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Commentary
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Tumor Stem Cells Commence Hormone Refractory Prostate Tumors and Hormone Therapy-Resistance

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Commentary

Prostate cancer is a commonly diagnosed cancer in the world. As the growth and maintenance of the prostate gland is regulated mainly by the hormone androgen, therapies to cut off androgen access have been employed to inhibit cancer growth [1,2]. Common applications include hormone therapy to deprive the presence of androgen, and anti-androgen therapy to block the androgen activity. After the hormone therapy to eliminate prostate tumors that require androgen for growth, the tumors may recur as they evolve to grow without androgen. They become hormone refractory prostate tumors, which are often lethal. The precise molecular mechanisms responsible for this cancer progression and therapy-resistance remain largely unknown. There was a stem cell hypothesis published in the 1990's, among other theories, to account for this cancer progression [3,4]. It is postulated that the presence of androgen receptor-negative stem cells in the tumors might be selected during therapy and then repopulate the tumors.

There are numerous investigations to examine the role of tumor stem cells. An earlier study by Chen et al. [5], isolated tumor stem cells in a cell culture system mimicking the progression of prostate tumor from androgen sensitive to hormone refractory, which could also relate further to clinical observations. Implication of tumor stem cells in the genesis of hormone therapy-resistance, and in the transform from androgen sensitive tumors to hormone refractory tumors is commented herein. Tumor stem cells were isolated in the form of spheres, 3D clusters of cells, from an androgen sensitive cell line. They can self-renew with or without androgen, and upon androgen deprivation, they differentiated into highly invasive androgen-insensitive neuroendocrine cells. Unknown was that these differentiated progenies could respond to androgenomic alteration. Upon re-exposure to androgen they reverse differentiated into the stem cells in spheres. Plasticity of the stem cells which can grow with androgen or without androgen has become a new paradigm. The multi-capacity of the stem cells and their progeny provides them the adaptability in different conditions to grow and differentiate, which underlie tumor survivability, and the finding is seminal.

Since stem cells can grow without androgen, they can survive androgen deprivation or anti-androgen therapies that eliminate tumors require androgen. When androgen is depleted, they proceed their development onto pathway without androgen. The presence of such stem cells has thereby underscored therapy-resistance, illustrating why the hormone therapy fails to kill all tumor cells. Hence the tumors persisted. In the absence of androgen, these stem cells mainly undergo differentiation into progeny. They can also replicate in the absence of androgen, and the tumors become androgen insensitive. The mechanism thus explains how the tumors which need androgen to grow evolve to those tumors that do not require androgen.

The stem cell properties have made it clear that together with the androgen axis they are both critical in shaping the initiation and post-initiation progression of prostate carcinogenesis. In this regard, the stem cells are both androgen-sensitive and androgen-insensitive, and their progenies are responsive to androgenomic mediation. They are the key players in 1) initiating tumorigenesis, and in 2) seeding out invasive progeny.

The prostate tumor stem cells have emerged as a critical target, as the androgen axis, for tumor elimination. With these two treatment targets, the elimination of tumor stem cells may become more fruitful.

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