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REVIEW

Prostate Cancer Stem Cells: Viewing Signaling Cascades at a Finer Resolution

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Abstract It is becoming characteristically more understandable that within tumor cells, there lies a subpopulation of tumor cells with "stem cell" like properties and remarkable ability of self-renewal. Many features of these self-renewing cells are comparable with normal stem cells and are termed as "cancer stem cells". Accumulating experimentally verified data has started to scratch the surface of spatio-temporally dysregulated intracellular signaling cascades in the biology of prostate cancer stem cells. We partition this multicomponent review into how different signaling cascades operate in cancer stem cells and how bioactive ingredients isolated from natural sources may modulate signaling network.

Keywords Prostate cancer stem cells · Apoptosis · Molecular therapeutics · Intracellular signaling

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Introduction

Subpopulation of primary prostate cancer cells having cell surface expression of CD133/AC133^{+}CD44$^{+}\alpha_2\beta_1^{hi}$ were noted to be potential candidates of prostate cancer stem cells (PCSCs) (Collins et al. 2005), it is now well known that cancer stem cells (CSCs) are known to share similar cell surface antigens with their normal tissue stem cell counterparts (Zhao et al. 2008). In line with this approach, there are direct pieces of evidence emphasizing on the concept that, malignant cells and human prostate epithelial cells express prostate stem cell markers, integrin α2β1, CD133 and CD44 (Gu et al. 2007; Li et al. 2008; Miki et al. 2007), and these prospective PCSCs generated xenograft tumors resembled the original tumor (Gu et al. 2007). It had also been experimentally verified that CD44^{+}cells isolated from prostate cancer cell lines had remarkably enhanced tumorigenic potential as compared to CD44^{-} cells (Patrawala et al. 2006), with the CD44$^{+}\alpha_2\beta_1^{+}$ cell population being enriched in PCSCs (Patrawala et al. 2007). More importantly, xenografting CD44 and CD133/AC141 expressing prostate cancer cells induced considerably increased tumor growth in mice as compared to tumor forming ability of CD133/AC141^{-}CD44^{-} cells (Dubrovska et al. 2009). Aldehyde dehydrogenase (ALDH7A1) silenced androgen-independent prostate cancer cells did not show tumor-propagating and metastasizing potential (van den Hoogen et al. 2011). Tumor forming ability of highly active ALDH expressing (ALDH^{hi}) prostate cancer cells was significantly notable (van den Hoogen et al. 2011). Confluence of information emphasized on the fact that low number of ALDH^{hi}CD44$^{+}\alpha_2\beta_1^{+}$ cells was required to efficiently induce secondary tumor growth in mice as compared to tumor formation by 10^4 ALDH^{low}-CD44$^{-}\alpha2\beta1^{-}$ cells. It was concluded that in a prostate

specific antigen (PSA)^{low} cell population ALDH^{hi}CD44^{+-} $\alpha_2\beta_1^+$ phenotype is enriched (Qin et al. 2012). In this review, we systematically put pieces of published cell type-specific studies together to summarize advancements in our understanding of PCSCs. In the upcoming section, we briefly discuss "seed and soil theory" and then focus our views on major findings related to intracellular signaling cascades which are dysregulated in PCSCs.

Seed and Soil Theory

Stephen Paget (1855–1926), an English surgeon is acknowledged deeply for his ground-breaking hypothesis that cancerous cells "seed" from the primary tumor undergo dissemination to different distantly located organs, but establishment of secondary growth occurred only in those tissues that provided a more fertile environment than others for the growth of metastatically competent cancer cells (Ribatti et al. 2006). Bone metastases are a multi-step and complicated procedure that operates through cancer cells mediated activation of bone marrow/bone (BM/B) stroma. This activation resulted in an imbalance between osteoclast directed resorption of the bone and osteoblast promoted formation of the bone thus interfering with hematopoiesis. Osteoblast response is noted in prostate cancer with a consequential increase in the rate of osteogenesis and osteosclerotic bone lesions. It has previously been shown that prostate cancer cells hijacked the hematopoietic stem cells niche to invade BM/B stroma.

