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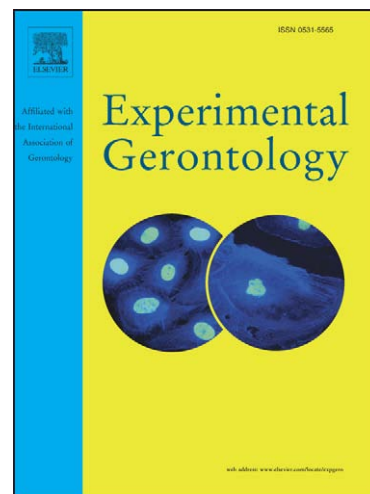
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Mini Review

## **Aging of the prostate epithelial stem/progenitor cell**

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### **Keywords**

Prostate; epithelial stem cells; aging; prostate cancer; tissue regeneration.

**Abstract**

Maintenance of the prostatic epithelial cell compartment is ensured by proliferation of adult epithelial progenitor or stem cells. These cells are characterized by an undifferentiated state, high proliferative capacity and long life span. Prostate progenitor/stem cells are localized in their stem cell-niche in the basal cell compartment in close contact to the basement membrane and the stromal cell compartment and are characterized by expression of the basal cytokeratins 5 and 14, high levels of integrins, CD44, the stem cell markers CD133 and ABCG2, and AR negativity. They give rise to secretory luminal (cytokeratins 8/18, CD57, AR, p27, PSA, PAP) and neuroendocrine cells (cytokeratins 8/18, CD57, CgA, NSE, NEPs), the two major cell types observed in the glandular epithelium.

A growing body of experimental evidence has identified the amplifying progenitor/stem cell (CD44<sup>+</sup>,  $\alpha_2\beta_1^{\text{hi}}$ , CD133<sup>+</sup>), as a putative origin of prostate cancer. Differentiation of this cell type can be affected by mutations in the intrinsic genetic program, by age-related changes in stromal-epithelial interactions or in the basement membrane /ECM composition. All these stochastic events occur during aging and can transform a normal prostate progenitor/stem cell into a cancer stem cells, a source of androgen-dependent and independent tumor cell clones. Thus, the heterogeneous and multifocal nature of prostatic cancer with a pleora of different tumor cell clones clearly reflects the differentiation capacity of the prostatic epithelial progenitor cells.

**Characterization of prostate epithelial stem/progenitor cells**

Stem and progenitor cells act as a regeneration system replenishing specialized cells, and also enabling the normal turnover and functional regeneration of organs in the adult organism. Stem /progenitor cells are defined by their ability to self-renew and their capacity to differentiate into specialized cell types. Toti- and pluripotent stem cells can give rise to any mature cell type, whereas multipotent stem/progenitor cells can differentiate into cells of a closely related cell family, e.g. epithelial cells. Stem/progenitor cells responsible for tissue homeostasis of various epithelial tissues with diverse architectural design and physiology like intestine, epidermis, mammary gland or cornea have been described and characterized (Blanpain et al., 2007).

The human prostate, an androgen-dependent walnut-sized sex accessory gland surrounding the urethra at the base of the bladder, serves a crucial function in the male reproductive tract by producing approximately 30% of seminal fluid providing nutrients and optimal ionic milieu and pH for sperm.

Prostate epithelial stem/progenitor cells (PESCs) have long been hypothesized to be present in the basal cell layer of the stratified prostate epithelium (Isaacs and Coffey, 1989), although only in recent years several markers for their characterization and localization have been investigated. In the murine prostate the actively proliferating cells were found to be located in the distal region of the prostatic ducts, whereas in the proximal ductal region cells with stem cell features (quiescent, high proliferation potential) were concentrated (Tsuji-mura et al., 2002). These cells were further characterized by high expression of the cell surface protein stem cell antigen 1 (Sca-1), coexpression of  $\alpha 6$  integrin and the antiapoptotic factor Bcl-2, and showed a higher efficiency to generate prostatic tissue in in vivo reconstitution assays when compared with Sca-1<sup>-</sup> cells or Sca-1 expressing cells from remaining regions of the duct (Burger et al., 2005). Bcl-2 is supposed to protect the PESCs from the apoptotic

effects of high levels of active TGF- $\beta$  produced by cells in the proximal niche to maintain the P ESCs in a dormant state (Salm et al., 2005).

