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Mini Review

# Emerging Role of Cancer Stemness in Prostate Cancer Recurrence and Management

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## Abstract

The importance of prostate cancer stemness in prostate tumor recurrence and mortality cannot be overemphasized and shouldn't be trivialized. Intra-tumoral heterogeneity complicated by the presence and enrichment for prostate cancer stem cell (PCSC) population in prostate cancer (PCa) patient or survivors have been implicated in the initiation, progression, aggressiveness, metastasis, treatment failures and recurrence of the disease. More studies are needed to bring clarity to the molecular mechanisms of PCa stemness and its role in the development of castration-resistant PCa. In addition, selective and effective therapies are needed to target PCSCs to prevent PCa aggressiveness and recurrence. An overview of the role and molecular mechanisms of PCSCs, as well as some currently proposed diagnostic, prognostic and therapeutic methods for eradicating PCSCs to prevent PCa recurrence and psychological 'fear of recurrence', have been discussed and summarized.

**Keywords:** Prostate Cancer Stem Cells; Cancer Recurrence; Fear of Cancer Recurrence; Cancer Stemness; Castration-resistant Prostate Cancer

## Introduction

The psychological "fear of cancer recurrence" (FCR) is very common and real among prostate cancer survivors [1]. Many studies have shown that about 70% of cancer survivors show clinical signs of depression, anxiety and constant fear/worry that their cancer will eventually return/recur [1-3]. Prostate cancer (PCa) remains the most diagnosed and the second leading cause of cancer death in US men [4]. The earliest management strategy for localized PCa involves the use of conventional therapies such as radical prostatectomy, chemotherapy, radiotherapy and later androgen deprivation therapy targeted at cancer inhibition or stopping cancer growth or metastasis [4]. Despite the many treatment options and reported high survival rate for PCa patients, a majority will eventually develop biochemical recurrence a few years into disease remission in the form of an aggressive and metastatic castration-resistant PCa (CRPC) [5]. PCa remission means the clinical signs and symptoms of the disease are clinically reduced (partial remission) or absent (complete remission) for a period of time following therapy.

PCa recurrence is characterized by the return/relapse of cancer in an individual after he has been treated and declared cancer-free or after a period during which cancer has been undetected in the prostate gland. PCa recurrence can be categorized into: (i) Local recurrence, in which the newly formed tumor is relocated in the prostate gland at the same place it had first been initially diagnosed; (ii) Regional recurrence, in which the newly formed tumor is located in or around the lymph nodes or organs very close to the prostate gland, where the original tumor occurred; (iii) Distant recurrence, which is when the newly formed tumor appears to have metastasized to a distant organ or another part of the body of the individual, far away from where it had occurred initially such as to the bones, lungs, liver, or brain [6].

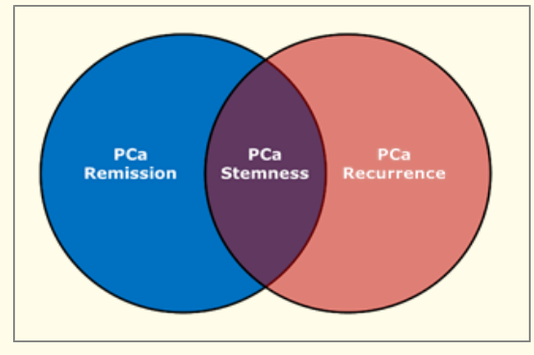


**Figure 1:** A schematic venn diagram showing the relationship between PCa remission, stemness and recurrence. PCa stemness is found at the intersection of both PCa remission and recurrence, which means the presence, absence or amount of PCSCs present in an individual may determine if they will have a prolonged remission or PCa recurrence.

Histologically, prostate tumors are known to be heterogeneous, which means they are made up of a variety of tumor cells with unique genotypic and phenotypic features in addition to the tumor-associated stroma or immune cells [7]. One of the most important tumor cells implicated in the initiation of PCa recurrence is a small side population of cells known as prostate cancer stem cells (PCSCs). PCSCs have been implicated in the initiation, progression and recurrence of PCa [8]. They have all the features of the normal stem cells and can express most stem cell markers. In addition, PCSCs have the capability for self-renewal, pluripotency and plasticity. They are known to be highly tumorigenic and have the capability for tumorsphere formation, chemoresistance, radioresistance, evasion of immune surveillance/attack and are very metastatic [9].

Two proposed theories/models for tumor heterogeneity has better improved our knowledge on this subject: stochastic or clonal evolution and cancer stem cell hierarchical models. The stochastic theory is based on the principle that due to genetic and epigenetic alteration or mutations that all cells within a tumor have the capability to form clones that can initiate the growth of a tumor i.e. tumor-initiating [10]. In contrast, cancer stem cell or hierarchical model is based on the principle that tumors are phenotypically heterogeneous and that tumor-initiating capabilities are restricted to only a subpopulation of cells within the tumor called cancer-initiating cells or CSCs [11]. The pioneering work on CSCs in hematopoietic cancer by Bonnet and Dick [12] has since been followed by many other outstanding studies that have identified CSCs in many solid tumors, including PCSCs in prostate tumors [13].