Expression profiling revealed markedly enhanced fascin homolog 1, asporin, SPARC-like 1, periostin, platelet derived growth factor receptor β, melanoma cell adhesion molecule, and prostate trans-membrane protein, androgen-induced-1. The results further indicated significant detection of these genes not only in bone stroma in mice bearing VCaP cells and C4-2B, but also in subcutaneously xenografted mice and orthotopic VCaP xenografts of both VCaP and C4-2B cells. Core osteoblastic bone metastasis-associated stroma transcriptome (OB-BMST) and OB-BMST overlapped partially with "stem cell niche" signature. RT-qPCR analysis confirmed upregulated expression of stem cell niche genes, including CD109, EPHA3, pleiotrophin (*PTN*) and SLIT3 in C4-2B and VCaP bone xenografts. SLIT3 and CD109, were considerably enhanced in the stroma of orthothopic VCaP. CD109 and PTN were notably overexpressed in the stroma of mice subcutaneously inoculated with C4-2B cells. However, surprisingly, none of these genes were significantly detected in the stroma of mice subcutaneously inoculated with VCaP cells. Upregulated pattern of genes was significantly noted in bone stroma of mice bearing pro osteolytic prostate cancer cells; however, still incomparable to expression levels detected in stroma of bones in mice bearing osteoinductive VCaP and C4-2B cells (Özdemir et al. 2014). OB-BMST/Core OB-BMST provides broader landscape of components of stem cell niche which can be validated as constituents of BM/B metastatic niche. In addition to their significant mechanistic role, they represent therapeutically targetable molecules. Targeting of this network may effectively inhibit homing properties of cancerous cells, growth and survival in the BM/B.

Epithelial to mesenchymal transition (EMT) was more significantly noted in mice orthotopically xenografted with LNCaP cancer cells treated with androgen deprivation therapy. There was a progressive reduction in luminal epithelial cell tumor yet CD44$^+$ and CK5$^{+/}$CK8$^+$ expressing tumor increased after 16th week (Shang et al. 2015). It was suggested that while 16–20 weeks tumor volume reduced with decreased epithelial markers than those of 12 weeks before androgen deprivation, they had increased stem-like cell markers with more metastatic foci formation (Shang et al. 2015). It is noteworthy that expression of transforming growth factor (TGF)-β1, TGF-β1 receptors and its downstream effector Smad3 was considerably enhanced in androgen deprived cancer cells. Expression levels of CD44 and vimentin were markedly enhanced in TGF-β1 treated CWR22RV1 and LNCaP cancer cells. EMT like cell may originate from CK8$^+$ luminal cell which de-differentiated to CD44$^+$/CK8$^+$ cell, which later acquire hallmark features of mesenchymal cells like higher expression of Vimentin and N-cadherin combined with low expression of E-cadherin (Shang et al. 2015). It is evident that androgen deprived cells re-wire different signaling cascades to fuel prostate cancer progression. The following sections will summarize the role of multiple signaling pathways that are relevant to prostate cancer and PCSCs.

Sonic Hedgehog Signaling

It is intriguing to note that Gli1 is expressed preferentially in one of four prostate stromal subtypes, subepithelial fibroblast-like cells and the subtype located in a closer vicinity of epithelial source of Sonic hedgehog (SHH). Exposing androgen depleted prostate cancer cells to multiple rounds of androgen, consequently induced regeneration and Gli1-expressing cells which exhibited self-renewal capacity, and notably depletion of smooth muscle cells was overcome via replenishing by preexisting smooth muscle cells (Peng et al. 2013). GLI reporter activity was noted to be remarkably enhanced in androgen-independent prostate cancer cells PC-3 and DU145. Morphological change was noted in the form of a distinct cobblestone-like appearance in LNCaP cells expressing

either GLI1 or constitutively active ΔNGLI2 mutant. Treating GLI1 expressing LNCaP cells with androgen receptor (AR) inhibitor bicalutamide did not influence its viability. Moreover, these cells had invasive potential and notably enhanced clonal growth. However, these cells did not show inherent stem cell properties as evidenced by absence of prostaspheres forming ability in suspension or colonies in soft agar (Nadendla et al. 2011). Mechanistically, it has been shown that treating prostate cancer ARCaPE cells with recombinant epidermal growth factor (EGF) protein considerably upregulated GLI-1 and p-ERK. However, treating cancer cells with GLI-1 inhibitor GANT61 remarkably reduced invasive potential of EGF treated cells (Zhu et al. 2013). It is therefore obvious that EGF induced intracellular signaling cross-talks with modulators of different pathways to synergistically promote cancer progression.

