Scottish Government Health Directorates Chief Scientist Office

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FOCUS ON RESEARCH

Antiandrogen therapy in prostate cancer: impact of auto-regulation of the androgen receptor gene and receptor point mutations

Researchers
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Aim
Normal prostate development and prostate cancer (PCa) are critically dependent on the hormone testosterone and hormone-deprivation remains the most widely used therapy for advanced disease. Unlike normal cells, PCa cells can circumvent this dependence on testosterone by genetic changes in a protein called the androgen receptor, which binds to and mediates the biological effects of testosterone in the cell. We have recently shown that the androgen receptor can negatively regulate its own expression (auto-regulation). Changes in the sequence of amino acids that make up the androgen receptor protein (point mutations) and the amount of receptor present are both likely to have a major impact on cancer progression and patient response to hormone therapy. The aim of the present project is to characterise the effect of point mutations in the androgen receptor on the negative-feedback controlling expression of the receptor in cells and how this may impact antiandrogen treatment.

Project Outline/Methodology
Prostate cancer cells, expressing either normal or mutated androgen receptor were analysed for negative auto-regulation activity. Treatment of cells with antiandrogens, allowed us to determine how receptor point mutations affect the actions of these currently used drug therapies.

Key Results
A panel of 15 point mutations in the androgen receptor, identified in patients with advanced/metastatic cancer, were analysed for their effects on auto-regulation of receptor activity and response to antiandrogens:

- We confirmed the dose-dependent negative regulation of the receptor gene by androgen.
- We identified a subset of point mutations that demonstrated altered activity, compared with the normal androgen receptor, for negative transcription.
- We identified two mutations with altered activity for both negative and positive gene regulation.
- Altered receptor proteins, which do not bind testosterone effectively switch off expression of the receptor gene in prostate calls.
- The antiandrogens, Casodex and Xtandi, failed to antagonise negative regulation by the androgen receptor.

Conclusions
In this study we have demonstrated, that point mutations in the androgen receptor, found in patients with advanced/metastatic disease, have altered activity with respect to both positive and negative gene regulation.

What does this study add to the field?
Previous studies have highlighted the role of androgen receptor gene amplification and increased protein levels as drivers of advanced, therapy resistant PCa. We now demonstrate that point mutations in the receptor protein can result in failure to negatively regulate receptor expression, thus disrupting the normal negative-feedback pathway controlling receptor levels. Together with our previous results, showing increased stability of the receptor protein, we have provided insight into the mechanisms whereby mutated androgen receptor may resist treatment and drive disease progression.

Implications for Practice or Policy
Our current results suggest that screening for the occurrence and frequency of receptor mutations in patients undergoing androgen ablation therapy is likely to help in stratifying patients, increasing the effectiveness of existing drugs and so improving both patient survival and quality of life.

Where to next?
Our findings to date suggest that point mutations in the androgen receptor could result in changes in both receptor message and protein stability, which may lead to increased activity depending on the cellular and molecular landscape of the cancer cells. Future research will focus on the mechanisms that result in the hijacking of the normal checkpoints controlling receptor levels in prostate cells and the consequences for androgen receptor targeted therapy.

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