**Words of Wisdom on The early effects of androgen deprivation on human prostate cancer (Greg Shaw et al Eur Urol.(2016) 70: 214-21.**

**Abstract**

For such an established and widespread treatment, we really know very little about the immediate effects of androgen deprivation on prostate cancers in man. Shaw *et al* (1) have now determined the consequences of a 7 day serum/tissue androgen depletion, by degarelix blockade of gonadatrophin releasing hormone, on global gene expression at the RNA and protein levels, confirmed morphologically by immunohistochemistry. In biopsies of radical prostatectomies, 749 genes were downregulated and 908 genes upregulated , including androgen receptor (AR), and new AR regulated genes were identified. The discussion focused on increased expression of Estrogen receptor alpha (ESR1), which has remained contentious for more than 20 years, and activation of estrogen-responsive genes. The authors concluded that ESR activation might provide intrinsic resistance, perhaps initiating the long-term failure of castration-based therapies.

**Expert’s Opinion**

Gene expression after castration therapy has obviously been studied before, but with inconsistent results. Kruithof-Dekker *et al* (2) determined that, within 3 months of total androgen blockade, upregulation of ESR1 was detectable, but predominantly in stromal cells - not seen by Shaw et al. Sporadic ESR1-expressing epithelial cells were present in both studies. The difference could result from (i) the degree/type of androgen suppression (Ref2 in (1)) (ii) biopsy timing after castration or even (iii) methodological differences over 20 years. I was surprised by the absence of detectable effects on Estrogen Receptor Beta expression (3).

Any analysis of heterogeneous biopsy material, without subfractionation of cell types, produces a bias towards the most common cell type(s), and was probably responsible for the relatively modest total gene expression changes (Suppl Tables 2/3). However, which *cells* remain viable? Are they indeed responsible for regeneration of normal prostate and/or cancer relapse, if resistance is intrinsic, rather than induced by the treatment? According to (2) the residual epithelial cells are likely to be basal, which agrees with observed reductions in e.g. luminal cytokeratins (Suppl table 3). But are they normal- or tumour-derived ESR1+ cells - and specifically Ki67+ /proliferative? Whilst there is considerable noise, the array data also indicated upregulation of RARRES1, an epithelial tumour suppressor gene, whose expression is controlled by retinoic acid, almost exclusively in the transit amplifying epithelium of *normal* prostate and skin (4,5). On this basis, the data may reflect regeneration of the normal prostate epithelium.

Shaw et al have opened another toolbox. Perhaps after 75 years we can finally use it to repair and improve castration therapies.

**References**

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**Conflict of Interest Disclosure**

The author has no relevant conflict of interest to declare.

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