

# Prostate cancer stem cells

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## KEY WORDS

prostate cancer ▶ stem cell ▶ cancer stem cell

## ABSTRACT

The Cancer Stem Cells (CSCs) hypothesis postulates that a minute subpopulation of cells is accountable for cancer initiation and progression. Unlike the stochastic and clonal evolution models, the CSC theory proposes that tumours are hierarchical and only the rare subset of cells at the top of the 'stemness hierarchy tree' are adequately 'equipped' biologically to initiate and drive tumourigenesis. CSCs have been implicated in various solid malignancies including prostate cancer (PCa), where their existence seems to provide an explanation for the failure of tumour eradicating therapies. As CSCs are thought to share many properties with normal stem cells, understanding normal stem cells should shed light on the pathomechanisms of cancer and, importantly, on potential therapeutic interventions. The purpose of this paper is to review the existing data on CSCs in PCa, their putative phenotypic markers, potential role in tumour biology and relevance to therapy.

## INTRODUCTION

The hypothesis of Cancer Stem Cells (CSCs) dictates that a small subpopulation of undifferentiated, self-renewing cells found in most, if not all, cancers is responsible for tumour initiation and sustained growth [1, 2]. CSCs are thought to originate from the stem cell compartments of normal organs and to share many properties with normal stem cells. They are also believed to be accountable for the failure of eradicating therapies [1, 2]. Therefore, an understanding of their biology should have significant clinical benefits. In particular, in prostate cancer (PCa), identification of PCa stem cells (PCSCs) holds promise to combat castration-resistant (CR) PCa, a major clinical challenge of contemporary urology.

A series of excellent reviews discuss a potential role of CSCs in development of various human cancers [3-6]. Here, we provide a concise updated summary of existing literature on CSC biology, putative markers and clinical relevance of CSCs in solid cancers with an emphasis on PCa.

### Stem cells

Stem cells are integral components of normal mammalian physiology. They differ in origin, location, proliferative potential and the range of cell lineages they are able to produce. All stem cells, regardless of their source, have two cardinal attributes: 1) longevity (the ability of indefinite self-renewal) and 2) multipotency (a capacity to give rise to progenitors and differentiated

progenies) [7]. The 'level' of potency decides on the position of the cell in the 'stemness hierarchy', where the supremacy resides in the zygote, the ultimate totipotent stem cell.

Multipotency and self-renewal are dependent on a number of determinants including transcription factors such as Oct4, Sox2 and Nanog, Bmi-1 oncogene, as well as activation of telomerase and several signalling pathways, in particular, PI3K, Wnt, and Notch [8-14].

Adult (or tissue) stem cells are believed to exist in almost all post-embryonic tissues. They reside in a specialized microenvironment, a so-called niche. This provides a physical anchor and, through a combination of direct and indirect interactions between neighboring cells and extracellular matrix (ECM) components, enables a balance between quiescence and self-renewal that supports stem cell identity. Attachment of a stem cell to the niche ensures that daughter cells leave the niche and move into new microenvironments where, being exposed to different extrinsic signals, they lose 'stemness' and commit to cell lineages specific to the tissue in which they reside [15]. Under physiological conditions a stem cell pool is important for maintaining the integrity of the tissue. Stem cells are also a key element in normal tissue regeneration and repair.

### The normal prostate

The double-layered epithelium of the human adult prostate makes up glandular structures, which are comprised of three principal types of cells identified by their morphological appearance, location, and phenotypic profile. *Luminal cells* (*CK8<sup>+</sup>/CK18<sup>+</sup>/AR<sup>+</sup>/PSA<sup>+</sup>/PAP<sup>+</sup>*), the main component of the lining of the glands, are terminally differentiated and phenotypically express cytokeratins 8 and 18, androgen receptor (AR), prostate specific antigen (PSA), and prostatic acid phosphatase (PAP). Their maintenance and function are androgen-dependent. *Basal cells* (*CK5<sup>+</sup>/CK14<sup>+</sup>/p63<sup>+</sup>/CD44<sup>+</sup>/AR<sup>-</sup>*) comprise less than 10% of the total epithelium, are relatively undifferentiated, and phenotypically express cytokeratins 5 and 14, p63, and CD44, but neither PAP nor PAS [16]. Expression of AR is low or undetectable and the cells are androgen-responsive, but not dependent. *Neuroendocrine cells* (*AR<sup>-</sup>*), the least frequent type, are terminally differentiated. They contain serotonin, calcitonin, and somatostatin, do not express AR, and are not dependent on androgen for their survival [17].

Normal prostate development and cytodifferentiation are critically dependent on complex epithelial-mesenchymal interactions and hormonal stimuli. An inductive role of prostatic stroma in epithelial differentiation has been elegantly demonstrated by a series of *in vivo* recombinant studies [18-20].