High levels of  $\alpha 6$  integrin has also been demonstrated for other stem/progenitor cells like basal keratinocytes in the epidermis and spermatogonial stem cells in the testis (Jones and Wagers, 2008). Expression of adhesion molecules like cadherins or integrins is important to maintain stem/progenitor cells in their niche in close proximity to supporting stromal cells, the basal lamina, extra-cellular matrix proteins and self-renewal signals (Jones and Wagers, 2008). Cadherins establish adherens junctions with the neighboring cells, while integrins are receptors for components of the extra-cellular matrix and major components of the basal lamina (laminin, collagen, fibronectin) and attach the cells to the latter.

Based on high expression of  $\alpha 2\beta 1$  integrin Collins and colleagues identified P ESCs in the basal layer of the human prostate. After immunomagnetic separation of the basal cells via their expression of the hyaluronan-binding surface glycoprotein CD44 clonogenic cells were enriched by rapid attachment to extra-cellular matrix proteins (Collins et al., 2001).

The CD133 (prominin-1) antigen was originally classified as a marker of primitive haematopoietic and neural stem cells monoclonal antibodies against this antigen were successfully used to enrich for haematopoietic stem cells, endothelial cells, neurons and glial cells. Similar to other tissues, in the human prostate a small number of cells (approximately 0.75% of the cells in the basal layer) express CD133 (Richardson et al., 2004). The clonogenic cells of the rapidly adhering  $\alpha 2\beta 1^{hi}$  cell population could be further enriched by CD133 selection cells and the proportion of CD133<sup>+</sup> cells within the  $\alpha 2\beta 1^{hi}$  cell population was approximately 1 in 4.

Expression of the ATP-binding cassette transporter family membrane efflux pump ABCG2 (Breast cancer resistance protein 1, BCRP1) is a conserved feature of stem

cells from a wide variety of sources (Zhou et al., 2001). ABCG2 was first identified in the MCF-7 breast cancer cell line and is associated with multi-drug resistance. The ATP-binding cassette transporter family proteins are responsible for the active efflux of the vital dye Hoechst 33342 resulting in a Hoechst low cell subpopulation termed side population (SP). Cells of the SP phenotype have been identified in a variety of tissues among them prostatic epithelium, where this population constitutes 1.38% of the cells (Bhatt et al., 2003). ABCG2-mediated efflux of androgen has been proposed to contribute to the maintenance of the PESC phenotype, which among other features is characterized by lack of androgen receptor (AR) protein (Huss et al., 2005).

#### **PESC function: tissue homeostasis**

The main function of the P ESCs is to preserve tissue homeostasis of the gland by giving rise to differentiated specialized progeny as there are secretory and neuroendocrine cells. The prostate is an androgen-dependent organ, that reduces its size dramatically upon androgen deprivation. This is mainly caused by apoptosis of luminal cells, while basal epithelial cells stay intact. Early experiments in rodents demonstrated, that administration of androgens renewed the prostate epithelium in castrated rats. The fact that basal cells remained intact upon androgen deprivation and gave rise to fully functional luminal cells after re-administration led to the stem cell theory of prostate growth proposing androgen independent stem/progenitor cells (Isaacs and Coffey, 1989).

Epithelial cell differentiation is a complex process governed by the expression of intrinsic genes that mediate differentiation and growth processes. Mesenchymal-epithelial interactions have an instructive role during the androgen-induced development of the prostate. Freshly isolated mouse prostate epithelial cells can

regenerate fully differentiated prostate tissue when combined with embryonic urogenital sinus mesenchyme and grafted in vivo (Cunha and Lung, 1978) but not when transplanted without supporting stromal cells. Stromal-epithelial interactions play also a key role in the maintenance of the adult prostatic epithelium (Sampson et al., 2007; Untergasser et al., 2005). The local extracellular matrix, stromal growth factors and androgens are essential for functional and morphological differentiation of the prostatic epithelium (Hayward et al., 1992).

