REVIEW

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The prostatic cellular and molecular kaleidoscope. Starting points for carcinogenesis

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Abstract

The prostate cancer is a heterogeneous disorder concealing different phenotypical and functional subtypes of cancer cells. This heterogeneity mirrors the normal prostate cell lineages whose alterations represent the starting points of the carcinogenesis mechanism. The histological structure of the prostate comprises two main types of cells: epithelial and stromal, with a stromal to epithelial ratio of 2:1. The prostate acini are lined by a contiguous layer composed of four different subtypes of epithelial cells: secretory luminal, basal, neuroendocrine, and transit-amplifying. The epithelial component is enclosed in a stromal tissue, consisting of several types of cells: smooth muscle cells (the most numerous cell type), fibroblasts, and myofibroblasts. Despite their quite similar morphological appearance in light microscopy, the molecular markers expressed by the normal epithelial and stromal prostatic components, as well as the stem cells show that the prostatic cells are not equal. Numerous efforts have been made to identify the profile of prostate stem cells, and their role in cellular turnover and morphogenesis of the prostatic tissue, by using experimental and/or human studies. Consequently, several hypotheses regarding the location and the phenotype of these cells were formulated and tested, mainly in animal models. The molecular mapping of normal human prostate tissue might be the key for unlocking the intricate mechanisms of prostate carcinogenesis. Within this context, the prostatic cancer stem cells are thought to play an important role in tumor initiation, progression, recurrence and also therapy resistance. The cancerous phenotype of a stem cell can be reached via multiple genetic trajectories and epigenetic alterations, resulting in different subclonal populations of cancer stem cells, thus explaining the heterogeneity of the prostatic neoplasia. Future efforts should be directed towards better understanding of the relationship and interactions between these cancer stem cells subpopulations, their microenvironments, and also towards characterizing the signaling pathways and molecules involved in the regulation of prostatic cancer stem cells. The results of these studies could offer a different, more comprehensible perspective for a new, molecular classification of prostate cancer, overlapping the existing histological one.

Keywords: prostate, histology, luminal cell, basal cell, stem cell, cancer stem cell.

Introduction

Benign prostate hyperplasia (BPH) and prostate cancer (PCa) are the most common prostatic disorders affecting a significant percentage of men during their lifetime, with major health and financial repercussions [1, 2].

PCa is a heterogeneous condition concealing different phenotypically and functionally subtypes of tumor cells [3]. Thus, for better understanding of its heterogeneity, one must dissect the biology of normal prostate cell lineages aiming to unveil the cell(s) of origin for PCa.

This review gives the reader an analysis of the histological and molecular features of normal prostate cells and their possible involvement in the carcinogenesis mechanism. The paper is structured in three main sections. The first summarizes the embryological and anatomical hallmarks that define the prostate, the second is centered on the molecular markers expressed by the normal epithelial and stromal cells as well as by the stem cells (SCs), and the third highlights the putative role of the cancer stem cells (CSCs) in the development of prostatic neoplasia.

Embryological and anatomical synopsis

The prostate is formed from a condensation of the mesenchymal tissue of the urogenital sinus, in the adjacent area of the pelvic urethra, in the early stages of the embryonic development [4–6]. Beginning with the 9th intrauterine (i.u.) week, by the marked densification of the mesenchyme in the posterior urethral segment, towards the rectum, and distally to its middle segment, the future prostate structure is shaped in the specific anatomic territory of the adult [5, 7]. The ejaculatory ducts make a way into this territory and head towards the future *verum montanum*, placed in the middle segment of the urethra.

Between the 10th and the 16th week of fetal development, under the influence of fetal testosterone on specific androgen receptors (ARs), five pairs of primordial prostatic buds (considered prostatic ductal progenitors) appear from the urogenital sinus epithelium and extend into the mesenchyme of the urogenital sinus, following a rearward direction with respect to the urethra [7]. The whole process involves signaling between the mesenchymal and epithelial components, demonstrated since the 70's [8].