### Stem cells in normal prostate

Evidence for the existence of a stem cell compartment in the normal mammalian prostate is based on experimental evidence in mice demonstrating that the adult murine prostate can undergo multiple rounds of castration-induced regression and androgen-induced regeneration [21]. As androgen ablation does not affect basal cells, it has been hypothesized that regenerative capacity,

that is the compartment containing cells with stem-like characteristics, must reside within the basal layer. This assumption is supported by a number of studies demonstrating not only that p63 (one of the markers of basal cells) is required for prostate organogenesis and development, but also that luminal secretory cells result from the differentiation of p63-expressing basal cells [22]. Location of the stem cell compartment close to the stroma fits the concept of a tissue-specific niche, which through its paracrine activity maintains identity of stem cells and their principal function of tissue regeneration. However, there are several reports of the existence of a subset of CR and hence androgen-independent cells with stem-like properties within the luminal compartment of the gland as well [21, 23]. Moreover, results of tissue recombination and grafting experiments by Kurita et al (2004) have shown that embryonic mesenchyme of urogenital sinus from p63<sup>-/-</sup> mice can regenerate prostate ductal epithelium which consists solely of cells with luminal phenotype [24]. This would suggest that precursors other than basal p63<sup>+</sup> cells do exist in the prostate and can give rise to luminal cells.

In the adult human prostate, a number of candidate phenotypic markers of stem cells have been proposed and several populations of putative stem cells reported. In particular, cells expressing surface molecules such as CD44 [16], integrin  $\alpha_2\beta_1$  and CD133 isolated from normal prostate epithelium have been shown to possess a capacity to differentiate into prostate-specific lineages and to have high proliferative and morphogenic potentials. This small population of presumed prostate stem/progenitor cells (CD44<sup>+</sup>/CD133<sup>+</sup>/ $\alpha_2\beta_1$ <sup>+</sup>) constitute approximately 1% of the basal layer, where they reside on the basement membrane, anchored by integrin  $\alpha_2\beta_1$  [25, 26]. They are morphologically intermediate between basal and luminal cells. Both localization and phenotype of these cells give support to their putative stem-like features and, therefore, to the developmental link and hierarchical relationship between the basal and luminal cells.

The most important characteristic of a true stem cell lies in its multipotency, i.e., an ability to recreate *in vivo*, from a single cell, a fully functional tissue, appropriate to its origin. Moreover, this property has to be maintained during successive transplantations. Despite an extensive worldwide search, the existence of stem cell pools in human peripheral organs remains yet to be conclusively proven due to significant technical difficulties and the limitations of available experimental models.

### Cancer stem cells

The concept that neoplasia is a disease of differentiation is not new. First connections between tissue development and tumour formation are associated with the work of the 19<sup>th</sup> century German pathologists Rudolph Virchow, Julius Cohnheim and Wilhelm Waldeyer. These advocates of the 'blocked ontogeny' theory postulated that tumour cells must come from normal embryonic cells 'left behind' in the adult organism and that carcinogenesis is closely linked to the arrest and/or distortion of a normal differentiation process [27]. It is claimed that tissue stem cells are the most likely targets of genetic instability as it is they alone whose life span is sufficiently long to acquire the necessary number of genetic changes required for malignant transformation [28]. A survival advantage for stem cells over differentiated cells, combined with clonal selection of cells maintaining stem-like properties and the ability to self-renew, converts normal cell renewal pathways into an engine of neoplastic proliferation. This concept seems to be true and applicable for teratocarcinomas, hematological malignancies and many types of carcinoma.

Due to the potential relevance of CSCs to cancer therapy, recent decades have witnessed an unprecedented revitaliza-

tion of the CSC hypothesis. An extensive search for CSCs, or more appropriately, tumour-initiating cells (TICs), has provided evidence to support the original hypothesis and to suggest that their biology is governed by molecular pathways known to be responsible for self-renewal of normal stem cells [29-35]. Thus considerable efforts are being made in the search for a fingerprint of 'stemness' common to normal stem cells and their malignant counterparts. Substantial data have been generated by gene and protein expression analyses resulting in a number of phenotypic markers reflecting a molecular definition of 'stemness'. Broadly, these include molecules involved in: i) maintaining pluripotency (e.g., transcription factors such as Oct 4, Sox2 and Nanog), ii) self-renewal (e.g., Bmi1), iii) cytoprotection (e.g., ABC transporters and ALDH, a detoxifying enzyme for alkylating agents such as cyclophosphamide) and iv) adhesion to the niche [8-10, 12, 36-38]. This list is not exhaustive and the panels of proposed markers vary between CSC systems.