Normal prostate epithelium is composed of at least five cell types (PESC, basal cells, transit amplifying cells, luminal secretory cells, neuroendocrine cells) which are supposed to be derived from PESC that are scattered among the basal cell compartment. There they undergo mitosis and give rise to basal cells, which are characterized by the basal cell markers cytokeratin 5 and 14 and CD44, androgen independence, a high proliferative capacity and a low apoptotic index (Schalken and van Leenders, 2003). The progeny of the basal compartment are intermediate transit amplifying cells that in turn give rise to heterogeneous subpopulations of intermediate cells that subsequently differentiate to luminal secretory and neuroendocrine cells (Hudson et al., 2001). The intermediate cell population is characterized by the expression of cytokeratin 19 (Hudson et al., 2001) and prostate stem cell antigen (Tran et al., 2002). Moreover, they still retain basal cytokeratins 5/14 and acquire luminal cytokeratins 8/18. Depending whether they differentiate into secretory or neuroendocrine cell lineages they express androgen receptors (AR) (Bonkhoff and Remberger, 1993) or Chromogranin A (CgA), neuron specific enolase (NSE) and human chorionic gonadotropin alpha (hCG $\alpha$ ) (Berger et al., 2007; Bonkhoff et al., 1994; Rumpold et al., 2002).

Under the influence of androgens intermediate cells differentiate into luminal secretory cells and express luminal cytokeratins 8/18, CD-57 (HNK-1 carbohydrate



epitope of cell adhesion molecules), AR, the cycline-dependent kinase inhibitor p27 (Waltregny et al., 2001), prostate specific antigen (PSA) and prostatic acidic phosphatase (PAP). Independent of the action of androgens subpopulations of intermediate cells differentiate into terminally growth arrested neuroendocrine cells, expressing a variety of neuroendocrine peptides (NEPs) (Di Sant'agnese, 1991). Prostate epithelial cell differentiation is schematically depicted in Figure 1.

### **The aged PESC and prostate cancer development**

Prostate cancer (PCa) is the most common diagnosed male malignancy in Western societies and the second most common cause of male cancer-related death with an estimated incidence of 232 090 new cases and 30 350 deaths in the United States in 2005 (Jemal et al., 2005). PCa is a multifocal, nonclonal and heterogeneous tumor mainly localized in the peripheral zone (over 70%) of the prostate (Abate-Shen and Shen, 2000).

Among the risk factors for the development of PCa age and the presence of androgens are most important followed by dietary factors, familiar predisposition and prostatic inflammation processes. Within the last years hereditary components, so called inherited PCa susceptibility genes like the interferon-induced RNase (*RNASEL*), macrophage-scavenger receptor (*MSR1*), 5- $\alpha$ -reductase type2 (*ARSRD5A2*) and cytochrome P-450 17A1 (*CYP17A*), have been identified that correlate with a high risk for development of PCa (Nelson et al., 2003). Interestingly, most of these predisposition genes are involved in host responses to infections or in metabolism of sex-steroid hormones.

Somatic mutations of stem/precursor cells, accumulating over a period of several decades can affect genes involved in growth regulation (*p27*; *NKX3.1*), cell signaling (*PTEN*), terminal differentiation (*AR*), DNA-protection (*GSTP1*) and repair (Bell and

Van Zant, 2004; Reya et al., 2001). The frequency of somatic mutations are dramatically increased by inflammatory processes. Prostatic inflammation is a common event observed in prostate tumorigenesis and glandular atrophy (De Marzo et al., 1999). Moreover, proliferative inflammatory atrophy (PIA) shares molecular traits with prostate intraepithelial neoplasia (PIN), that is accepted as the most likely preinvasive stage of adenocarcinoma of the prostate (Bostwick and Qian, 2004; Nelson et al., 2003). The most frequent tumor-associated genetic event identified to date is fusion of the 5' untranslated region of the androgen-regulated gene *TMPRSS2* to the oncogenic ETS transcription factor family members, *ERG* and *ETV1* that are commonly overexpressed in PCa (Tomlins et al., 2005).

Mutations in these genes responsible for normal prostate development, differentiation and growth regulation are thought to trigger initiation and then progression and metastasis of PCa (Isaacs et al., 1995). As tumor cells express luminal characteristics, classically mutated luminal cells were thought to be the origin of PCa. However, after initially successful androgen ablation therapy of the strongly androgen-dependent primary adenocarcinomas in most cases highly aggressive androgen independent tumors recur, that may express some basal cell characteristics. Therefore it is hypothesized that prostate cancer cells may be derived from stem cells or intermediate transit amplifying cells (Figure 1) as stem cells possess many features in common with those of the tumor phenotype, including self-renewal, pluripotency in differentiation and high replicative potential. Furthermore mutations that initiate tumor formation seem to accumulate in cells that persist throughout life, as suggested by the exponential increase of cancer incidence with age, while non-stem/precursor cells are generally destined for terminal differentiation within a window of time too short for acquisition of sequential mutations that must affect both copies of a wild-type tumor suppressor (Hanahan and Weinberg, 2000).

