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Review

Animal models relevant to human prostate carcinogenesis underlining the critical implication of prostatic stem/progenitor cells

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ABSTRACT

Recent development of animal models relevant to human prostate cancer (PC) etiopathogenesis has provided important information on the specific functions provided by key gene products altered during disease initiation and progression to locally invasive, metastatic and hormone-refractory stages. Especially, the characterization of transgenic mouse models has indicated that the inactivation of distinct tumor suppressor proteins such as phosphatase tensin homolog deleted on chromosome 10 (PTEN), Nkx3.1, $p27^{KIP1}$, p53 and retinoblastoma (pRb) may cooperate for the malignant transformation of prostatic stem/progenitor cells into PC stem/progenitor cells and tumor development and metastases. Moreover, the sustained activation of diverse oncogenic signaling elements, including epidermal growth factor receptor (EGFR), sonic hedgehog, Wnt/β-catenin, c-Myc, Akt and nuclear factor-kappaB (NF-κB) also may contribute to the acquisition of more aggressive and hormone-refractory phenotypes by PC stem/progenitor cells and their progenies during disease progression. Importantly, it has also been shown that an enrichment of PC stem/progenitor cells expressing stem cell-like markers may occur after androgen deprivation therapy and docetaxel treatment in the transgenic mouse models of PC suggesting the critical implication of these immature PC cells in treatment resistance, tumor re-growth and disease recurrence. Of clinical interest, the molecular targeting of distinct gene products altered in PC cells by using different dietary compounds has also been shown to counteract PC initiation and progression in animal models supporting their potential use as chemopreventive or chemotherapeutic agents for eradicating the total tumor cell mass, improving current anti-hormonal and chemotherapies and preventing disease relapse.

Contents

Abbreviations: ADT, androgen deprivation therapy; AI, androgen-independent; ALDH, aldehyde dehydrogenase; AR, androgen receptor; ARR_2, two androgen-responsive regions; BM, bone marrow; CXCR4, CXC chemokine receptor 4; CK, cytokeratin; ECM, extracellular matrix; EGFR, epidermal growth factor receptor; EMT, epithelial–mesenchymal transition; FGF, fibroblast growth factor; HIF-1α, hypoxia-inducible factor-1α HRPCs, hormone-refractory prostate cancers; IGF, insulin-like growth factor; IL-6, interleukin-6; MAPKs, mitogen-activated protein kinases; MMPs, matrix metalloproteinases; NOD/SCID, nonobese diabetic/severe combined immunodeficient; NE, neuroendocrine; NF-κB, nuclear factor-kappaB; Nrf2, nuclear factor (erythroid-derived 2)-like 2; PB, probasin; PC, prostate cancer; PI3K, phosphatidylinositol 3′-kinase; PINs, prostatic intraepithelial neoplasms; PIP3, phosphatidylinositol 3,4,5-trisphosphate; PRL, prolactin; PTEN, phosphatase tensin homolog deleted on chromosome 10; pRb, retinoblastoma protein; Sca-1, stem cell antigen-1; SDF-1, stromal cell-derived factor-1; SHH, sonic hedgehog; STAT, signal transducer and activator of transcription; SV40, simian virus 40; Tag, antigen-coding region; TGF-β, transforming growth factor-β; TRAMP, transgenic adenocarcinoma of the mouse prostate; UGSM, urogenital sinus mesenchymal; uPA, urokinase-type plasminogen activator; VEGF, vascular endothelial growth factor

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1. Introduction

Human prostate cancer (PC) is a heterogeneous and multifactorial disease that proceeds through multisteps of defined pathological and cytological stages. In general, the PC etiopathogenesis occurs through the formation of pre-cancerous lesions designated as prostatic intra-epithelial neoplasms (PINs), tumor development follows by the progression to locally invasive and metastatic disease stages that are often accompanied by the acquisition of a hormone-refractory phenotype by PC cells [1–7]. Although the etiopathological causes of the human PC development are not well established, the risk factors often associated with PC initiation include intense oxidative stress, chronic inflammation and hormonal changes, and more particularly with advancing age [3–5,8–10]. Numerous investigations have also revealed that the alterations in a defined subset of key gene products and molecular pathways typically occur along PC etiopathogenesis and progression. The genetic disruption, epigenetic silencing and/or decreased expression through different mechanisms of diverse tumor suppressor genes that control cell cycle progression such as tensin homolog deleted on chromosome 10 (*PTEN*), homeodomain-containing transcription factor *Nkx3.1*, cyclin-dependent kinase inhibitor $p27^{KIP1}$, *p53* and retinoblastoma (*pRb*) may provide a critical role for PC development (Fig. 1) [11–17]. Moreover, the sustained activation of diverse oncogenic signaling cascades such as epidermal growth factor receptor (EGFR), sonic hedgehog, Wnt/β-catenin, stromal cell-derived factor-1 (SDF-1)/CXC chemokine receptor 4 (CXCR4) and downstream effectors such as Akt and nuclear factor-kappaB (NF-κB) frequently occurs during PC progression to locally invasive, metastatic and hormone-refractory PCs (HRPCs) (Fig. 1) [3,4,18–32]. These tumorigenic cascades can cooperate for the sustained growth, survival, invasion, metastases and treatment resistance of PC cells [33–36]. In addition, the release of different oncogenic factors by activated myofibroblasts and intense remodeling in extracellular matrix (ECM) components in the tumor reactive stroma at the primary and secondary neoplasms is generally involved in the malignant transformation of PC cells and disease progression and metastases (Fig. 1) [3,4,7,9,37–39].