### Prostate cancer

PCa is the commonest cancer in men and second commonest cause of cancer-related death. The incidence of PCa has gradually increased worldwide since the 1960's. In Western Europe over 100 000 men are diagnosed with PCa and 35 000 die annually [39]. Primary PC is predominantly of luminal phenotype and hence AR<sup>+</sup> and androgen-dependent (AD), so that eliminating or reducing endogenous androgens by surgical or chemical castration results in subjective and objective improvement in approximately 80% of patients. However, this benefit lasts only for a median period of ~2 years in men with metastatic bone disease after which there is relapse and death ensues within 6-12 months [40]. Neither the pathogenesis of PCa nor the mechanisms underlying disease progression are fully elucidated. There is therefore a need to further the understanding of the origins of PCa at a cellular level and to evaluate the potential contribution of stem cells.

### Prostate cancer stem cells

That PCa regrowth occurs even with castrate levels of testosterone points to the existence of a distinct stem-like population of CR cells with tumour-initiating capacity. Multiple cell types have been proposed as the true initiators of human PCa. As cells displaying basal phenotype are frequently found in metastases [41], it was proposed that to survive and expand in an androgen-deprived environment and not to express AR, PCa-initiating cells ought to be phenotypically identical to the normal prostate basal stem-like cell i.e., CK5<sup>+</sup>/CK14<sup>+</sup>/AR<sup>-</sup>/p63<sup>+</sup>/ $\alpha_2\beta_1$ <sup>hi</sup>/CD133<sup>+</sup>/CD44<sup>+</sup> [25, 26, 41]. Several lines of evidence support this hypothesis. For example, as demonstrated by clonogenic assays, only cells expressing putative PCSC markers had self-renewal potential *in vitro* [42]. Furthermore, under stimuli inducing cell differentiation *in vitro*, these supposedly primitive cells gave rise to progenies phenotypically consistent with human differentiated prostatic luminal cells (CK18<sup>+</sup>/AR<sup>+</sup>/PAP<sup>+</sup>) [42]. Subsequent study by Patrawala and co-workers (2006) showed that a population of highly purified CD44<sup>+</sup> cells from xenograft human PCas were enriched in tumorigenic and metastatic progenitors. Indeed, CD44<sup>+</sup> PCa cells have been shown to have increased tumorigenic potential *in vivo* as compared to their CD44<sup>-</sup> counterparts [43]. Gu and co-workers (2007) reported that clonally-derived PCa cells transfected with human telomerase reverse transcriptase (hTERT) were able to reconstitute the original tumour *in vivo* [44]. Consistent with the stem cell characteristics, hTERT<sup>+</sup> PCa cells expressed both early progenitors (CD44 and Nestin) and embryonic stem cell markers (Oct4, Sox2 and Nanog) and were AR<sup>-</sup> and p63<sup>-</sup>. More recently, Birnie et al, using gene expression profiling, demonstrated that the fusion gene *TMPRSS2-ERG*, frequently found in CR

aggressive PCa and associated with PSA failure, was expressed in  $\alpha_2\beta_1^{\text{hi}}/\text{CD133}^+$  prostate epithelial cells [45].

Although substantial evidence supports the basal stem-like cell as the main 'PCa-initiator', several studies in rodents have shown that PCa may also originate from the luminal cell layer of the prostatic epithelium. For example, Wang and co-workers (2009) identified in murine prostate a rare luminal cell subset of CR NKx3.1-expressing cells (CARNs) that display stem cell properties. Targeted deletion of the *Pten* suppressor gene in these cells led to development of PCa, closely mimicking disease progression in man [46]. Although the existence of multiple stem cells could be species-specific reflecting distinctive anatomy of the multilobular murine gland, it is likely that, the luminal cell layer in the human prostate also houses a distinct non-overlapping stem cell population, oncogenic transformation of which may give rise to the development of CR disease [47]. Demonstration that luminal epithelial stem-like cells might be efficient targets of tumour-initiating activating mutations would be in agreement with a commonly accepted model of PCa development into a tumour of a predominantly luminal phenotype (CK8+CK18+/ AR+/PSA+/PAP+) [48]. However, even if several populations of cells capable of cancer initiation exist in the prostate, the 'stemness lineage hierarchy' seen in the normal gland appears also to be maintained in PCa and the basal stem-like cells are by far the most efficient targets of oncogenic stimuli resulting in neoplastic transformation. Recent functional studies provide support to this hypothesis demonstrating that activation of oncogenic pathways in human prostate basal cells leads to recapitulation of tumour initiation and progression in immunodeficient mice that histologically closely mimics human PCa, with expansion of luminal and concomitant loss of basal cells [49, 50].