Recent experimental evidence confirms the important role of the Wnt gene family in the embryonic development of the prostate [9]. The Wnt5a protein, identified in the periductal stroma and the distal ducts epithelium, is highly expressed in all prostatic lobes during morphogenesis [9]. Postnatal, however, the Wnt5a expression dramatically decreases in the ventral lobes, while persisting in the dorsal and lateral lobe at maturity [9]. Wnt5a expression is regulated by the intervention of steroid hormones: testosterone with inhibitory effect, and neonatal estrogens with stimulating effect [9].

The development of prostatic buds consists of three successive phases [10]: (*i*) the conditioning phase, controlled by embryological determined signals through, which the site of formation is established, in the area of the urogenital sinus; (*ii*) the initiation phase, corresponding to the early formation of the prostatic buds; (*iii*) the elongation phase, characterized by proliferation, adhesion and cell migration, responsible for the growth of the prostatic buds in the adjacent mesenchyme.

The upper pairs of prostatic buds have mesodermal origin and will form the transition and periurethral zones of the prostate, while the lower pairs have endodermic origin and will form the peripheral areas of the prostate [4, 5]. The prostate's central area originates from the inclusions of Wolf mesonephric ducts in the mesenchymal area surrounding the ejaculatory ducts and occupying the entire base of the prostate in development [6].

The presence of the stroma is absolutely necessary because it provides, through a controlled number of cell divisions, the size of the neonatal prostate (less than 1 cm in diameter), after which the stimulation of the proliferation of the branched duct system is stopped [4, 5].

Anatomically and clinically, the prostate has four zones [6]. The central zone, located around the ejaculatory ducts, includes approximately 25% of the glandular component. The peripheral zone, located concentrically around the central area, occupying the posterior and lateral areas of the prostate, contains approximately 70% of the prostatic glands. The transition area, located around the prostatic urethra in the lateral lobes, comprises approximately 5% of the glandular tissue. The periurethral area, located adjacent to the prostatic urethra in the middle lobe, accounts for less than 1% of the prostatic acini. Additionally, the antero-median area of the prostate, located ventrally in relation to the prostate urethra and responsible for the anterior convexity of the gland, consists exclusively of fibromuscular stroma, that represents the non-glandular component.

Histological and molecular traits in normal prostate tissue. Are all cells equal in the prostate?

Histologically, the prostate gland is formed of multiple epithelial acini arranged in a fibro-muscular stroma. The human prostate contains two main types of cells: epithelial and stromal cells, with a stromal to epithelial ratio of 2:1 [11]. Despite their quite similar morphological appearance in light microscopy, the molecular markers expressed by the normal epithelial and stromal prostatic components, as well as the SCs show that the prostatic cells are not equal.

The epithelial component

The epithelial component is organized into a contiguous layer composed of four different subtypes of cells, as follows: secretory luminal (accounting for 60%), basal, neuroendocrine (NE), and transit-amplifying (TA) (constituting the rest 40% of total epithelia) [5, 6].

The major cell type of the normal prostate, defining the acini, is represented by the luminal cells.

The luminal cells are columnar and present a clear cytoplasm that reveals their secretory capacity [5, 6]. Regardless the prostate zones, this aspect is due to the presence of numerous small, uniform vacuoles, optical apparently empty. The highest vacuoles density is noted in the peripheral and transition zones, with a distinct clear trait, whereas in the central zone these cells have a light basophilic cytoplasm because of a lower number of vacuoles, more widely spaced [12]. The electron microscopy shows microvilli, Golgi complex, and secretory granules with lipid or non-lipid content that form the vacuoles [5, 6].

The luminal cells represent the exocrine component of the epithelium, secreting prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP) into the lumen. In addition, the luminal cells express other molecular markers, such as cytokeratins CK8 and CK18, CD57 (glycoprotein with cell adhesion function), p27Kip1 (a cell cycle inhibitor) and high levels of androgen receptors [13, 14].

