Asian Journal of Urology (2016) 3, 203–210

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/ajur

Review

The evolving landscape of prostate cancer stem cell: Therapeutic implications and future challenges

Eun-Jin Yun, U-Ging Lo, Jer-Tsong Hsieh*

Department of Urology, UT Southwestern Medical Center, Dallas, TX, USA

Received 7 June 2016; received in revised form 8 September 2016; accepted 8 September 2016
Available online 20 September 2016

KEYWORDS
Prostate cancer;
Cancer stem cell;
Normal stem cell

Abstract Prostate cancer (PCa) is the most common cause of malignancy in males and the second leading cause of cancer mortality in United States. Current treatments for PCa include surgery, radiotherapy, and androgen-deprivation therapy. Eventually, PCa relapses to an advanced castration-resistant PCa (CRPC) that becomes a systematic disease and incurable. Therefore, identifying cellular components and molecular mechanisms that drive aggressive PCa at early stage is critical for disease prognosis and therapeutic intervention. One potential strategy for aggressive PCa is to target cancer stem cells (CSCs) that are identified by several unique characteristics such as immortal, self-renewal, and pluripotency. Also, CSC is believed to be a major factor contributing to resistance to radiotherapy and conventional chemotherapies. Moreover, CSCs are thought to be the critical cause of metastasis, tumor recurrence and cancer-related death of multiple cancer types, including PCa. In this review, we discuss recent progress made in understanding prostate cancer stem cells (PCSCs). We focus on the therapeutic strategies aimed at targeting specific surface markers of CSCs, the key signaling pathways in the maintenance of self-renewal capacity of CSCs, ATP-binding cassette (ABC) transporters that mediate the drug-resistance of CSCs, dysregulated microRNAs expression profiles in CSCs, and immunotherapeutic strategies developed against PCSCs surface markers.

1. Introduction

Prostate cancer (PCa) is the most frequently diagnosed cancer and has the second highest mortality rate among men in the United States. It is also listed as one of the five most diagnosed cancers worldwide, especially in western developed countries [1]. Recently, the incidence and mortality rate of PCa rose significantly in several Asian countries

* Corresponding author.
E-mail address: jt.hsieh@utsouthwestern.edu (J.T. Hsieh).
Peer review under responsibility of Second Military Medical University.

http://dx.doi.org/10.1016/j.ajur.2016.09.006

such as Japan, Korea and China [1]. At the early stage, PCa is multi-focal and can be managed effectively by surgery, high-intensity focused ultrasound therapy (HIFU), or radiotherapy. However, the advanced-stage of PCa, characterized by acquisition of invasive phenotypes, leading to bone metastases, is generally incurable [2]. It is becoming increasingly clear that heterogeneous tumor cell populations, which may arise from different cancer stem cells (CSC) subpopulations, are hierarchically organized. CSCs were first described in acute myeloid leukemia [3], and later, were also identified in various solid tumors including PCa [4]. CSCs are defined as small subsets of cells within a tumor that are highly tumorigenic with unlimited self-renewal capacity and can also regenerate non-tumorigenic progeny. Particularly, CSCs seem to be more resistant than differentiated tumor cells to conventional therapies [5,6]. Therefore, the CSC theory is likely to facilitate the understanding of tumor progression and expedite the development of effective therapeutic strategies targeting CSCs.

Here, we review the current knowledge of CSCs and the relationship between CSCs and metastatic castration-resistant prostate cancer (CRPC). In addition, we will address the therapeutic implications and challenges for targeting CSCs and discuss emerging and innovative approaches for the treatment of CRPC. Understanding the link between CSCs and metastatic CRPC will facilitate the development of novel therapeutic approaches and improve the clinical outcomes of PCa patients.

2. Normal prostate stem cells and CSCs

Stem cells have been defined as cells that have the ability to perpetuate themselves through self-renewal and to differentiate into mature tissue types [7,8]. Self-renewal is crucial to stem cell function, because it is required for stem cells to persist for the lifetime of the animal. Moreover, while stem cells from different organs may vary in their developmental potential, all stem cells must self-renew and regulate the relative balance between self-renewal and differentiation. While CSCs are not necessarily derived from normal stem cells, this fraction of tumor cells possesses many functional similarities with normal stem cells (NSCs) such as self-renewal capacity and pleuripotency [9]. Therefore, understanding the regulation of NSC is also fundamental to understanding the regulation of CSCs.