It is widely accepted that the development of carcinoma is due to accumulation of somatic mutations in epithelial cells supported by the permissive tumour microenvironment. In prostate, recent studies have revealed that ECM, fibroblasts, blood vasculature and inflammatory cells have significant impact on transition from pre-invasive to invasive growth of PCa and should be regarded as crucial and active participants in tumourigenesis. Tumour stroma is recognized as a source of paracrine growth factors such as frizzled-related protein 1 (SFRP1), TGF $\beta$ 1, and stromal cell-derived factor 1 (SDF-1/CXCL12) that maintain and potentiate survival and growth of the tumour [51-54]. Signalling via the SDF-1-chemokine receptor type 4 (CXCR4) axis leading to activation of anti-apoptotic pathways and stimulation of cell motility and invasion is known to regulate the metastatic behaviour of tumour cells [55]. Interestingly, the receptor for SDF-1 (SDFR-1, or neuropilin) is expressed by putative human PCSCs and activation of downstream targets such as JAK-STAT and NF $\kappa$ B pathways has been associated with the PCSC phenotype [45]. It appears only logical that the stroma of the tumour provides a specialized niche and influences the fate and behavior of PCSCs but the nature of the relationship and its biological consequence are poorly understood. That expression of focal adhesion and ECM-integrin signaling pathways are up-regulated in CSCs from human PCa as compared to the normal counterparts (both  $\alpha_2\beta_1^{\text{hi}}/\text{CD133}^+$ ), seems however to confirm these powerful reciprocal interactions [45].

Nothing is known, though, about the sequence of PCa-initiating events. Results of existing studies lead to several questions, which include distinguishing between cause and effect for the CSC and its niche. Is 'stemness' an inherent property of distinct types of cells, or acquired during a dynamic process induced and controlled by environmental cues? Can CSCs become niche-independent?

Answers to these questions are of paramount relevance for the development of potential therapeutic strategies.

### Therapeutic implications

Since the work of Huggins and Hodges [56], androgen deprivation therapy (ADT) is the mainstay of management for progressive advanced PCa. Depriving PCa cells of hormonal stimuli can result in eradication of most cancer cells and so regression of androgen dependent (AD) tumours but in most cases the disease relapses and progresses to CR PCa. The molecular mechanisms underlying alterations of cell sensitivity to androgens are not well understood and several possibilities that may be responsible for evolution to the CR state have been proposed [57, 58]. Evidence from xenograft models and clinical material indicates that the switch to CR growth could result from either adaptive responses to ADT and evolution of CR clones [59] or the selection/outgrowth of pre-existing (pre-treatment) CR and AR-independent cells. The observation that ADT can destroy secretory luminal epithelial cells while those with basal cell-like characteristics preferentially survive suggests that intrinsically resistant cells do exist in the gland and is consistent with the concept of PCSCs.

The existence of AR<sup>-</sup> poorly differentiated clones, equipped with active mechanisms to evade irradiation or cytotoxic therapies, would offer an explanation for disease recurrence and development of the CR state. Furthermore, if PCSCs did form a dormant reservoir for tumour regrowth, ADT would have an adverse effect on disease progression and, by activating normally quiescent AR<sup>-</sup> PCSCs to repopulate the tumour, could promote CR evolution [54]. Thus, targeting of PCSCs could provide lasting, curative effects. Unfortunately, if the numbers of true PCSCs is as low as implied by the CSC hypothesis, selective eradication of these cells would be extremely difficult, if possible. Identification and inhibition of self-renewal signalling pathways such as PI3K, Wnt, and Notch [29-33, 60, 61] seem to offer an alternative and more feasible approach.

### Conclusions and perspectives

While the CSC hypothesis has exciting clinical implications, there are still many unresolved issues. The most important concern is raised by identification of these unique cells, their genetic and phenotypic fingerprint, pathways and networks that control their biology, hormone sensitivity and responsiveness to paracrine environmental stimuli. The achievement of this task is hampered by a lack of suitable models. To date the gold standard to confirm CSC phenotype is serial transplantation into an animal model, where the cell recapitulates histologic heterogeneity of the original tumour. However, as human tumour cells implanted heterotopically into a normal animal niche are undoubtedly subjected to selective pressure due to incomplete immunosuppression and species- and site- specific composition of the stroma and hence its paracrine activity, this model does not precisely mimic the original human disease. Thus extrapolation from the key experimental set-up to verify CSC functional characteristics has to be treated with caution, leaving the true identity of the cell yet to be determined.

The existence of CSCs in most tumours raises little doubt about their role. The current challenge is to unravel distinguishing molecular profiles for the CSC and determine the molecular pathways of their self-renewal activity in order to target them specifically for therapeutic purposes. As there are remarkable parallels between normal stem cells and cancer stem cells, advancing knowledge of stem cell biology will have significant implications for the attempts to defeat cancer or, at least, to tame its aggressive behaviour.

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