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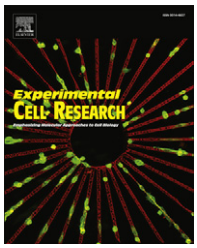

Review Article

Biology and clinical implications of CD133$^+$ liver cancer stem cells

*Stephanie Ma**

Department of Clinical Oncology, State Key Laboratory for Liver Research, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong

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ABSTRACT

Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver, accounting for 80%–90% of all liver cancers. The disease ranks as the fifth most common cancer worldwide and is the third leading cause of all cancer-associated deaths. Although advances in HCC detection and treatment have increased the likelihood of a cure at early stages of the disease, HCC remains largely incurable because of late presentation and tumor recurrence. Only 25% of HCC patients are deemed suitable for curative treatment, with the overall survival at just a few months for inoperable patients. Apart from surgical resection, loco-regional ablation and liver transplantation, current treatment protocols include conventional cytotoxic chemotherapy. But due to the highly resistant nature of the disease, the efficacy of the latter regimen is limited. The recent emergence of the cancer stem cell (CSC) concept lends insight into the explanation of why treatment with chemotherapy often may seem to be initially successful but results in not only a failure to eradicate the tumor but also possibly tumor relapse. Commonly used anti-cancer drugs in HCC work by targeting the rapidly proliferating and differentiated liver cancer cells that constitute the bulk of the tumor. However, a subset of CSCs exists within the tumor, which are more resistant and are able to survive and maintain residence after treatment, thus, growing and self-renewing to generate the development and spread of recurrent tumors in HCC. In the past few years, compelling evidence has emerged in support of the hierarchic CSC model for solid tumors, including HCC. And in particular, CD133 has drawn significant attention as a critical liver CSC marker. Understanding the characteristics and function of CD133$^+$ liver CSCs has also shed light on HCC management and treatment, including the implications for prognosis, prediction and treatment resistance. In this review, a detailed summary of the recent progress in CD133$^+$ liver CSC research with regard to identification, regulation and clinical implications will be discussed.

Abbreviations: HCC, hepatocellular carcinoma; CSC, cancer stem cell; SP, side population; TGFβ, transforming growth factor β; DNMT, DNA methyltransferase; Line-1, long interspersed nuclear element-1; TP53INP1, tumor protein 53-inducible protein 1; HBsAg, surface antigen of the HBV; ABC, ATP-binding cassette; HBx-ΔC, C-terminally truncated HBx

**Corresponding author.* Fax: +852 2816 9126.
E-mail address: stefma@hku.hk

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Contents

Cancer stem cells

Cancer is hierarchically organized and composed of a heterogeneous population of cells, among which researchers have now provided solid evidence of the existence and importance of a cancer stem cell (CSC) subpopulation. Other commonly used terms for "cancer stem cells" include "tumor-initiating cells" and "cancer-initiating cells"; all referring to the same compartment of cells in a tumor that bears both cancer and stem cell-like properties. CSCs are now defined as a group of cells having the ability to initiate tumor growth, self-renew and differentiate. Other common, but not defining characteristics of CSCs include its rarity within a tumor, expression of stem cell-like markers expression, the ability to metastasize and resist standard therapy. Despite the common misconception and the resemblance of CSCs to normal stem cells, CSCs do not necessarily have to originate from normal stem cells. The specific origin of CSCs—whether a defined subset of cells is destined to become CSCs when they are formed, whether CSCs are transformed from normal stem cells, or whether they originate from more differentiated cells (i.e. progenitor cells and mature cells that acquire self-renewal and tumor initiation abilities after genetic lesions)—remains to be elucidated.

The CD133 molecule

CD133 was the first identified member of the prominin family of pentaspan transmembrane glycoprotein (5-transmembrane). It is also commonly known in humans and rodents as Prominin 1 (PROM1) [1]. The specific function and ligands of CD133 are still largely unknown, but they are known to be distinct in their restricted localization to cellular/plasma membrane protrusions. CD133 was first found as a marker of primitive hematopoietic stem and progenitor cells [2] and then later also found to classify endothelial progenitor cells, neuronal and glial stem cells, human fetal liver and stem cells in cord blood and peripheral blood. Although the biological function of CD133 is still unclear to date, CD133 is now widely recognized as a stem cell marker for both normal and cancerous tissues. And indeed, CD133 alone or in a combination with other markers have been used for the isolation of stem cells from tissues like bone marrow, brain, kidney, prostate, liver, pancreas and skin. In more recent studies, CD133 is also used for the identification and isolation of putative cancer stem cell (CSC) subpopulations from malignant tumors of brain, prostate, liver, pancreas, colon, renal, etc [3].

CD133 as a marker of primary and metastastic liver cancer stem cells

Following the early attempts to isolate CSCs in hepatocellular carcinoma (HCC) through identification of a side population (SP) using the DNA-binding dye Hoechst 33342 in 2006 by two independent Japanese group of researchers [4,5], significant efforts have been made to further characterize CSCs of this deadly disease. In particular, CD133 has drawn momentous attention as an important liver CSC marker. CD133$^+$ cells were first reported to mark a CSC subset in HCC by Suetsugu et al. [6]. In that study, the authors found CD133$^+$ cells isolated from Huh7 HCC cell line to possess higher proliferative and tumorigenic potentials. In addition, when compared with their CD133$^-$ counterparts, CD133$^+$ cells were found to express lower levels of mature hepatocyte markers, glutamine synthetase and cytochrome P450 3A4 (CYP3A4) [6]. Similar findings were also subsequently reported in 2007 where Yin et al. found CD133$^+$ cells isolated from SMMC-7721 HCC cells demonstrated an enhanced clonogenicity *in vitro* and tumorigenicity *in vivo* [7]. Work from our own research team also contributed to the further characterization of liver CSCs using the CD133 surface marker [8–10]. With the beliefs that normal stem cells and CSCs share similar properties that controls both self-renewal and differentiation processes and that normal stem cells are activated during the process of liver regeneration, we first attempted to utilize a severe partial hepatectomy model in which over 70% of the mouse liver was removed, to study the role of normal stem cells in the process of liver regeneration. Expression profiling of RNA extracted from different time points collected during the liver regeneration process found expression of Prominin-1, the homolog of human CD133 in mice, to be significantly up-regulated during early liver restoration [8]. Subsequent analysis of CD133 expression in a panel of human liver cells lines found CD133 expression to positively correlated with the cell line's ability to initiate tumor formation *in vivo*. Compared to CD133$^-$ counterparts, CD133$^+$ subsets isolated from HCC cell lines PLC8024, Huh7 and HepG2 were found to exhibit both cancer cell and stem