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RESEARCH HIGHLIGHT

# Prostate cancer stem cells: molecular characterization for targeted therapy

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**The article published recently in *Cell Stem Cell* from the laboratory of Dr Tang showed the existence and molecular fingerprints of prostate cancer stem cells (CSCs), and this report opens newer avenues for developing and designing novel therapeutic strategies for targeted elimination of these CSCs toward prostate cancer therapy.**

Prostate cancer (PCa) statistics are alarming, and the disease poses one of the most intriguing cancer problems of the twenty-first century. Screening strategies involving serum prostate-specific antigen (PSA) measurement in men over 40 years of age have substantially increased the rate of cancer detection but have not decreased the mortality. This begs the question whether PSA expression is the right detection tool for identifying aggressive PCa or not especially, because the level of serum PSA cannot distinguish the indolent from aggressive PCa. While there is a consensus that cancer is a highly heterogeneous disease, PCa is also heterogeneous harboring myriad types of cells in terms of their molecular make-up. Complete molecular characterization of PCa especially the incurable form of castrate-resistant PCa (CRPC) subtype is lacking. Additionally, a large yet controversial body of evidence suggests that within the different PCa cell subtypes, there exists an enriched population of highly resistant cancer stem cells (CSCs) or more commonly accepted as cancer stem-like cells (CSLCs) population. CSCs or CSLCs within the tumor are believed to be the cells that drive PCa progression and metastasis. However, the origin, identity and molecular characterization of CSCs or CSLCs that is relevant to clinical stages of PCa remain a hotly debated topic.

In a major step forward, Dean Tang and his group in their recent *Cell Stem Cell* article provide new insights supporting the presence of a subclass of cells that have low or no PSA ($PSA^{-/lo}$) expression that are enriched in CSC markers.[1] In support of the true CSC model, the identified $PSA^{-/lo}$ cells have the propensity to self-renew, maintain long-term propagation and most importantly show castration resistant traits. These findings have shed light on the existence of CSCs in PCa, and these findings have the potential to develop new strategies for targeted therapeutics specifically against the resistant subpopulation of cells, which may be responsible for CRPC and subsequent metastatic disease.

For a long time, researchers have independently reported that the serum PSA levels become inconsistent with the increase in Gleason score.[2] This is primarily because the higher the Gleason score, the more heterogeneous a tumor becomes. Additionally, serum PSA is false positive-prone (7 out of 10 men in this category may not have PCa) and false negative-prone (2.5 out of 10 men with PCa have no elevation in PSA).[3] The standard classification based on serum PSA scoring is low risk: PSA$<$10 ng ml$^{-1}$, Gleason score$\leqslant$6, and clinical stage$\leqslant$T2a; intermediate risk: PSA=10–20 ng ml$^{-1}$, Gleason score=7, or clinical stage=T2b/c; high risk: PSA$>$20 ng ml$^{-1}$, Gleason score$\geqslant$8, or clinical stage$\geqslant$T3.[4] However, according to the recent study,[1] the tumor cell PSA levels do not usually adhere to this classification in high Gleason grade tumors.

In their investigations on differentiated areas in high Gleason score untreated PCa, it was found that most PCa cells stained strongly positive for PSA. However, tumors with poorly differentiated or undifferentiated areas could be identified in which *PSA* expression would be heterogeneous, although the implication of such findings need further investigations. On the other hand, investigations in CRPC presented as undifferentiated tumors, lacking glandular structures and PSA staining. These data are especially intriguing, since these tumors had PSA-positive foci yet PSA staining was absent. What is most striking is the observation that there is an inverse correlation between the tumor *PSA* mRNA levels and tumor grade and enhanced metastasis (i.e., Gleason 9/10 prostate tumors tend to have lower levels of *PSA* mRNA). These findings are consistent with earlier reports where hormone refractory tumors showed statistically significant lower *PSA* mRNA levels compared to hormone-naive tumors. In contrast, serum PSA enhancement was correlated with poor survival and comparative to other previously published findings.[5] The authors also investigated other markers such as transmembrane protease serine 2 (TMPRSS) whose expression is regulated by androgen receptor and it is associated with poor prognosis. These new findings certainly could be put to test many of the existing standard methods that have been utilized clinically to classify PCa.

