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Editorial

EDITORIAL

Strategies to Identify and Target Cells of Origin in Prostate Cancer

Wouter R. Karthaus, Charles L. Sawyers

See the Notes section for the full list of authors' affiliations.

Correspondence to: Charles L. Sawyers, MD, Human Oncology and Pathogenesis Program, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, New York 10065, USA. (e-mail: sawyersc@mskcc.org).

Resistance to androgen deprivation therapy remains the major clinical hurdle for treating metastatic prostate cancer. Although next-generation antiandrogens like enzalutamide and abiraterone extend survival (1,2), castration resistant prostate cancer (CRPC) remains a clinical challenge. Recent sequencing efforts have revealed several mechanisms of resistance giving rise to CRPC, largely through androgen receptor gene amplification or mutation, or through alterations that indirectly restore downstream androgen receptor signaling (3,4). In addition, there is evidence that CRPC tumors acquire stem-like properties such as increased expression of stem/progenitor markers (5), a finding that has sparked interest in defining and targeting prostate cancer stem cells, as with other cancers that evolve to drug resistant stages.

In the current issue of JNCI, Yoo et al. use genetically engineered mouse models to show that Bmi1+/Sox2+ cells within the prostate have cancer stem-like characteristics and that tumors arising from these cells can be targeted with a small molecular inhibitor of BMI1 (6). To place these findings in context, it is important to review the two major epithelial cell types in the normal prostate: luminal cells, which rely on androgen signaling for function and survival, and basal cells, which are androgen independent (7). Although early studies relying on transplantation and cell seeding assays suggested basal cells were prostate stem cells of the prostate (8), more recent work using lineage tracing and organoid culture has revealed the presence of stem cells within the luminal lineage (9–11). During castration, approximately 90% of luminal cells undergo apoptosis, whereas basal cell numbers remain largely unaffected. Upon exogenous testosterone addition, the prostate regenerates to its original size, and normal prostate function is fully restored. Within the 10% remainder of luminal cells, at least two distinct subsets of cells have been identified that have in vivo repopulating capacity: one expressing Nkx3.1 called CARNs (Castration Resistant Nkx3.1 positive cell) (9) and one expressing Bmi1 postcastration called CARBs (12). NXK3.1 encodes a prostate-specific homeobox protein that plays a developmental role in prostate specification (13), whereas BMI1 is member of the polycomb repressor complex 1 and has been implicated in the maintenance of stem cells in several tissues (14). Both CARNs and CARBs can serve as a cell of origin in mouse models of prostate cancer initiated by *Pten* loss.

The current report by Yoo et al. (6) builds on the earlier CARB study (12) by showing that tumors initiated by *Pten* loss specifically in these Bmi1+ cells initially have a luminal phenotype with androgen dependency. When treated with castration, luminal tumors regress and remain dormant for approximately 3 months but with evidence of luminal-to-basal lineage switching (**Figure 1A**). This finding is reminiscent of recent work by several groups implicating lineage plasticity (loss of luminal epithelial features) as a general mechanism of resistance to castration, enzalutamide, or abiraterone. Notably, in these examples, the plasticity is initiated by genomic deletion of TP53, RB1, or PTEN in various combinations (15–17). Interestingly, one common feature in all these examples is the reprogramming factor SOX2, whose increased expression is essential for lineage plasticity (and enzalutamide resistance) initiated by combined TP53/RB1 loss (16).

After demonstrating that prostate tumors can evolve from CARBs in intact mice in the *Pten* model, Yoo et al. (6) used a retracing strategy with the R26R-confetti allele to show that Bmi1-expressing CARBs within the tumor were responsible for driving castration resistance. They next asked if these tumors could be targeted using the Bmi1 small molecule inhibitor PTC-209 (18). Inhibition of Bmi1 resulted in decreased expression of Sox2 and increased cellular senescence, consistent with well-known regulation of the *INK4a/ARF* locus by Bmi1. PTC-209 treatment also resulted in a statistically significant delay in tumor recurrence after castration, suggesting that targeting prostate cancer stem cells could be an effective strategy to prevent resistance to hormone therapy.

