

**Pro-tumorigenic role of ER $\alpha$  in prostate cancer cells****Luc Furic, Mitchell G. Lawrence, and Gail P. Risbridger**

The importance of estrogen actions in the etiology of prostate cancer (PC) has been widely accepted following the demonstration that androgens, in combination with estrogens, can induce neoplastic lesions in the prostate [1]. The tumor microenvironment is crucial in this process since tissue recombination assays showed that stromal ER $\alpha$  is required for neoplastic transformation. The apparent lack of epithelial ER $\alpha$  expression in the majority of PC previously led to the notion that direct estrogen action in tumor cells is only through ER $\beta$ , a paralog of ER $\alpha$  with antitumor activities. However, we recently reported ER $\alpha$  positive epithelial cells in approximately half of the patients with aggressive, high Gleason score tumors [2].

As we reported, not all epithelial cells in a given tumor are positive for ER $\alpha$  expression. Similar findings of heterogeneous ER $\alpha$  expression have been published recently in a distinct cohort of PC patients in which epithelial ER $\alpha$  expression correlates with poor patient prognosis [3]. What causes a subset of PC cells to express ER $\alpha$  is currently unknown. Previous work demonstrated that ER $\alpha$  expression can be silenced by promoter methylation, and it is likely that re-expression of ER $\alpha$  in PC cells involves chromatin modifications. With advances in cell sorting technology (using intracellular fluorescent probes) and progress in isolating viable cell populations directly from human prostate tissues, we are confident that gene expression analysis of ER $\alpha$ -positive PC cells is achievable and represents an important step towards understanding the pro-tumorigenic role of epithelial ER $\alpha$  in PC.

Alternatively, we generated an ER $\alpha$  specific gene expression signature from murine PTEN-null prostate epithelial cells and gene ontology analysis revealed that ER $\alpha$  regulates the expression of a wide range of mRNAs coding for proteins involved in carbohydrates metabolism [2]. The loss of PTEN facilitates downstream activation of mTORC1 and both events are associated with increased glycolytic and proliferative activity in tumors [4]. Our demonstration that ER $\alpha$  sustains this glycolytic environment [2] could be specifically associated with PTEN-loss and it will be important to assess the role of ER $\alpha$  in prostate tumors harboring different genetic aberrations (e.g. TMPRSS2-ERG fusion, MYC overexpression, etc). In the context

of the loss of PTEN, we also showed that downregulation of ER $\alpha$  decreases the proliferative potential of PC cells. This reduction in proliferation was accompanied by inhibition of the phosphorylation of ERK1/2, AKT and MNK, key kinases of the MAPK and PI3K pathways. This is in agreement with the “non-genomic” model of ER $\alpha$  action in breast cancer where a pool of ER $\alpha$  is associated with the plasma membrane to direct the activation of the MAPK and PI3K pathways. In addition, the ability of ER $\alpha$  to regulate gene expression at the transcriptional level, and to modulate the activity of signaling pathways that impinge on mRNA translation efficiency, potentially adds a layer of complexity to the gene expression program of ER $\alpha$  in cancer cells. This hypothesis was explored in breast cancer MCF7 cells and revealed that ER $\alpha$  directly regulates the translational efficiency of target mRNAs [5].

Recent results from Rubin & colleagues [6] not only support our findings that subsets of PC cells express ER $\alpha$ , but show that ER $\alpha$  regulates the expression of a long non coding RNA (NEAT1) which is associated with poor prognosis. ER $\alpha$  has also been shown to regulate the expression of multiple miRNAs in breast cancer cells [7]. Considering that our gene expression profiling was performed using microarrays representing only mRNAs, this precluded us from identifying the “noncoding” transcriptional profile of ER $\alpha$ . Future work to assess if miRNAs are regulated by ER $\alpha$  in PC will bridge the gap between transcriptional and translational profiling of PC cells expressing ER $\alpha$ .

Overall, these findings provide a framework in which further experiments could be designed to validate ER $\alpha$  as a biomarker of poor prognosis in PC or as a direct therapeutic target. This could lead to the preclinical testing of pure antagonists of ER $\alpha$  in ER $\alpha$ -positive PC.

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Luc Furic: Department of Anatomy and Developmental  
Biology, Monash University, Clayton, VIC, Australia

**Correspondence:** *Luc Furic*

**Email:** [luc.furic@monash.edu](mailto:luc.furic@monash.edu)

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