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Re: Regenerative Potential of Prostate Luminal Cells Revealed by Single-cell Analysis:

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Expert's summary:

Growth of the prostate gland, a male sex accessory organ that contributes to ejaculate fluid, is dependent on androgens. Castration-induced androgen deprivation leads to rapid involution of the prostate due to apoptosis of androgen-dependent epithelial cells, while in response to androgen replacement there is regeneration of the gland [1]. The epithelial lineage hierarchy for a normal prostate gland involves basal and luminal secretory cells, which constitute most of the prostate glandular epithelium, surrounded by stroma, which contains fibroblasts, endothelial cells, nerves, and stem/progenitor cells. The study by Karthaus et al revealed that prostate regeneration after involution occurs not only via stem cells but also via a subset of persisting luminal epithelial cells. Prostate luminal cells from adult mouse and human-derived organoids express stem-like and differentiation genes that are sustained under androgen depletion. Single-cell profiling unveiled a shared gene cluster in the prostate cell lineage, comprising *NKx3-1*, *PSCA* (stem-like), AR-regulated genes, and neuregulin-2 (mesenchymal cell driver of luminal regeneration), that promote regrowth of the gland in response to androgens.

Expert's comments:

In the normal prostate, androgen deprivation disrupts stroma-epithelial interactions that ultimately lead to a decrease in the size/weight of the gland. Epithelial stem-cell units populated by progenitor cells (initially defined by John Isaacs as transit-amplifying cells [2]) reach differentiation maturity with a proliferative response to androgens that results in prostate regrowth. In prostate cancer, castration-induced androgen deprivation therapy (ADT) is based on this dependence on the androgen signaling axis and its targeting. However, therapeutic resistance and tumor relapse emerge in most patients because of a luminal stem-cell population (NKx3-1-positive) resistant to ADT, identified as a cell of origin for prostate cancer a decade ago [3]. Exploitation of mouse models advanced our understanding of the interlineage relationship and intralinear heterogeneity, as well as of lineage plasticity, in prostate tumor initiation, metastatic progression, and therapeutic

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resistance [4]. Rb1 loss facilitates lineage plasticity and metastasis (initiated by *Pten* mutation) and loss of Trp53 confers resistance to ADT [5]. However, the controversy as to whether the human prostate lineage hierarchy is identical to the murine cell lineage remains. The authors showed that in both human-derived organoids and mice, stem-like luminal and differentiated cell populations contribute to prostate regeneration after androgen ablation. Molecular profiling validated the acquisition of regenerative capacity by both cell types in mice and humans, as evidenced by the response to androgen replacement. As prostate cancer–originating cells display distinct phenotypes that correlate with aggressive clinical behaviors [6], gene function profiles represent actionable targets for overcoming therapeutic resistance in advanced disease across the cell lineages.

Temporal reprogramming of well-differentiated luminal cells to confer proliferating privileges in prostate tumor regrowth is relevant in recalibration of the transit “stemness” of prostate cell subpopulations that drive tumor resistance and disease recurrence; knowledge of this process will allow restoration of therapeutic vulnerability beyond ADT.

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