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RESEARCH HIGHLIGHT

Castrate-tolerant cells: what are the implications for the treatment of localized prostate cancer?

Gail Risbridger and Renea Taylor

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More effective treatment of prostate cancer relies on eliminating cells that survive androgen withdrawal therapy. The discovery that castrate-tolerant tumour cells pre-exist in localized prostate cancer, prior to androgen withdrawal or progression to castrate-resistant disease, supports the notion that neo-adjuvant therapies might be considered in the management of early stage prostate cancer. Advances in our ability to xenograft human prostate cancer provides a unique model system to study individual patient responses and test the preclinical efficacy of novel compounds for men with localized disease.

Prostate cancer is the second most common cancer in men and most men are diagnosed with localized disease that has not spread within the body. About one-third of the men with localized disease will go on to develop advanced disease that is usually treated by androgen deprivation/castration therapy. Although the bulk of the tumour regresses, treatment inevitably fails, resulting in progression to incurable castrate-resistant prostate cancer (CRPC). In our recent study, specimens from men with localized disease were grafted into host mice and when the mice were castrated, castrate-tolerant prostate cancer cells were identified in the human xenografted tissues. The cells have stem cell-like features and can regenerate the tumour when androgens are restored.[1] Since the castrate-tolerant, cancer stem-like cells are in localized prostate cancers, several questions arise to stimulate further research. Are these cells precursors of CRPC disease? If so, should we find ways to target and remove them with neo-adjuvant therapies before CRPC develops? Alternatively, by removing the bulk of the tumour, does castration therapy provide a selective advantage for the growth of a lethal castrate-tolerant cell subpopulation and accelerate the emergence of CRPC disease?

Monash University, Clayton, Vic. 3800, Australia
Correspondence: Professor G Risbridger (gail.risbridger@monash.edu)

Tumours from men with localized prostate cancer are difficult to engraft because the take rates are notoriously low,[2] but we recently developed a reliable protocol that faithfully maintains the original pathology.[3] The methodology is laborious and requires exacting coordination between urology, pathology and research scientists and, most importantly, consent to participate from the patients themselves. This advance now permits the investigation of a collection of individual patient specimens to observe the collective features and responses to castration within a group of localized tumour specimens.

An unresolved question in prostate cancer is whether or not the cancer cells that survive androgen withdrawal pre-exist in early-stage localized tumours, or emerge in later stages of progressive disease. Thus, the potential cells of origin of CRPC remain unknown. Identifying a lethal subpopulation of castrate-tolerant cells implies that the former theory is correct, but further work is needed to prove the stem-like cancer cells are precursors of CRPC. Molecular phenotyping to compare the original tumour graft to the castrate/regenerated tumour is likely to show common and different features that should shed some light on this question. Furthermore, a molecular signature of CRPC tumours was recently published[4] and it will be interesting to see if the castrate-tolerant cells share any of their hallmarks.

An important question for the clinician is how does this change the management of men with localized disease? In Japan, men with localized disease can receive androgen-deprivation therapy (ADT) (see Asian consensus statement for NCCN clinical treatment guideline for prostate cancer; http://www.nccn.org), but in most Western countries, ADT is usually offered to men with recurrent, advanced disease. Does advanced ADT provide survival benefit for patients, or does it accelerate progression to CRPC by selecting out the castrate-tolerant cells from the bulk of the tumour which are present in localized tumours? Further investigation may allow castrate-tolerant cells to be better targeted with neo-adjuvant therapies in order to prevent prostate cancer recurrence. Earlier treatment with novel androgen blockade compounds such as abiraterone, at the time of ADT, may provide improved outcomes.[5] The answers to these important clinical questions are unknown.

The complexity of interpreting experimental results from individual patients is always challenging, but the insights are undoubtedly different to studying serially transplanted tumour lines that have been used in laboratories world-wide for many years. The xenografting approach revealed varying responses in each patient specimen that might predict patient outcome or response to therapy. The model can now be used to study the differing genotype and phenotype of castrate-tolerant cells from individual men with localized prostate cancer, to reveal common molecular signatures and individual markers of aggressive disease. The castrate-tolerant cells are a significant therapeutic target for neo-adjuvant treatment, which could potentially prevent progression to lethal CPRC if effectively eliminated in earlier stage localized disease.

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