The basal layer is formed of flattened cells, with little cytoplasm and hyperchromatic nuclei, arranged above the acinar basal membrane. The absence of the contractile filaments marks the difference from the basal cells present in the mammary gland [5, 15]. The basal cells express multiple molecular markers: p63 (member of p53 suppressor gene family), cytokeratins CK5 and CK4, Bcl-2 (an anti-apoptotic factor), CD44 (a cell adhesion molecule) and hepatocyte growth factor (HGF) [13, 16]. In comparison to the luminal cells, they have a low to undetectable expression of AR, that makes their survival independent of androgen levels [17].

In the basal and luminal layers reside rare NE cells, solitary or in small clusters [5, 18–20]. The electron microscopy shows that these cells never reach the acinus lumen, but the open type presents thinly distributed apical processes directed towards the lumen, whereas the closed type do not present any apical extensions; they all have dendrite-like processes expanding below, to the basement membrane and between the closest basal or luminal cells [21]; the cytoplasmic secretory granules have different ultrastructural features that sustain their heterogeneity [22]. The identification of NE cells was based on histochemical or immunohistochemical techniques that reveal their neuroendocrine secretion. The main neuroendocrine markers are chromogranin A (a neuron-specific enolase) and synaptophysin [20], but the cells can also produce other different neuropeptides [*i.e.*, serotonin, bombesin, calcitonin, somatostatin, neurotensin, thyroid-stimulating hormone (TSH)-like peptide] [18]. They too, like the basal cells, are insensitive to androgen [20]. The role of these cells is still unclear; most probably, their secretion products support the epithelial cell growth and differentiation by a paracrine mechanism initiated in response to neuronal stimuli [20].

In between the basal and the luminal cells resides a small group of TA cells, without morphological distinct features, but with dual expression of both basal and luminal cell markers, namely CK5, CK8, CK14, CK18, AR, and PSA [23].

The stromal component

The stromal component that encloses the epithelial acini consists of several types of cells: smooth muscle cells (the most numerous cell type), fibroblasts, and myofibroblasts.

Differences between the phenotype of the cells in the subepithelial stromal space are reported: most of these cells express vimentin, and the smooth muscle cells at this level were desmin+/alpha-smooth muscle actin (α-SMA)+/ caveolin-1+, but the deeper-lying interstitial cells predominantly express CD34 and vimentin [24]; the mast cells present here are c-kit+/tryptase+ [24].

The stem cells component

The cellular hierarchy of the prostatic epithelium is maintained by a small population of undifferentiated, SCs, capable of self-renewal and differentiation [25].

Numerous efforts have been made to identify the profile of prostate SCs, and their role in cellular turnover and morphogenesis of the prostatic tissue, by using experimental and/or human studies. One of the first proofs of the existence of prostatic SCs was experimentally supported by the multiple regeneration cycles of the normal prostate tissue in response to androgen deprivation/ restoration [26, 27].

Consequently, several hypotheses regarding the location and the phenotype of these cells were formulated and tested, mainly in animal models [25, 27–31].

Some works based on murine models show that in between the basal epithelial cells reside SCs responsible for the maintenance and renewal of both luminal and basal cell population. This renewal is possible by the slow turnover of either distinct lineage-restricted cells (CK5+ basal / CK8+/CK18+ luminal cells) [28] or bipotent progenitor cells organized in small group [25].

A study on mice prostate using *in situ* lineage tracing demonstrates that the regeneration of the prostate epithelium is based upon pluripotent basal SCs located at the junction between proximal ducts and the urethra [29]. Undergoing continuous renewal, these basal SCs eventually generate bipotent basal progenitor cells, which migrate along the ductal network, giving rise to luminal cells that restores the luminal population lost *via* constant apoptosis. A second small luminal unipotent SCs group is responsible for the renewal of the most proximal luminal cells, ensuring little support to the duct formation [29].

The molecular profile of basal cells leads to the identification of several subpopulations, only some of them having SCs potential.

