that Akt phosphorylation (pAkt) corresponds to prostate-specific antigen (PSA) recurrence (Ayala et al. 2004, Kreisberg et al. 2004). As AR(S210) is a substrate for pAkt, it is likely that pAR(S210) increases as a result of the increase in pAkt and that it also causes an increase in ERβ. Unfortunately, Zellweger et al. did not stain their tumors for pAkt, so we will not know whether this theory is true or not. But it may be hypothesized that perhaps, in increasing ERβ, the cell is really trying to overcome the effects of pAkt!

But what happens in CRPC? Zellweger et al. show that in CRPC, pAR(S210) levels are increased compared with their levels in HNPC (CRPC, 62.1; HNPC, 38.9, P<0.0001). However, we note that ERβ levels are not increased as much and that the correlation between pAR(S210) and ERβ is weaker in CRPC than in HNPC. Therefore, it is likely that whatever caused the link between ERβ and pAR(S210) in HNPC is disrupted in CRPC. pAR(S210) signaling itself may be disrupted in CRPC. The supplementary data of Zellweger et al. show that in HNPC, but not in CRPC, pAR(S210) correlates with serum levels of PSA, which indicates AR activation. This means that in HNPC, pAR(S210) and ERβ correlate with survival because they correspond to higher AR activity, whereas in CRPC, these factors are irrelevant because they no longer control AR activity.

What controls survival in CRPC? According to data provided by Zellweger et al. (2013), the answer is likely to be AR gene amplification. They show that compared to 1% of the patients with HNPC, 42% of the patients with CRPC entertained AR gene amplification. AR gene amplification corresponded to higher AR protein levels as determined by immunohistochemistry. Curiously, the authors note that the percentage of cells staining for nuclear AR (an indicator of AR activity) remains the same in HNPC and CRPC, but the intensity of nuclear staining increases. As they stain cells in a tissue microarray where all the sections are equally treated, the difference in staining cannot be explained as variations in the staining procedure. Perhaps, as in Zellweger et al. (2013), pathologists really need to take both intensity and percentage of staining into account when scoring for AR in PC.

Interestingly, while higher AR levels correspond to decreased survival in HNPC, in CRPC, this relationship is flipped and lower AR levels correlate with decreased survival in the latter. The lesson to be learnt from this is that complete eradication of the AR levels and AR activity should not be a goal of CRPC therapy because then other forces that are probably suppressed by the AR come into play. This may be because the AR is a very important gene in our lives, and the body may strive to maintain it to the best of its ability.

Thus, the paper by Zellweger et al. (2013) shows that tumor development and progression is initially controlled by ERβ, perhaps spurred on by pAR(S210), but this effect is lost with the advent of CRPC, when AR gene amplification takes over, as the authors speculate, perhaps in response to lower levels of androgens in the body. The exact cause of the switch is not known yet, but with science progressing at the current speed, it is possible that we will know soon what it is that disrupts the balance and pushes the cell over to CRPC.

Declaration of interest
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References
Kreisberg JI, Malik SN, Prihoda TJ, Bedolla RG, Troyer DA, Kreisberg S & Ghosh PM 2004 Phosphorylation of Akt (Ser473) is an excellent predictor of poor clinical outcome in prostate cancer. Cancer Research 64 5232–5236. (doi:10.1158/0008-5472.CAN-04-0272)
Zellweger T, Sturm S, Rey S, Zlobec I, Gsponer JR, Rentsch CA, Terracciano LM, Bachmann A, Bubendorf L & Ruiz C 2013 Estrogen receptor β expression and androgen receptor phosphorylation correlate with a poor clinical outcome in hormone-naïve prostate cancer and are elevated in castration-resistant disease. Endocrine-Related Cancer 20 403–413. (doi:10.1530/ERC-12-0402)

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