Androgen signalling and steroid receptor crosstalk in endocrine cancers

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Introduction

In this issue, we bring together some fascinating aspects and novel insights into androgen signalling in endocrine cancers, focusing mostly on prostate cancer, but inclusive of breast, ovarian and endometrial cancers. One intriguing area of investigation covered herein is the crosstalk between androgen receptor (AR) and estrogen receptor (ER) signalling, not only in breast cancer but also in prostate cancer. Although it has long been known that androgen and estrogen sex hormones exert antagonistic influences during sexual development, the significance of their interplay and its consequences for disease development and progression are only beginning to be explored at the molecular level. Certainly, the intertwining of these two distinct research domains will provide fertile ground for new discoveries and will feature strongly in future endocrine-related cancer research.

Androgens and prostate cancer

Androgens are a major driver of prostate development, through the activation of different gene expression programs in stromal and epithelial cells and via modulation of the interactions between malignant and non-malignant prostate epithelial cells. Even in the metastatic, castration-resistant forms of prostate cancer, androgens are key survival factors. Thanks to an integration of data on whole genome AR-binding sites and androgen-responsive gene networks, researchers are now starting to unravel how androgens and the AR mechanistically regulate cell survival, proliferation and cancer-specific changes in

metabolism in prostate cancer cells. Barfeld *et al.* (2014) bring clarity to how androgens impact on the different hallmarks of cancer of the prostate.

Several older and newer therapies for metastatic prostate cancer target the AR signalling axis. Unfortunately, prostate cancer cells seem able to readily adapt to these therapies via a variety of mechanisms. Under chemical castration conditions, autonomous androgen synthesis can occur in cancer cells, whereby expression of enzymes involved in androgen synthesis is enhanced and expression of enzymes involved in androgen metabolism is diminished. This altered intracrinology is now being targeted clinically by use of CYP17A1 inhibitors. Penning discusses the different enzymes involved in intracrine androgen homeostasis and the dangers and pitfalls that need to be taken into account in the further development of compounds that adopt this type of therapeutic strategy (Penning 2014).

Several other mechanisms have been described that might explain the maintenance of AR signalling under conditions of low androgen levels in castrate-resistant prostate cancer which involve changes in levels or intracellular location of AR-associated co-regulatory proteins (Gonugunta *et al.* 2014) or AR-regulated miRNAs (Selth *et al.* 2012). Gonugunta *et al.* (2014) describe the role of PELP1, not only in the regulation of AR activity in prostate cancer, but also in the regulation of ER activity in breast cancer. Another mechanism that explains the continued role of AR as a survival factor for prostate cancer cells, even under hormone deprivation, is the expression

of truncated AR variants that are no longer dependent on hormone for activation. From Ware *et al.* (2014), we learn that these variants are clinically relevant prognostic factors in prostate cancer, for which the development of new therapies and markers are desperately needed.

It is becoming increasingly clear that the AR remains an important drug target in metastatic prostate cancer, even in castration-resistant forms of the disease, including resistance to enzalutamide and/or abiraterone. This warrants the continued search for alternative AR antagonists, which target either the ligand-binding domain or new strategies that target the amino-terminal domain of the AR (reviewed in Helsen *et al.* (2014)).

It is extremely important to realise that there is a downside of systemic AR targeting in prostate cancer. Indeed, as summarised in this issue by Allan *et al.* (2014), complications of androgen deprivation should be closely monitored and managed clinically, and preclinical work should endeavour to prevent these side effects which negatively impact on quality of life, e.g. by developing selective AR antagonists.

Finally, the AR, like most steroid receptors has long been known to be a substrate for kinases and phosphatases. While the specific functions of ER phosphorylation have been described in great detail (Skiris *et al.* 2010), the reports on AR post-translational modifications have been confusing. Koryakina *et al.* (2014) start to bring clarity to this field, reviewing the current status of the kinases and phosphatases that target the AR and their possible role in prostate cancer.

Androgens in breast and other female tissues

Nieto *et al.* (2014) summarise the growing evidence on the significance of AR signalling in breast development and homeostasis in female mice, while McNamara *et al.* (2014) and Tarulli *et al.* (2014) focus on the emerging role of the AR in breast cancer. It has been known for decades that AR is expressed in a large proportion of breast cancers and that clinical and laboratory evidence indicated that AR signalling regulates the activity of breast cancer cells. However, the complexity of this activity and its apparent plasticity depending on disease context has only recently been appreciated. McNamara *et al.* (2014) summarise recent data on the complexities of AR signalling in breast cancer, including the clinical utility of assessing serum androgen levels or AR expression levels as prognostic factors in breast cancer, how ER status influences AR action in breast cancer cells and the role of AR/ER molecular crosstalk in this disease. This work is highly

topical as clinical trials examining the efficacy of AR-targeting therapies (used for prostate cancer) in women with metastatic breast cancer are currently underway. On a more hypothesis-generating angle, Tarulli *et al.* (2014) integrate recent data on the role of AR and NOTCH signalling in breast development to propose that crosstalk between these pathways plays a significant role in breast morphogenesis and carcinogenesis.

Extending beyond the breast, Gibson *et al.* (2014) discuss the AR, not only as a possible factor in the aetiology of endometrial and ovarian cancers, but also its potential use as a therapeutic target for these diseases. In endometrial cancer, androgens seem to have an anti-proliferative effect, while in ovarian cancers androgens seem to have pro-proliferative effect. This article highlights a fertile new area for future research and is also an example of how investigation of AR signalling in endocrine-sensitive female tissues has largely been neglected.

Estrogens in prostate cancer

Testosterone activates the AR, but can also be converted into estrogen by aromatization in both females and males. Estrogens are the natural ligand for two receptors: ER α (ESR1) and ER β (ESR2). Surprisingly, these two receptors have very different roles, not only in biology but also in pathologies such as breast and prostate cancers. Nelson *et al.* (2014) discuss the emerging roles of the two ERs and variants thereof in prostate cancer biology. This article complements the one by Gonugunta *et al.* (2014), which reviews evidence for crosstalk between AR and ER β via the PELP protein in prostate cancer. The article by Nelson *et al.* (2014) is very topical and like the articles examining AR activity in female endocrine cancers highlights an avenue for future research in male endocrinopathies that has been relatively ignored.

Conclusions

Clearly, basic knowledge on sex steroid signalling in prostate and breast cancers is rapidly progressing, with cross fertilisation taking place because of the emerging roles of ERs in prostate cancer and AR in female cancers of the breast, ovary and endometrium. While many basic molecular aspects need further elucidation, new therapeutic targets and clinical applications are already apparent. It is only through collaborations and exchange of ideas that we will be able to step toward the goal of personalised medical approaches to the treatment and

prevention of breast and prostate cancer, and extend these to encompass other endocrine cancers. We hope that this series of articles inspires further cross fertilisation of thought and investigative effort to achieve these important goals.

Declaration of interest

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