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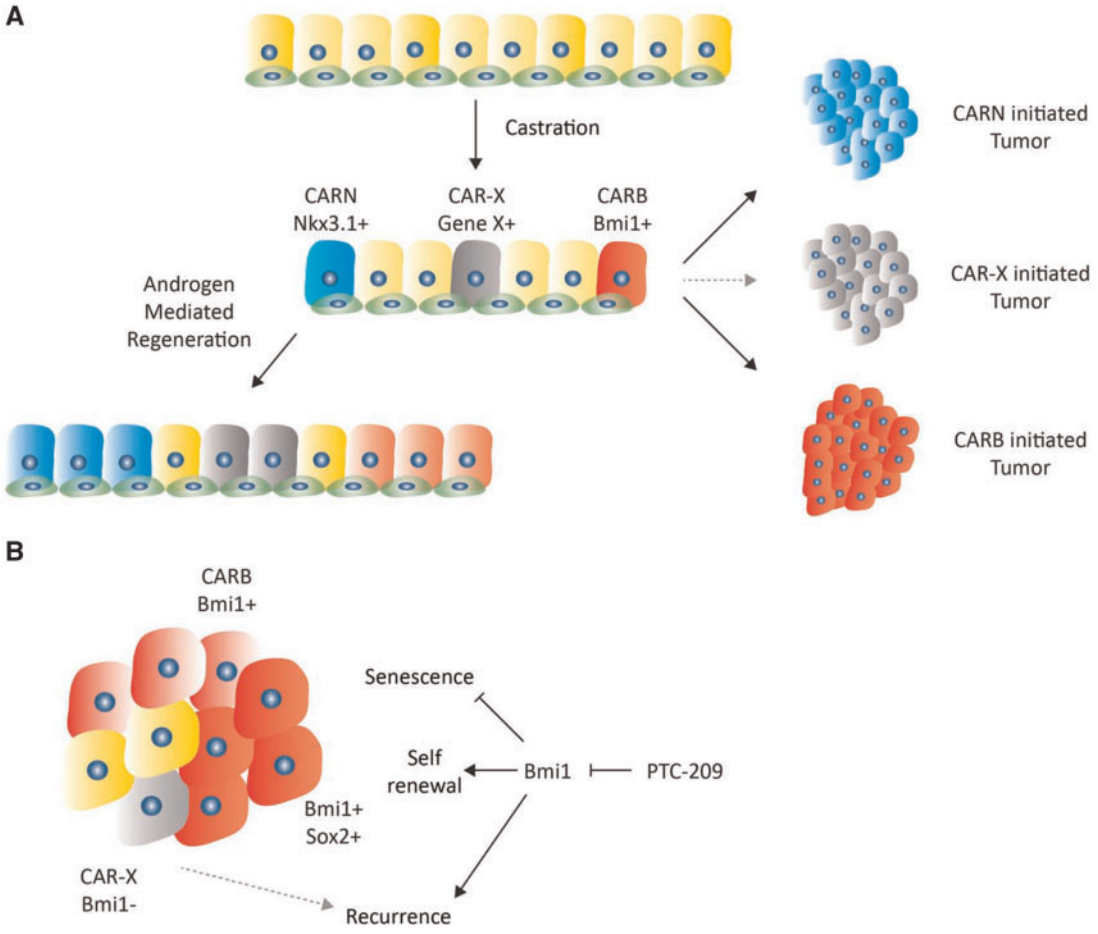

Figure 1. Model of prostate cancer stem cell heterogeneity. **A)** Schematic overview of prostate epithelium showing luminal cells (larger, upper) and basal cells (smaller, lower). After castration, two distinct stem cells have been identified: Nkx3.1-positive CARN cells and Bmi1-positive CARB cells that contribute to androgen mediated regeneration. Moreover, both can serve as a cell of origin for prostate cancer. CAR-X (gray) depicts the possibility of additional luminal progenitor cells distinct from CARNs and CARBs. **B)** Several distinct cell types are present in CARB-initiated tumors, including Bmi1-positive, Bmi1/Sox2-double positive, and Bmi1-negative cells. Inhibition of Bmi1 with the small molecule PTC-209 leads to an increase in senescent cells and a delay in recurrence. Recurrence is potentially driven by alternate cancer stem cells populations, such as CAR-X. CARN = castration resistant Nkx3.1 positive; CARB = castration resistant Bmi1 positive.

While provocative, clinical testing of BMI1 inhibitors in prostate cancer requires further consideration. First, PTC-209 is an early stage compound with limited potency and poor pharmacokinetic properties that make it a poor candidate for clinical development; however, a newer BMI1 inhibitor PTC596 may be more promising (19). In addition, BMI1 is broadly expressed and implicated in self-renewal and stem cell maintenance in many tissues, raising potential concerns about toxicity if continuous BMI1 inhibition is required to prevent hormone therapy resistance. Assuming these hurdles can be overcome, there is the additional question of whether BMI1 inhibition alone would be sufficient to target all the relevant prostate cancer stem cells. Specifically, CARBs and CARNs define two distinct populations of luminal stem cells, and it is possible that CARNs or other BMI1-negative stem cell populations could emerge (20,21), particularly in light of growing evidence for lineage plasticity (Figure 1B). This concern would be particularly relevant in tumors with TP53 or RB1 loss, which account for a substantial fraction of CRPC cancers. On an optimistic note, technologies for single cell analysis of whole transcriptomes (single cell RNA-seq) offer the promise of bringing increasing clarity to the complex and heterogeneous populations of cancer-initiating cells in prostate cancer as well as other tumor types, and will be an important tool to track the evolution of tumors treated with stem cell therapy.

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Notes

Affiliations of authors: Human Oncology and Pathogenesis Program, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, New York 10065, USA. (WRK, CLS); [2]Howard Hughes Medical Institute, Chevy Chase, Maryland 20185, USA (CLS).

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