A paper that reports seven basal cell subpopulations indicates the subpopulation defined by the p63+/CK5−/ CK14− expression as the most appropriate multipotent SCs, able to efficiently differentiate into all prostatic cells [30]. On the other hand, two distinct subpopulations of the basal prostatic cells were defined based on their tumor-associated calcium signal transducer 2 (Trop2) expression, only the one that express high levels of Trop2 having SC characteristics – not only in murine but also in human prostate [31].

Many potential surface markers for these prostatic SCs were considered in murine experimental research, such as p63, CD44, aldehyde dehydrogenase (ALDH) [13]. Moreover, stem cell antigen 1 (Sca-1/Ly6a) [32], with co-expression of integrin α6 (CD49f) and Bcl-2, or 5-bromo-2'-deoxyuridine (BrdU) labeling [33] were observed in cells from the proximal region of the prostatic duct. Prostatic cells with high proliferation potential and differentiation features were isolated by Lawson *et al.* [34], and characterized by CD45−/CD31−/Ter119−/Sca-1+/ CD49f+ immunohistochemical profile. Another potential prostatic SC marker, CD117 (also known as stem cell factor receptor), was expressed by a small population of prostatic cells in the proximal region of the mouse prostate, that originated normal, functional, secreting prostate tissue after multiple isolations and *in vivo* transplantation procedures [35].

The identification and characterization of SCs in human prostatic tissue are more difficult than in animal models. Therefore, the research regarding the leading prostatic stem niche is far to be completed [26, 36]. Unlike the mouse prostatic SCs, the human prostatic SCs are distributed in different compartments within the basal epithelial layer, throughout the acini and ductal regions of the prostate, and express CD133 (promonin-1) and $\alpha 2\beta 1$-integrins as specific markers [37–39]. Integrin receptors have been hypothesized to play a fundamental role in the maintenance and activity of SCs [38, 39]. Solid evidences show that SCs expressing these two markers are able to regenerate and differentiate into two distinct types of prostatic cells, namely neuroendocrine and TA cells [37, 40, 41]. By division and maturation, TA cells becomes intermediate cells that finish their differentiation as mature luminal cells characterized by specific markers [37, 41–43].

Among prostate epithelial SC, the presence of stromal SCs is also reported, performing the function of replacing and renewing the stromal cell population that suffers due to normal tissue turnover, trauma, or aging [36]. These cells, able to differentiate into several cell lineages (fibroblasts, smooth muscle cells, adipocytes), express vimentin, CD117, stem cell factor (SCF), CD34 and Sca-1, and present a remarkable proliferative activity [36].

A crosstalk between the epithelial SCs and the stromal SCs, *via* Sonic hedgehog (Shh) signaling, sustains their symbiotic behavior [44]. The crosstalk molecules include members of transforming growth factor beta (TGFβ) superfamily, the insulin-like growth factors, the fibroblast growth factors, the platelet-derived growth factor, which eventually trigger differentiation into one specific stromal cell lineage [44].

Prostatic cancer stem cells – theories and phenotype

Prostatic CSCs are characterized as tumor cells with the ability to self-renew and to differentiate themselves in all types of cells in prostate tumors [45–47]. CSCs are thought to play an important role in tumor initiation, progression, recurrence and also therapy resistance. The mechanism of prostatic cancer development is not fully understood, and in the present is studied *via* two main models: the clonal (stochastic) evolution model, which postulates that all cancer cells are tumorigenic and the CSCs origin model, which considers that only a small population of SCs are responsible for cancer development. Due to the heterogeneity of the prostate cancer, these two models should not be considered as conflicting [48].

The first evidence of CSCs was documented in acute myeloid leukemia [49]. The leukemic progenitor cells, isolated and selected using immunophenotyping of

hematopoietic SCs (CD34+/CD38−), confirmed to have a dual ability: to reproduce the leukemic blastic cellular hierarchy and to exhibit considerable self-renewal capabilities [50].

Defining the cells-of-origin for prostate cancer, on the other hand, has proven to be quite a laborious process. However, the expected results might contribute to deciphering the complex process of carcinogenesis.

Considering the luminal-like appearance and phenotypical features of many prostatic neoplasms, the luminal cell was thought to be the cell-of-origin for human PCa, being well known the fact that the predominant tumoral immunoprofile is AR+ and CK8+ [51].