Despite a variety of genetic and environmental factors, age is the most significant risk factor for the development of the malignancy. Within aging precursor/stem cells accumulate several mutations that lead to neoplastic transformation, when mutations affect genes involved in terminal growth arrest or differentiation (Bell and Van Zant, 2004; Reya et al., 2001). These transformed cells give rise to transit amplifying daughter cells that in turn are not able to differentiate appropriate into columnar secretory cells and form precancerous proliferative lesions associated with chronic inflammation (PIA) (De Marzo et al., 1999; van Leenders et al., 2003). Acquisition of further mutations and genomic instabilities in turn lead to transition of inflammatory lesions into low and high grade prostatic intraepithelial neoplasms (PIN), that are heterogeneous, non-clonal and accumulate age-dependently (De Marzo et al., 2003). Most of these damaged transit-amplifying cells will differentiate into the intermediate/luminal phenotype that utilizes androgens and stroma-derived andromedins for proliferation, but not for terminal differentiation. These primary adenocarcinomas are strongly androgen-dependent and express luminal (PAP, PSA, AR, K8/18, as well as intermediate cell markers (PSCA, pp32). To some lower extent transit-amplifying cells will also differentiate into intermediate/ neuroendocrine cells that express CgA, NSE, K5, and Bcl-2 (Schalken and van Leenders, 2003) and focally build subpopulations in the adenocarcinoma (Bonkhoff, 2001).

This primary androgen-sensitive adenocarcinomas contain predominantly intermediate /luminal phenotypes and can be effectively treated by androgen-ablation therapy. Nevertheless, many tumor patients fail this therapy and die of recurrent androgen-independent PCa (AIPC). Several pathways of selection of androgen independent tumor phenotypes by which AIPC can develop have been proposed, all of which may be operative (Craft et al., 1999; Feldman and Feldman, 2001). These pathways include selection of antiapoptotic basal/intermediate phenotypes either

from transformed precursor cells or transdifferentiation from intermediate/ luminal cells under androgen-ablation (Long et al., 2005), selection for androgen-independent neuroendocrine/intermediate phenotypes either from malignant precursor cells or transdifferentiation from intermediate/ luminal cells under androgen ablation therapy (Bonkhoff, 2001) and selection for luminal/intermediate phenotypes with mutated AR signaling (Feldman and Feldman, 2001). These mechanisms are referred to in the literature (Feldman and Feldman, 2001) as the hypersensitive pathway (overexpression of the AR), the promiscuous pathway (mutations of the AR decrease its specificity), the outlaw pathway (ligand-independent AR activation) and the bypass pathway (overexpression of antiapoptotic genes, differentiation to androgen-independent neuroendocrine phenotypes).

The presence of prostate cancer stem cells that continuously resupply the tumor cell population and are not affected by androgen-depletion therapy also represents a potential mechanism for tumor survival in the androgen-depleted environment. In recent years evidence for the existence of prostate cancer stem cells with similar properties similar to prostate epithelial stem cells emerged. By the use of markers established for normal prostate epithelial stem cells a cancer stem cell population out of tumor tissue was identified (Collins et al., 2005). The prostate cancer stem cells were isolated by their expression of the surface marker profile  $CD44^+/\alpha_2\beta_1^{hi}/CD133^+$ , that was expressed in approximately 0.1% of the tumor cells independent of the tumor's Gleason grade or metastatic state. These cells were able to regenerate phenotypically mixed populations of nonclonogenic cells and were invasive in Matrigel, indicating their tumor cell origin.

**Conclusions**

During the past few years our knowledge of the PESC increased considerably. Their regeneration and differentiation potential was investigated and various stem cell markers were identified. Furthermore the presence of androgen-independent prostate cancer stem cells with the ability to give rise to androgen dependent differentiated tumor cells was demonstrated. The similarity with PESC of the healthy prostate supports the stem cell origin theory of the prostate cancer stem cells. Mutations accumulated during lifetime and / or age related changes (e.g. inflammation; PIA) of PESC or their niche lead to changes in the balance between cell division and differentiation which manifests in the development of PINs. Subsequently mutations and autocrine / paracrine mechanisms further amplify this imbalance which proceeds to PINs and finally PCa. Androgen-ablation therapy then leads to the selection of AIPC phenotypes. A better understanding of the role of aged / mutated PESC in the processes leading to the development of androgen-dependent and –independent PCa will hopefully lead to new preventive and therapeutic treatments for these malignancies.