To aid in the isolation and development of drug targets against PCSCs by basic and translational researchers, many studies have been devoted to the characterization of surface markers that can be used to distinguish PCSCs from other prostate tumor phenotypes [14]. Some of the commonly used PCSCs surface markers include CD44, CD133, $\alpha_2\beta_1$ integrin and ALDH1, among others [15]. Some researchers have suggested that the use of 2 or more PCSC markers may be more accurate and effective in identifying PCSCs in prostate tissues or cell lines. For instance, CD44+/$\alpha_2\beta_1^{high}$/CD133$^+$ stem-like cells were found to be more tumorigenic and pluripotent compared to cells with single markers (i.e. CD44+, $\alpha_2\beta_1^{high}$, or CD133$^+$) or without the markers (i.e. CD44-/$\alpha_2\beta_1^{low}$/CD133$^-$ cells) [16]. Apart from stem cell markers, the expression of stemness-related transcriptional factors has also been considered to identify and therapeutically target PCSCs. Transcriptional factors, such as NANOG, MYC, OCT4, SOX2 and KLF4, among others have been shown to be expressed by PCSCs at different and significant levels compared to other prostate tumor phenotypes [17].

Other studies have sort to understand the molecular mechanism by which PCSCs survive the initial therapeutic insult. Some of the identified mechanisms include, (i) Dysregulation of PTEN/PI3K/AKT signaling pathway [18]; (ii) Dysregulation of RAS/MAPK signaling pathway [19]; (iii) Upregulation of the Wnt, Notch, NFκB and Hedgehog signaling pathways [20]; (iv) Overexpression of STAT3 signaling pathway; (v) Metabolic reprogramming [21]; (vi) Epithelial to mesenchymal transition (EMT) [22]; and (vi) Overexpression of multi-drug resistant genes/ABC transporters [23-24].

Targeting these stemness mechanisms have been attempted in recent basic studies and clinical trials [25]. Although, there are currently no FDA approvals for CSC therapies just yet, some already approved drugs for other purposes or diseases have shown promise and are gradually being tested at different phases of clinical trials [26]. Some of the therapeutic targets for PCSCs include, (i) Therapies targeted against PCSCs by conjugating cytotoxic compounds with antibodies or nanoparticles that can bind with PCSC biomarkers (CD44, CD133 and ALDH1) in prostate tumor. This technique has only been demonstrated *in vitro* and *ex vivo* [16]; (ii) Targeting survival pathways, such as PI3K/AKT/mTOR, STAT3, NF-κB, Wnt/β-Catenin, Notch, Sonic hedgehog, TGFβ and RAS/MEK/MAPK signaling pathways in PCSCs by developing small molecule inhibitors against these pathways [27,28]; (iii) Differentiation therapies, which involve the administration of compounds, such as vitamin A analogs and histone deacetylase inhibitors that can enhance the maturation and irreversible differentiation of cancer stem cells or that inhibits self-renewal activity of cancer stem cells [29]; (vi) Targeting multidrug-resistant genes, in which therapies are developed against expression of multidrug-resistant genes, like ABCG2, p-glycoprotein that is overexpressed in PCSCs. multidrug resistant therapies, including fumitremorgin C, verapamil and cyclosporine A, zosuquidar (LY335979), tariquidar (GTR9576) and elacridar (GF1209180) have been successful *in vitro* [30,31]. Some natural phytochemical compounds, such as metformin, genistein, salinomycin, curcumin, vitamin D and sulforaphane have shown promise against PCSCs [32-35].

Though more studies are still needed on prostate tumor heterogeneity and recurrence, we now have a clearer knowledge on the important roles of PCSCs in driving tumor aggressiveness, metastasis, chemo-radioresistance and castration-resistant PCa recurrence, which has created a more comprehensive outlook on treatment strategies for cancer management. Rather than just administering therapies directed at the fast-growing tumor mass, we are beginning to see the emergence of therapies directed against the slow dividing PCSCs [25,36]. Newer and better models, such

as 3-dimensional spheroids and organoids systems are now being developed to study PCSCs, prostate tumor microenvironment and castration resistance [37]. There is no doubt that the elimination of PCSCs, the bedrock of PCa origin and recurrence, presents a promising approach to prolong the survival of PCa patients as well as prevent PCa recurrence and effectively manage psychological FCR.

## Conclusion

PCSCs have been demonstrated to be present in the core of both PCa cell lines and *in vivo* tumor in a small population with capabilities for unlimited self-renewal, transdifferentiation, sphere formation and chemo-radioresistance. Great understanding of the survival mechanisms and characteristics of PCSCs is vital in the process of developing novel precision therapies to exclusively target and eradicate the tumor-initiating/CSCs in prostate tumor and to ultimately prevent relapse or recurrence of prostate cancer. We hope that the development of novel therapies that selectively eradicate PCSCs will help reduce psychological burden of "fear of cancer recurrence" in PCa survivors.

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**Volume 2 Issue 5 July 2018**