The normal prostate epithelial stem cell differentiates into three epithelial cell types, basal, luminal, and rare neuroendocrine [10]. Basal cells express high molecular weight cytokeratin (CK) including CK5 and CK14, and also Bcl-2, CD44, p63 but not androgen receptor (AR) [11—13]. Terminally differentiated luminal cells express low molecular weight CK such as CK8, CK18 and also express AR [12]. Luminal cells secrete prostate-specific antigen (PSA) and prostate-specific alkaline phosphatase (PAP) into the glandular lumen in an androgen-dependent manner. Unlike the majority of secretory luminal cells, neuroendocrine (NE) cells express synaptophysin and chromogranin A, but not AR or PSA and also secrete neuropeptides including serotonin, bombesin, calcitonin and somatostatin [10,14].

Androgen-deprivation of rodent models provides evidence for the presence of normal prostate stem cells (NPSCs) within the basal compartment of the prostate gland. Basal cells preferentially survive during castration whereas most of the luminal cells are lost through programmed cell death [15,16]. However, the cellular origin of the NPSCs is not always certain. For example, the luminal population of castration-resistant Nkx3.1-expressing cells (CARNs) express CK18 and AR but not basal markers [17] and these cells exhibit stem cell characteristics and can regenerate prostatic tissue after androgen replacement [17]. In addition, the cellular origins of PCa remain a subject of debate. In mouse models, it has been shown that basal and luminal populations can both serve as cells of origin for PCa [18,19], however, only basal cells have been shown to be efficient targets for transformation in human PCa [20]. Also, *in vivo*, PCa with stem cell characteristics survive castration, express a luminal progenitor phenotype with low AR expression, and possess tumor-initiating potential after androgen replacement [21]. In contrast, PCSCs may also be derived from NSCs with malignant transformation because CRPC is androgen-independent and basal cells can be identified from a majority of metastasis [22]. In addition, some key molecules that normally regulate self-renewal and survival of NSCs (e.g. p63, Bcl-2, and hTERT) are preferentially localized in basal compartment [12,14]. However, human PCa has a markedly luminal phenotype which has led to the idea that PCa arises from a fully differentiated luminal cell. Shen et al. [23] demonstrated that CARNs, which are a luminal stem cell population, are a cell type of origin for certain types of PCa. Also, a recent study showed that both populations of $CD49f^{hi}$ basal cells and $CD26^{hi}$ luminal cells generated a mixture of $CK5^{+}$ basal cells and $CK8^{+}$ luminal cells. However, only purified luminal cells could generate organoids with a glandular architecture under established organoid culture conditions, suggesting that luminal stem cells are capable of regenerating the normal glandular architecture of human prostate [24].

Another possible origin of PCSCs might be through cell fusion between stem cells and other types of cells including differentiated cells, stromal cells, or inflammatory cells [25]. Cell fusion may allow for the combination of self-renewal properties of NSCs with the accumulated mutations in differentiated cells to attain a fully neoplastic transformation. As an example, it has been shown that bone marrow derived cells can fuse with neoplastic epithelium to promote tumor development and metastasis through creation of CSCs [26]. Although the origin of PCSCs still remains controversial, it is also possible that PCa might have acquired CSCs features through genetic/epigenetic changes.

3. Isolation and identification of PCSCs

Hematopoietic stem cell markers have provided the paradigms for identifying and isolating CSCs in solid tumors including PCa [27,28]. In prostate, the biomarkers CD44, stem cell antigen (Sca-1), CD133 (prominin-1), and ABCG2 are commonly used for fluorescence-activated cell sorting (FACS) to isolate NSCs [14,19,29]. A unique PCSC marker(s) has not yet been found, although certain markers of "stemness" that are generally present in various NSCs and