Increasingly, it is being realized that overexpression of Hedgehog resulted in PCSCs formation with metastasizing potential. In vivo investigations revealed that SHH signaling mediated transformation into malignant $P63^+$ basal/stem cells that further undergone differentiation characteristically into AR^- and AR^+ progeny in mice intraprostatically injected with Shh-expressing vector. Overexpression of Patch1 and Smo in cell membrane was noted in $P63^+$ basal/stem cells of the SHH vector injected prostates, in regions of primary prostatic intraepithelial neoplasia lesions. In advanced prostate cancer lesions, Patch1 or Smo protein expressing $P63^+$ cancer cells were noted. $P63^+$ cells increased significantly in the lymph nodes and prostates injected with SHH expressing vector (Chang et al. 2011). It has been convincingly revealed that SHH overexpressing DU145 and LNCaP cells demonstrated resistance against a chemotherapeutic drug, paclitaxel (Statkiewicz et al. 2014).

Certain attempts have been made to inhibit SHH induced signaling in prostate cancer cells with encouraging results. Organic derivative of arsenic trioxide, Darinaparsin reportedly downregulated Gli-2 transcriptional activity and considerably inhibited tumor growth in mice xenografted with DU145 prostate cancer cells (Fig. 1) (Bansal et al. 2015). In accordance with the finding that prostate cancer tumor sphere forming cells possessed CSC properties, both colony formation and tumor sphere formation of prostate cancer cells were significantly inhibited upon treatment with genistein. Genistein exerted inhibitory effects on Hedgehog-Gli1 pathway and CSC marker CD44 (Zhang et al. 2012). Future studies should identify additional phytochemicals and synthetic agents with minimal off-target effects for targeting SHH signaling to treat prostate cancer progression.

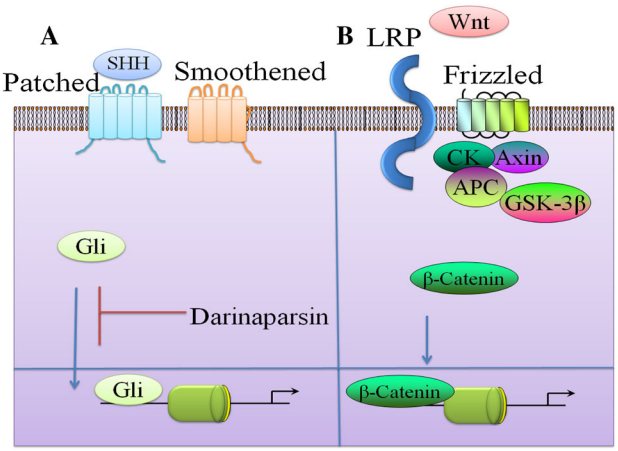

Fig. 1 **a** SHH mediated signaling and **b** Wnt mediated signaling. Darinaparsin has been shown to inhibit Gli mediated transcriptional activity

Wnt Signaling

Wnt induced intracellular signaling through a receptor complex consisting of Frizzled (FZD) and low-density lipoprotein receptor-related protein 5 (LRP5) and LRP6. Ligand-receptor interaction facilitated release of β-catenin from the "degradation machinery" (shown in Fig. 1). It is noteworthy that Wnt3a treatment enhanced nuclear accumulation of β-catenin along with notable rise in CD44 and CD133 expression. It has previously been shown that WNT activity regulates self-renewal potential of prostate cancer cells with "stem cell" like properties independent of activity of AR (Bisson and Prowse 2009).

There are diametrically opposing roles of glycogen synthase kinase (GSK)-3β in modulation of PCSCs. AR79, a GSK-3β inhibitor, has been shown to effectively promote tumor growth in NOD/SCID mice subcutaneously injected with cancer cells. Moreover, astonishingly, AR79 increased the proportion of $ALDH^+/CD133^+$ cells by approximately 100 % in C4-2b and 200 % in DU145 (Jiang et al. 2013) derived tumors. In vitro study revealed that clonogenicity, size of subpopulation of cells and migratory potential were notably decreased as a result of pharmacological inhibition of GSK-3β. Moreover, tumorigenicity and metastasizing potential were significantly reduced in cancer model upon treatment with GSK-3β inhibitor. F-actin is a cytoskeletal protein and reportedly linked with GSK-3β activity and inhibition of GSK-3β resulted in impairment of polymerization of F-actin. Cancer stem cell-associated α2β1 integrin was notably reduced in GSK-3β inhibited prostate cancer cells (Kroon et al. 2014). Puzzling information obtained from GSK inhibitors treated tumors which need further validation and

investigation. It will be essential to comprehend context dependent regulation of GSK-3β in prostate CSCs.

