PROSTATE CANCER

Acting alone

Prostate cancer is commonly treated with drugs that lower serum testosterone levels often in combination with competitive androgen-receptor (AR) antagonists. Although these therapies are initially effective in slowing the growth of the tumour, it eventually becomes resistant, resulting in hormone-refractory (HR) disease. There are various models to explain this resistance, but a study by Charles Sawyers and colleagues shows that increased AR expression is the defining factor in this process.

To examine the mechanisms of HR prostate tumour growth, Sawyers and colleagues performed microarray-based gene-expression profiling analysis on seven hormone-sensitive (HS) and HR prostate cancer xenograft pairs. In an analysis of 12,000 probe sets, only the *AR* messenger RNA was differentially expressed in all seven pairs of tumours. This was surprising, as the authors expected that expression levels of other signalling factors would also be altered. Their findings indicate that *AR* overexpression alone is sufficient for this switch. Indeed, the authors found that transgenic overexpression of *AR* could convert HS tumours into HR ones, and that reduction of *AR* mRNA levels by RNA interference could slow tumour growth in the presence of androgen.

But how could increased *AR* expression alone be sufficient to allow tumours to grow in the presence of an AR antagonist or at very low hormone levels? The authors showed that the ability of AR to bind ligand, to localize to the nucleus and to bind DNA is required for growth of HR tumours, so perhaps the modest increase in receptor concentration simply allows the AR to use lower levels of androgen. This would predict that very high concentrations of an AR antagonist such as bicalutamide could overcome the excess levels of AR. The authors, however observed the opposite phenomenon — that bicalutamide and other AR antagonists function as agonists in cells that express high levels of AR. This phenomenon has also been observed in patients.

They performed gene-expression profiling on HR cells in the presence and absence of bicalutamide, and found that drug treatment actually led to upregulation of a subset of AR-responsive genes. But how could this happen? One clue was a change in the quantity and composition of co-activators and co-repressors that were recruited to the promoters of AR-responsive genes in *AR*-overexpressing cells. Sawyers suggests that a modest change in the level of AR protein might upset the balance of cofactors that regulate transcription of AR target genes, so when more AR is present, antagonists can no longer inhibit transcription.

So, molecules that are designed to specifically target the ligand-binding domain of AR, prevent AR nuclear translocation or impair assembly of AR transcription complexes on target genes might be more effective means of treating HR prostate cancer.

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References and links

ORIGINAL RESEARCH PAPER Chen, C. D. *et al*. Molecular determinants of resistance to antiandrogen therapy *Nature Med.* **10**, 33–39 (2004)