Another important finding presented in this paper is related to the correlation between low PSA and CSCs. Although the idea of CSCs is still controversial, their presence in many different tumor models has been verified.[6] CSCs have been characterized in great detail in different tumor models and have been shown to carry certain key features including self-renewal capacity, propensity to form spheroids and in general showing resistance to different chemotherapeutic regimens.[7] In PCa,

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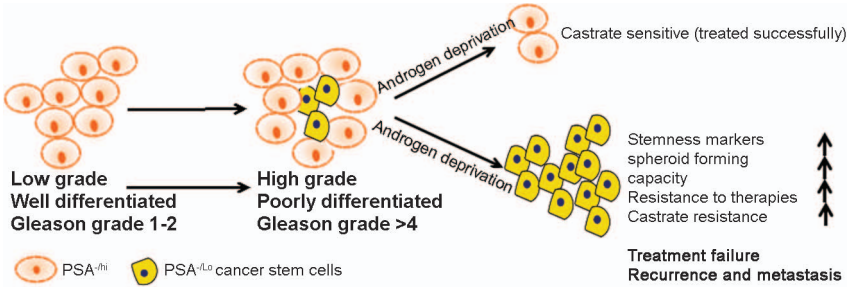


**Figure 1** Prostate Cancer (PCa) Harbor Cancer Stem Cells(CSCs) or Cancer Stem-like Cells (CSLCs). Low Gleason grade PCa have a well differentiated tissue morphology with cells carrying high prostate-specific antigen (PSA) ($PSA^{+/hi}$) positive tumor cells that express PSA. However, as the tumor progresses (with increase in Gleason score>4), it becomes heterogeneous both genetically and phenotypically. This heterogeneous mass carries different types of cells. Qin *et al*. in their article[1] have identified a specific subset of cells in this heterogeneous tumor mass as recognized by their low PSA levels and propensity to form spheroids. These cells express stemness markers and are resistant to castration/androgen deprivation therapy. It is proposed that these low PSA or no PSA expressing cells are the true CSCs (CSLCs) that are responsible for tumor cell resistance to therapy resulting in tumor recurrence and metastasis.

CSCs have been widely investigated (1200 articles in PubMed (including this spotlight paper) when searched using keywords 'prostate cancer stem cells' on 17 May 2012). CSCs have been hypothesized to escape androgen deprivation therapy, chemo- or radiation therapy, and thus the presence or enrichment of CSCs in PCa appears to play a role in disease recurrence and metastasis, once the tumor becomes CRPC. However, as presented in their paper, the observation that $PSA^{-/lo}$ could be a driver of CSC is a totally new finding. Through an elegant experiment, these authors showed that commonly used PCa cell line LNCaP with low tumor PSA levels have superior sphere forming capacity compared to $PSA^{+}$ cells. The resultant distinct cell populations could self-propagate in long-term culture conditions and showed increased expression of CSC makers. Animal tumors derived from very low number of such sorted $PSA^{-/lo}$ cells showed high rate of tumor growth and long-term tumor propagation. As expected, these tumors were refractory to different therapies including castration in contrast to CSC marker-negative cells-derived tumors. Taken together, their investigations on clinicopathological findings showed that low PSA mRNAs were correlated with poor overall survival. However, this study could have been benefited from investigation on the characteristics of epithelial-to-mesenchymal transition phenotype in the $PSA^{-/lo}$ LNCaP cells especially because epithelial-to-mesenchymal transition and CSCs are inherently linked, and such morphological transition from epithelial (round) to mesenchymal (elongated) has also been established as a driver of tumor recurrence and metastasis.

This article has major implications questioning conventional wisdom in categorizing PCa, i.e., based on PSA dependent Gleason grade scoring system. Additionally, it also provides the scientific basis in support of the existence of CSCs (CSLCs) and molecular evidence supporting the proponents of the hypothesis that a distinct subpopulation of cells with CSCs (CSLCs) characteristics does exist in prostate tumors (depicted in Figure 1). It is our expectation that these specialized cells could be successfully targeted by new strategies focusing on the elimination of CSCs (CSLCs) toward the cure of patients diagnosed with PCa especially the CRPC for which curative treatment is lacking.

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