Estrogen receptor beta is an important modulator of prostate carcinogenesis

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Background

Prostate cancer (PC) is the commonest, non-cutaneous cancer in men, with no cure for the advanced, castration-resistant form of the disease (CRPC). CRPC develops in almost all men treated with androgen deprivation therapy (ADT), which aims to slow tumour growth and progression by reducing levels of circulating testosterone, the 'male' hormone and main driver of PC. Once diagnosed, the average survival for men with CRPC is 18 months. This is in spite of new chemotherapies, which have shown only moderate benefit.

Estrogen (the 'female' hormone) has been shown to be important in PC development. It has been shown that both estrogen and testosterone are required for the development of PC. The actions of estrogen are mediated in tissue by two receptors; estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ), both of which are found in the prostate. ERα is thought to mediate the 'bad,' tumour-promoting effects of estrogen, whereas ERβ is thought to be mostly protective and tumour-suppressive. However, recent evidence would suggest that ERβ may also have a harmful, tumour-promoting effect within the prostate. The aim of my research, therefore, is to improve understanding of the role of ERβ and to establish whether it represents a target for PC treatment.

Summary of work

There are numerous, apparently contradictory reports in the literature regarding the role and mechanisms of ERβ in benign and cancerous prostate tissue. This is thought to be due to poor ERβ antibody specificity. The first phase of the project, therefore, has been to undertake detailed characterisation and validation of ERβ antibodies for subsequent use. Following validation of the antibodies, a panel of PC cell lines was evaluated for ERβ expression in order to identify a cell culture model that could subsequently be used to study the biological mechanisms of interest.

Antibody validation

Four ERβ antibodies were tested in a breast cancer cell line with ERβ expression that can be switched on and off by doxycycline: Novocastra mouse ERβ, Pierce ERβ1 PPG5/10 (MAI-81281), MC10 ERβ mouse monoclonal (gift from Dr. J. Hawse, Mayo Clinic) and CWK-F12 ERβ mouse monoclonal (gift from Dr. B. Katzenellenbogen, University of Illinois). The CWK-F12 and MC10 antibodies were further validated using a recently developed assay combining immunoprecipitation (IP) with mass-spectrometry (Rapid Immunoprecipitation Mass spectrometry of Endogenous protein – RIME), and again found to be highly accurate and specific in the detection of ERβ.

Prostate cell line characterisation

A panel of PC cell lines was assessed for expression of ERβ to see whether they could serve as useful models for studying the disease. Using several experimental approaches, PC cell lines were found to express little or no ERβ, indicating that they would not be useful experimental models for future experiments planned in this project.

Key findings and Significance of Results

The work described has demonstrated that the ERβ antibodies MC10 and CWK-F12 can accurately detect ERβ protein in multiple experimental conditions and will be very useful for ongoing work in the project.

The characterisation of PC cell lines has demonstrated that they all express very low levels of ERβ. This calls into question the findings of previous studies, which have extensively relied on these cell lines to study ERβ biology.

Future work

In the short-term, future work will focus on developing inducible ERβ-expressing PC cell lines to use as models for studying the disease. In the longer term, experiments will be conducted to determine how ERβ interacts with DNA to exert its effects. The results will be correlated with clinical outcome data to determine the utility of ERβ as either a prognostic marker or treatment target.

Further funding

I will not be applying to The Urology Foundation for further funding relating to this project as I currently hold a MRC Clinical Research Training Fellowship.