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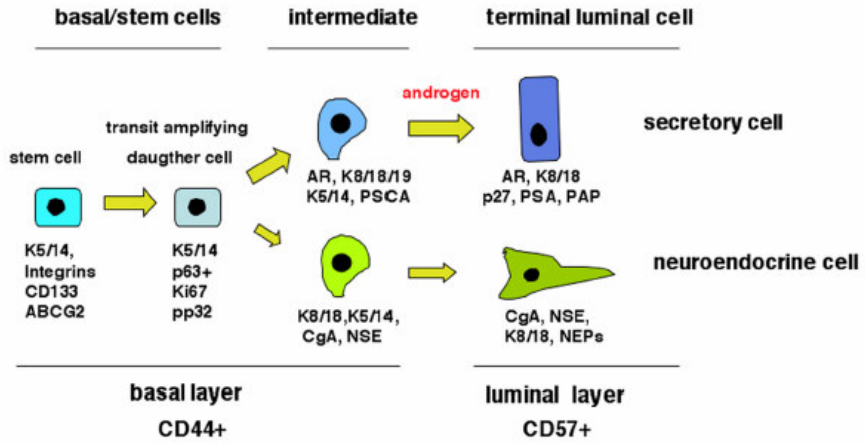
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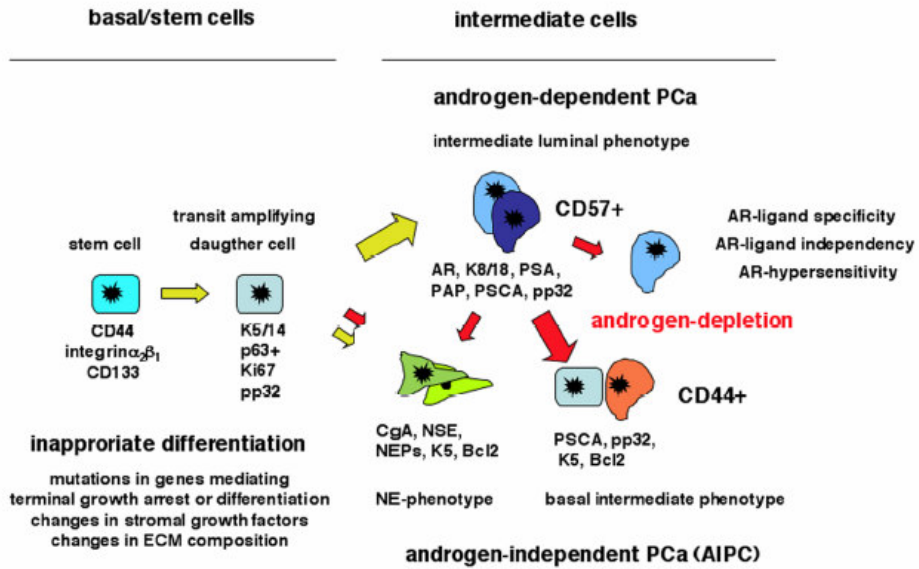
**Figure legend****Figure 1. Prostate epithelial cell differentiation from basal progenitor/stem cells and PCa development.**

This model is based on the hierarchical stem cell model of the prostate epithelium and on the observed tumor cell phenotypes in primary and advanced PCa. Stem/progenitor cells located within the proliferative basal cell compartment give rise to exocrine (secretory) and neuroendocrine cells within the glandular epithelium. Terminal differentiation is mediated by stromal growth factors, ECM, androgens and genes responsible for terminal growth arrest and differentiation. Accumulation of mutations in prostate epithelial stem/progenitor cells through lifetime, changes in stromal growth factors and ECM composition lead to a changed stem/progenitor phenotype. Prostate cancer stem cells give rise to transit amplifying daughter cells that in turn are not able to differentiate appropriately into columnar secretory cells and form androgen-dependent tumors. Androgen-independent PCa phenotypes are selected upon androgen-depletion therapy.

Normal prostate differentiation



PCa development and progression



ACC