Cancers of the breast and prostate: a stem cell perspective

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Soon after the initial demonstration that the normal breast epithelium is composed of at least two functionally distinct progenitors (K5⁺ and K14⁺, Axin2⁺, CD24⁻/CD49hi, s-SHIP⁺, label-retaining cells, CD1d⁺, Procr⁺, Axin2⁺, CD61⁺ and Lgr5⁺ cells), lineage tracing studies have shown that the basal cell layer harbors both unipotent (some K5⁺, K14⁺, zSMA⁺) and bipotent (some K5⁺, Procr⁺, and Axin2⁺) stem cells whereas luminal progenitor cells are unipotent as the K8⁺ luminal cells have never been observed to give rise to basal cells in vivo in the normal mammary gland. Basal MaSCs and most luminal progenitor cells are ER⁻/PR⁻. Interestingly, in a basal-like breast cancer model induced by Brca1 loss, luminal progenitors are likely the cell of origin for the tumors, suggesting that luminal cells may be reprogrammed to undergo basal-like transdifferentiation by oncogenic insults.

Breast cancer is the first human solid tumor in which evidence for CSCs was presented (Al-Hajj et al. 2003). By now, multiple populations of breast cancer stem cells (BCSCs) have been reported including CD44⁺ CD24⁻ and ALDHhi populations as well as side population (SP) and differentiated luminal layer expressing steroid hormone receptors (ER, PR, AR, etc) and a basal or myoepithelial (for breast) cell layer expressing transcription factor p63 but not steroid hormone receptors. The tumors in both organs present mainly as a luminal phenotype in that most tumor cells express steroid hormone receptors (Fig. 1). Consequently, inhibition of steroid hormone signaling via blocking receptor function and hormone synthesis represents the major clinical intervention in both cancers. In this issue, five leading groups in the field discuss the cells of origin and CSCs in breast and prostate cancers, expounding on the potential clinical relevance.

Streekumar et al. (2015) present a comprehensive, up-to-date, overview on the complex hierarchy of murine mammary stem cells (MaSCs). Multiple populations of adult MaSCs have been reported including CD29hi CD24⁻/CD49hi, s-SHIP⁺, label-retaining cells, CD1d⁺, Procr⁺, Axin2⁺, CD61⁺ and Lgr5⁺ cells. Lineage tracing studies show that the basal cell layer harbors both unipotent progenitors (K5⁺, K14⁺, zSMA⁺) and bipotent (some K5⁺, Procr⁺, and Axin2⁺) stem cells whereas luminal progenitor cells are unipotent as the K8⁺ luminal cells have never been observed to give rise to basal cells in vivo in the normal mammary gland. Basal MaSCs and most luminal progenitor cells are ER⁻/PR⁻. Interestingly, in a basal-like breast cancer model induced by Brca1 loss, luminal progenitors are likely the cell of origin for the tumors, suggesting that luminal cells may be reprogrammed to undergo basal-like transdifferentiation by oncogenic insults.

Breast cancer is the first human solid tumor in which evidence for CSCs was presented (Al-Hajj et al. 2003). By now, multiple populations of breast cancer stem cells (BCSCs) have been reported including CD44⁺ CD24⁻ and ALDHhi populations as well as side population (SP) and
label (e.g. PKH26) retaining cells. Simões et al. (2015) focus their discussions on the role of steroid hormones in regulating BCSCs. As most of the reported BCSC populations, like their normal counterparts, are ER$^{-}$ and PR$^{-}$, both estrogen and progesterone influence BCSC abundance and activities via indirect mechanisms. Depending on the experimental context, estrogen may either promote or diminish BCSC activity. Nevertheless, anti-estrogen therapies seem to primarily target ER$^{-}$ breast cancer cells leading to enrichment of dormant ER$^{-}$ BCSCs, which could become ‘reactivated’ to mediate endocrine therapy resistance and metastasis. Unlike estrogen, progesterone seems to clearly promote the expansion of BCSCs, suggesting that anti-progesterone drugs may find clinical use in targeting BCSCs. Although the underlying mechanisms remain obscure, the BCSC-promoting effects of progesterone are likely to be mediated via paracrine/juxtacrine signaling (Simões et al. 2015).

The prostate, like the breast, is a hormonally regulated glandular organ with androgens mainly regulating the luminal epithelial cells. Strand & Goldstein (2015) review the literature pertaining to the relationship between basal and luminal cells as well as their involvement in both benign prostatic diseases (BPH) and prostate cancer. Although proliferation of basal/stem cells may contribute to BPH, primary prostate cancer notably shows a decrease or loss of basal cells. Transplantation assays identify a population of basal cells (i.e. CD49$^{hi}$ Trop2$^{+}$) as the cell of origin for human prostate cancer whereas lineage-tracing studies implicate murine luminal cells as the preferred target of tumorigenic transformation. The reason underlying this discrepancy remains unclear. Shibata & Shen (2015) focus on stem cells and CSCs in GEMMs of prostate cancer. They present an up-to-date overview on various populations of murine prostate stem/progenitor cells and their potential lineage relationship during development, adult homeostasis, and regeneration. Importantly, GEMM studies have revealed the presence of castration-resistant stem/progenitor cells in the normal prostate that retain stem cell properties upon androgen deprivation. Finally, they discuss several CSC populations (e.g. LSC$^{hi}$, CD166$^{hi}$, CD133$^{+}$) reported in various GEM models of prostate cancer. Along these lines, they discussed limitations and caveats associated with current approaches in assaying CSCs using cell cultures and transplantations.

Multiple populations of CSCs in human prostate cancer (i.e. PCSCs) have also been reported (Rybak et al. 2014, Liu et al. 2015). Deng & Tang (2015) dissect the relationship between AR and PCSCs. They present abundant evidence for heterogeneity in AR expression in untreated primary, treatment-failed and castration-resistant, and metastatic tumors. The prominent AR heterogeneity raises the possibility that the AR$^{-}$ prostate cancer cells will not be responsive to the clinical antiandrogen therapies and may thus represent a cellular source of therapy resistance. Interestingly, nearly all
reported PCSCs populations in untreated cultures, xenografts, and patient tumors are AR\textsuperscript{−}, similar to the ER\textsuperscript{−} phenotype of BCSCs. These AR\textsuperscript{−} PCSCs have been associated with therapy resistance and disease recurrence. On the other hand, as most castration-resistant clinical tumors clearly harbor AR\textsuperscript{+} cancer cells and clones, the authors offered a provoking hypothesis that PCSCs in some recurrent tumor clones might be AR\textsuperscript{+}.

Collectively, papers in this issue provide an up-to-date review on breast and prostate tumorigenesis from a stem cell perspective and offer fresh insight on not only the etiology of the two prevalent cancers but also developing novel therapeutics targeting heterogeneous cancer cell populations.

Declaration of interest
The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of this editorial.

Funding
Work in the author's lab was supported, in part, by grants from NIH (NCI R01-CA155693), DOD (W81XWH-13-1-0352 and W81XWH-14-1-0575), CPRIT (RP120380), and MDACC Center for Cancer Epigenetics.

References


Strand DW & Goldstein AS 2015 The many ways to make a luminal cell and a prostate cancer cell. Endocrine-Related Cancer 22 T187–T197. (doi:10.1530/ERC-15-0195)

Received in final form 26 August 2015
Accepted 27 August 2015