According to some studies using tissue regeneration-based assays, the cell-of-origin for PCa can only be of basal type [52], whereas more recent studies involving genetic mouse models claim that both basal and luminal cells can account for the origins of PCa, mentioning the fact that the luminal cells are more prone to tumorigenesis [51].

There are still major inconsistencies regarding the origin of CSCs in human prostate, but several explanations can be taken into consideration [48, 53]. The obvious and most pertinent explanation is that both luminal and basal prostatic cells can act as neoplastic cells of origin, influenced by different modifications of the micro-environment. Such alterations include inflammation or other aggressive factors and can induce measurable enhancement of basal-to-luminal differentiation *in vivo* [44, 54]. A better understanding of the functional role and different phenotypical profile of the two basal and luminal cells might reside in gene expression studies [53].

The most studied markers for prostate CSCs are CD24, CD44, CD133, CD166 and $\alpha 2\beta 1$-integrins. However, a full marker panel is not yet established, due to the diversity of prostatic histotypes [55–57].

The first mention of an abnormal prostatic SCs population is attributed to Isaacs & Coffey [58], but it was Collins *et al.* [38] who identified basal SCs (CK5+/CK14+/p63+/AR–), overlapping with the expression of $\alpha 2\beta 1$-integrin in CD44+/CD133+ prostate cells, by using radical prostatectomy specimens. These results strengthen the CSCs theory of prostatic neoplasia. However, recent experimental studies in mice using BM18 human PCa xenograft demonstrated the expression of SCs markers, as well as luminal markers, such as NKX3-1, CK18 and AR in a population of castration-resistant prostatic tumor cells (CARNs), supporting the CSCs origin of prostatic cancer [59]. These cells were able, after castration and androgen replacement, to generate prostatic tumors, emphasizing that stem-like cells with luminal phenotype are probably the cells of origin for therapy resistant prostate cancer.

Subsequently, other works [60, 61] suggest that prostatic CSCs seem to be androgen-resistant, due to the dysregulation of AR signaling, thus cancer relapse and recurrence may be due to the surviving of the poorly differentiated prostatic CSCs, despite the death of differentiated prostatic tumor cells (primary the bulk of the neoplastic cell population).

An appropriate microenvironment that supports prostatic CSCs, even after a radical prostatectomy, can be the explanation for tumor relapse [62]. Several studies [62, 63] have shown that cancer cell subpopulations can crosstalk with other normal cells in their habitat, using them for their own benefit, perhaps for the maintenance of stem-like features which gives them AR resistance. A recent study [63] supported that SPARC protein (a glycoprotein, responsible for the extracellular matrix repairing) has a critical role in mediating the cooperation between CSCs and non-CSCs, describing that the aggressiveness and metastatic potential of CSCs subpopulation can be enhanced by the presence of non-CSCs. Also, different cells, such as bone-marrow derived mesenchymal SCs, could be recruited from the tumor microenvironment and can interact and boost prostate cancer progression [64].

The cancerous phenotype of a SC can be reached *via* multiple genetic trajectories and epigenetic alterations, resulting in different subclonal populations of CSCs, thus explaining the heterogeneity of the prostatic neoplasia. Future efforts should be directed towards better understanding of the relationship and interactions between these CSCs-subpopulations, their microenvironments, and also towards characterizing the signaling pathways and molecules involved in the regulation of prostatic CSCs.

Final remarks

The prostate cancer is a heterogeneous disorder concealing different phenotypical and functional subtypes of cancer cells. This heterogeneity mirrors the normal prostate cell lineages whose alterations represent the starting points of the carcinogenesis mechanism. The molecular mapping of normal human prostate tissue might be the key for unlocking the intricate mechanisms of prostate carcinogenesis. Therefore, further studies could offer a different, more comprehensible perspective for a new molecular classification of prostate cancer, overlapping the existing histological one.

Conflict of interests

The authors declare that they have no conflict of interests.

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