Importantly, a growing body of experimental evidence has also revealed that the accumulation of genetic and/or epigenetic alterations in prostatic stem/progenitor cells or their early progenies may lead to their malignant transformation into highly tumorigenic and migrating PC stem/progenitor cells, also designated as PC- and metastasis-initiating cells (Figs. 1 and 2) [4,40–49]. It has been shown that the highly tumorigenic PC stem/progenitor cells expressing specific markers such as telomerase, CD133, $CD44^{hi}$, $\alpha_2\beta_1$-$integrin^{hi}$, multidrug transporter $ABCG2^{hi}$ and aldehyde dehydrogenase ($ALDH^{hi}$) but low or undetectable androgen-receptor (AR) level and endowed with a high self-renewal ability and an aberrant differentiation potential can give rise to the total PC cell mass [40,43,47–51]. Therefore, these immature PC cells can provide important functions in PC initiation, progression, metastases at distant tissues and resistance to current therapies [40–49,52–55]. In support with this, several prostate regenerative system and transplantable primary xenograft models as well as diverse transgenic mouse models of PC have indicated that the PC stem/progenitor cells can provide critical roles for prostate carcinogenesis, metastases at distant sites and resistance to androgen ablation therapy and chemotherapy [56–62]. In this matter, we review recent gain-of- and loss-of-function studies using different prostatic tissue regenerative systems and animal models of PC suggesting the critical implication of specific gene products deregulated in PC stem/progenitor cells for PC development and metastases. The emphasis is on the data obtained from transgenic mouse models of PC, including *PTEN* knockdown transgenic mice that are representative of the genetic and epigenetic alterations often observed in PC patients during disease etiopathogenesis and progression. In addition, recent advances on the validation of different dietary compounds as potential chemopreventive and chemotherapeutic agents for treating the PC patients at early and late stages of disease are also reviewed.

2. Implications of the malignant transformation of prostatic stem/progenitor cells into highly tumorigenic and migrating PC stem/progenitor cells during prostate carcinogenesis and metastases

Several investigations have revealed the presence of a small subpopulation of prostatic stem/progenitor cells expressing specific stem cell-like markers such as telomerase, CD133, $CD44^{hi}$, $\alpha_2\beta_1$-$integrin^{hi}$, stem cell factor receptor KIT (CD117), tumor-associated calcium signal transducer (Trop-2), $ALDH^{hi}$, $ABCG2^{hi}$, Bcl-2 and/or stem cell antigen-1 (Sca-1) in mouse but low or undetectable AR level in human and rodent prostate glands [4,50,63–65]. These multipotent prostatic stem/progenitor cells endowed with a high self-renewal ability localized within the basal cell layer of the prostatic epithelium were able to drive prostate regeneration by giving rise to basal cells, neuroendocrine (NE) cells and the total epithelial cell mass including secretory luminal epithelial cells expressing AR and cytokeratin 8 (CK8)/CK18 [4,64,66]. More specifically, it has been reported that the prostate involution in the mouse model following androgen withdrawal may be restored due to the persistence of a self-renewing stem cell-like subpopulation in basal epithelial compartment enriched in the proximal region of the prostate gland that can regenerate the prostate gland upon androgen restoration [4,66]. For instance, a single subpopulation of $KIT^{+/-}$ prostatic stem cells from C57BL/6 mouse donors, which was implanted with rat embryonic urogenital sinus mesenchymal (UGSM) cells under the renal capsule of host athymic nude mouse, was able to generate a functional and secretion-producing prostate *in vivo* [66].

Accumulating lines of experimental evidence also suggest that the occurrence of genetic and/or epigenetic alterations occurring in adult prostatic stem/progenitor cells during the lifespan may result in their malignant transformation into highly tumorigenic and migrating PC stem/progenitor cells, also designated as PC- and metastasis-initiating cells (Figs. 1 and 2) [3,4,40,41,43,47,49,67,68]. In fact, the progressive accumulation of specific genetic aberrations in prostatic stem/progenitor cells and their progenies during chronological aging leading to the inactivating mutations in distinct tumor suppressor genes such as *PTEN* and *p53* and sustained activation of diverse oncogenic products is frequently associated with PC initiation and disease development (Figs. 1 and 2) [3,4,11,12,14–17,45,69]. The alterations in different tumor suppressor proteins are necessary to prevent the irreversible growth arrest designated as cellular senescence and apoptotic cell death induced in response to particular oncogenic events, thereby