Surprisingly, CSCs propagated to form three dimensional tumor spheroids and differ from CSCs in monolayer culture. Notable difference in CSCs from spheroids and monolayers was the down regulation of FZD1 and upregulation of adenomatous polyposis coli (APC) and Wnt1 (Goksel et al. 2014). Wnt may be upregulated as a compensatory mechanism to sustain Wnt induced signaling. However, FZD1 decrease and APC increase mediated effects on CSC activity needs further analysis to elucidate the interplay using reconstruction and gene silencing strategies.

Flavopiridol, a flavonoid derived from a plant has attracted considerable attention has entered into clinical trials. Contemporary study also indicated flavopiridol mediated inhibitory effects on cell proliferation of $CD133^{high}/CD44^{high}$ prostate CSCs (Soner et al. 2014). CD44 variant 6 (CD44v6) over expression was noted in lymph node metastases including surrounding stromal cells and cancer cells and primary prostate cancer tissues. Wnt induced signaling modulators including β-catenin and p-β-catenin were notably reduced in CD44v6 silenced cells (Ni et al. 2014). Data suggested that dysregulation of different signaling proteins could lead to the activation of Wnt based signaling modulators. LRP5 inactivation resulted in reversal from mesenchymal to epithelial form and reduction in colony formation. Tumor volume was smaller in BALB/c nu/nu mice injected with PC-3 cells transfected with dominant negative LRP5 (Rabbani et al. 2013). Lymphoid enhancer-binding factor-1 (LEF1), a key transcription factor is involved in transducing Wnt induced signals intracellularly with notable involvement in migration and invasion of prostate cancer cells. LEF1 was noted to be post-transcriptionally controlled by microRNA-34a (miR-34a) in prostate cancer cells. Down regulation of miR-34a promoted upregulation of LEF1 to mediate EMT (Liang et al. 2015).

TGF-β Signaling

It has been investigated that TGF-β signaling inhibition in NRP-152, a non-tumorigenic basal epithelial cell line retrovirally transduced with dominant-negative TβRII induced malignant transformation. It was further noted that apoptosis induction was inhibited in Smad2 silenced NRP-152 cells (Yang et al. 2009).

Reactive stroma is tumor-promoting and myofibroblasts have been noted to be densely located in reactive stroma. Mice xenografted with TGF-β1 expressing LNCaP cells and human prostate-derived mesenchymal stem cells developed central core of α-SMA^{+} myofibroblasts (Kim et al. 2014).

TGF-β treatment dramatically enhanced $CD44^{+}CD24^{-}$ population in LNCaP and DU145 cells and poly r(C) binding protein-1 (PCBP1) was notably reduced (Chen et al. 2015). However, TGF-β treated LNCaP cells reconstituted with PCBP1 did not show enrichment of population of $CD44^{+}CD24^{-}$ cells. Tumor growth was significantly inhibited in NOD/SCID mice injected with PCBP1 overexpressing LNCaP enriched stem cells (Chen et al. 2015).

In conclusion, TGF signaling contributes in generation of PCSC population and negatively regulates tumor suppressors. It will be exciting to note how TGF signaling inhibitors effectively target PCSCs in combination with available therapeutic options in pre-clinical studies.

Next we discuss how hypoxia regulates PCSCs and also summarize reported agents with notable efficacy against PCSCs.

Role of Hypoxia

Mounting evidence is also shedding light on hypoxia induced proliferation, invasion and induction of stem cell characteristics and EMT in prostate cancer cells as evidenced by sphere formation, colony formation and the expression changes of EMT and CSC-related markers. However, pristimerin, a naturally occurring triterpenoid dose dependently reversed hypoxia induced stem cell features and EMT in the prostate cancer cells (Zuo et al. 2015). Sunitinib, a multi-tyrosine kinase inhibitor substantially reduced vascular density. Similarly combinatorially treated groups (Sunitinib + Radiotherapy) had dramatically impaired tumor vascularization (Diaz et al. 2015).

Non Coding RNA

H19, Long Noncoding RNA considerably induced sphere formation and stemness markers in RWPE-1, immortalized human prostate cell line. H19 expressing RWPE-1 cells displayed expression of NOTCH1, OCT4, s-SHIP and SOX2 (Bauderlique-Le Roy et al. 2015).

