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To target or not to target the enemy within localized prostate cancer

Gail Risbridger* and Renea Taylor

Monash University; Clayton, VIC, Australia

Prostate cancer is one of the most common types of cancer in men, and when it is diagnozed, most men have localized disease and are treated with radiotherapy, radical prostatectomy surgery, or go on to active surveillance. About one-third of these men will go on to develop aggressive disease, and at this stage, androgen deprivation therapy (ADT) is standard of care and elicits a rapid atrophic response, reducing the bulk of the tumor. Inevitably the course of progression resumes and the tumors become castration-resistant, developing different mechanisms to evade ADT. Much has been learned about the mechanisms by which tumors evade and adapt to ADT to allow resumption of tumor growth in the absence of systemic hormonal input. Evidence shows prostate cancer cells adapt to low systemic androgens by activating androgen receptor (AR) mutations and amplifications that enhance the sensitivity to androgens as well as utilizing testosterone synthesized from adrenal androgens or de novo by the tumor cells themselves after ADT.[1,2] It is further postulated that castrate-resistant stem-like cells facilitate the progression to CRPC in a step-wise process, beginning with a subset of cells that survive ADT and then adapt to the presence of low systemic testosterone, resulting in the emergence of CRPC.[3,4] However, a central unresolved question is whether or not the lethal subtype of castrate-resistant prostate cancer cells pre-exist in early-stage localized prostate cancer, or emerge in later stages of progressive disease. Thus, the cells of origin of CRPC remain unknown.

The aim of the study by Toivanen and colleagues was straightforward: are castrate-tolerant cells present in localized prostate cancer specimens? The reason that this simple study had not been conducted previously was because xenografting primary human prostate cancer from localized tumors was of very low efficiency. Our improved methods overcame this roadblock in translational research. Another advantage of using primary human tissues was the ability to track individual patient tissue responses and identify their diversity, something that is not possible when using cells lines.[5-7]

Using xenografted specimens from 12 men with localized disease, the study showed castration of the host mice led to rapid regression, but not disappearance of the tumors. The residual tumor foci that persisted had stem cell-like features and appear to be growth-quiescent, but when testosterone stimulation was restored to the host animals, the residual cells regenerated tumors that were histologically similar to the original specimens. This work by Toivanen et al. indicates that some prostate cancer cells can survive castration and later repopulate the tumor when androgen stimulation is available.

The questions that arise from these studies are numerous. Thus far, there is no indication that these castration-tolerant cells in localized tumor specimens are the definitive precursors of the cells found in more advanced CRPC. It is technically challenging to directly show the castrate-tolerant cells generate CRPC, but is a challenge that needs to be addressed. Comparison of the molecular features of xenografted localized vs. regenerated tumors should be informative. Either the molecular features will be similar or different and may or may not share characteristics of CRPC signature recently described by Grasso and coworkers.[8]

While waiting for this information to emerge, the question remains: what are the implications of this discovery (see **Fig. 1**)? If there are castrate-tolerant cells in localized tumors, are they indolent, in which case there is no need to treat them, or are they potentially cancer repopulating, and should adjuvant treatments be considered that co-target them, especially for men who are deemed to be at high risk of relapse? ADT is not normally given to men with localized disease, but in some Asian countries (e.g., Japan) this treatment approach is more common. Do castrate-tolerant cells prevail when these men receive ADT, and is there any difference in their disease progression? An alternate view is that any castrate-tolerant cells (or the precursors) have the potential to be lethal and should be considered as therapeutic targets, but the question is how to target them? What treatments could work alongside castration to prevent tumor regeneration; is there a case to consider more effective androgen blockade, such as earlier treatment with abiraterone acetate?

We can say with certainty that these questions need to be resolved. The work described by Toivanen et al. is but a first step in further discovery using human patient specimens and present interesting challenges to the field of localized prostate cancer research.

*Correspondence to: Gail Risbridger; Email: gail.risbridger@monash.edu
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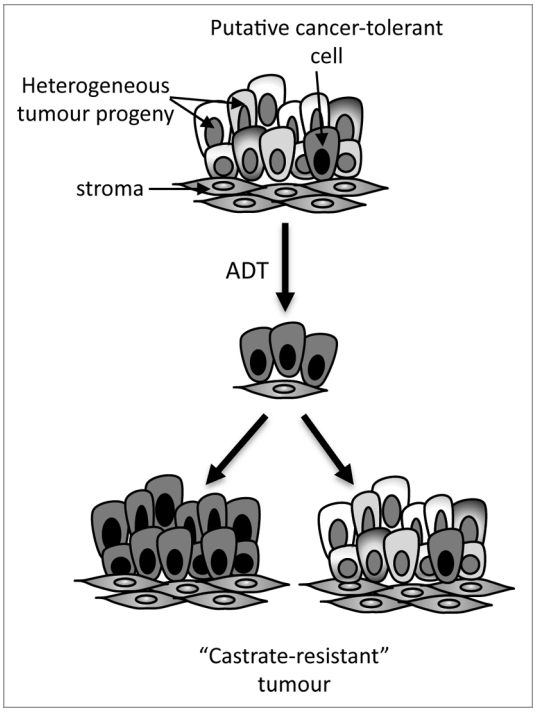

Figure 1. Prostate cancer-initiating cells. In localized, androgen-dependent prostate cancer (left panel), cancer-initiating cells (CICs) proposed to be a rare subpopulation, distinguishable from the bulk of the tumor by its ability to survive treatment and regenerate tumor mass. The identity of these cells is less defined than in other solid tumors, but CD133 has been postulated to enrich for prostate cancer CICs. The expression status of AR in human CD133+ CICs remains under debate, but the tumor bulk is AR+ and therefore androgen-dependent. Following failed front line therapies (i.e., radical prostatectomy or radiotherapy), patients commonly undergo androgen deprivation therapy (ADT). Recurrent disease following this treatment leads to advanced disease, known as castrate-resistant prostate cancer. In these tumors, the residual cancer cells gain the ability adapt to the androgen-deplete environment and synthesize their own androgens de novo in order to mediate maintain cancer cell survival and growth. It is unknown whether the adaptive ability is common to all cancer cells, or restricted to CICs from the earlier stage tumor.

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