Prostate cancer cells expressed more stem cell markers including CD133, Nanog and CXCR4 when co-cultured with HMC-1 cells. Mechanistically it was shown that AR silenced cancer cells induced expansion of $CD133^{+}$ stem cell population (Li et al. 2015). An interesting finding of the study was upregulation of lnc-RNA HOTAIR in prostate cancer cells co-cultured with HMC-1 cells. lnc-RNA HOTAIR worked synchronously with PRC2 to transcriptionally downregulate AR (Li et al. 2015). PRC2 mediated

gene silencing of AR was not noted in HOTAIR-silenced prostate cancer cells. Considerably higher number of metastatic foci was noted in mice orthotopically xenografted with CWR22Rv1 cells and HMC-1 cells (Li et al. 2015).

Therapeutic Targeting

N-(2-hydroxypropyl) methacrylamide (HPMA) copolymers have been shown to considerably improve solubility, bioavailability and prolonged circulation time. PI3 K/mTOR inhibitor GDC-0980 conjugated to HPMA copolymer efficiently reduced relative proportion of $CD133^+$ cells. Significantly, combinatorial treatment consisting of P-(GDC-0980) and P-docetaxel also decreased the proportion of $CD133^+$ cells remarkably (Zhou et al. 2015).

Mice xenografted with Testicular nuclear receptor 4 (TR4) over-expressing cancer cells had significantly increased tumor burden (Lin et al. 2015). Similarly, TR4 overexpressing cancer cells had an upregulated CD44 and revealed EMT phenotype as evidenced by dramatically enhanced levels of N-Cadherin and Vimentin (Lin et al. 2015).

Natural Agents Mediated Targeting

Berberis libanotica Ehrenb (BLE) considerably reduced number of prostaspheres by more than 50 % and highly resistant CSCs serially treated with BLE indicated markedly reduced expression of stem cell markers specifically CD44 and CD166 (El-Merahbi et al. 2014). Quercetin and green tea synergistically inhibited colony formation and tumor cell invasion of both PC-3 cells and LAPC-4-AI cells. $CD44^+/CD24^-$ stem-like LAPC-4-AI cells were also reduced when combinatorially treated (Wang et al. 2015). EGCG in combination with Quercetin has previously been shown to inhibit self-renewal capacity of $CD44^+\alpha2\beta1^{+-}$ $CD133^+$ CSCs isolated from primary prostate tumors. Moreover, EGCG and Quercetin inhibits EMT by down regulating slug, vimentin and snail and markedly inhibited CSC's migratory and invasive potential (Tang et al. 2010).

Strigolactone, a plant hormone produced in roots is reported to modulate biological mechanisms in cancer cells. In accordance with this approach, synthetic strigolactone analogues have been shown to modulate gene network in stem cells (Pollock et al. 2014).

Anticancer activity of curcumin has sparked interest in pursuing designing of its synthetic analogues. CMC2.24, a structural analogue of curcumin with notable activity. SBT-1214 and CMC2.24, synergistically induced cell death of $CD133^+$ cells. Different constitutively over-expressed stem cell-related genes were notably inhibited when treated combinatorially (Botchkina et al. 2013).

Flavopiridol, a flavone efficiently exerted growth inhibitory effects at 500 and 1000 nM on$CD133^{high}/CD44^{high}$ PCSCs (Soner et al. 2014). It is noteworthy that natural agents remarkably target PCSCs. and thus a deeper understanding of the signaling cross-talks will be helpful in the identification of therapeutically targetable proteins.

Conclusion

There is a significant and rapid advancement in our understanding of the molecular biology of PCSCs, and increasingly it is being realized that dysregulation of intracellular signaling cascades plays a key role. However, there are existing knowledge gaps which need to be bridged. How prostate cancer cells escape from apoptotic cell death mechanism is an insufficiently studied area. Moreover, miRNA expression profiling of PCSCs needs detailed investigation. In addition, identification of natural agents with potential to effectively target PCSCs will prove to be helpful in translation of laboratory findings to the clinical setting, which is urgently needed. Phenotype of PCSCs is an output of multiple signaling networks, therefore effective and targeted drug design requires sharper concept of key nodes in the PCSC signaling networks. In accordance with the concept that PCSCs are therapeutically resistant, there is a need to design mechanism-based drug combinations. Additionally, comprehensive information about molecular biomarkers that provide clues of pathway activity and identification of efficacy predictors will be helpful for patient selection and stratification.

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