CD133, Stem Cells, and Cancer Stem Cells: Myth or Reality?

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Abstract CD133, a member of the prominin family, is found in a variety of tissues with at least three variants. The function of CD133 is not well understood, but its expression is subject to changes in the microenvironment cues including bioenergetic stress. Knockout of CD133 does not affect renewal, but mammary gland branching. A point mutation of CD133 (R733C) leads to retinal disorder. CD133 is found in embryonic stem cells, normal tissue stem cells, stem cell niches, and circulating endothelial progenitors as well as cancer stem cells. Maintenance of stemness in cancer may be attributable to asymmetric cell division in association with a set of embryonic expression signatures in CD133+ tumor cells. CD133 could enrich cancer stem cells, which are associated with chemoresistant phenotype. High CD133 is associated with poor survival in a variety of solid tumors, including lung, colon, prostate, etc. Monitoring CD133+ cells in peripheral blood, and targeting CD133 in cancer, may further predict and improve the clinical outcomes.

Keywords CD133 · Cancer stem cells · Endothelial progenitors · Colorectal cancer

Introduction

CD133 (or AC133), a member of prominin family, was first discovered from hematopoietic stem cells initially discovered in 1997 by Yin and colleagues [1••, 2•]. At the same time, Asahara and others reported that bone marrow–derived circulating endothelial progenitors (CEP) participate in postnatal angiogenesis including tumor, inflammation, and tissue regeneration [3, 4••]. Interestingly, CEP express CD133, which has been recently used to enrich and mark normal tissue stem cells as well as cancer stem cells from a variety of solid tumors [5••, 6–12]. CD133 can enrich cancel stem cells (CSC) up to approximately 200 fold from the human tumor tissue, and these CSC exhibit limitless self-renewal capacity, sustain long-term culture, and form tumor xenograft in immunodeficient mice that fully recapitulate the pathological features of the human tumor [5••, 6–12]. A single CD133-positive colon cancer cell is capable of differentiating into neuroendocrine,
Expression and Functions of CD133 in Cancer

CD133 is a cholesterol interacting penta-span transmembrane glycoprotein (120 kd) with two reported 3 isoforms—CD133-1 [1••], CD133-2 [28], and CD133-3 [29]. CD133-1 mRNA was more prominent in fetal brain and adult skeletal muscle but was not detected in fetal liver and kidney, adult pancreas, kidney, and placenta. CD133-2, not CD133-1, is a cell surface antigen recognized by anti-CD133 monoclonal antibodies that are used for isolation of hematopoietic stem cells and is found in multiple stem cell niches marked by co-expression with β-integrin in the basal layer of human neonatal epidermis. Loss of CD133-2 correlates with gain in a terminal differentiation. Recently, another splice variant, CD133-3, was found in epididymis and testes [29]. Prominin is associated with membrane protrusions and vesicles export highly conserved across many different species [30, 31]. Extracellular membrane traffic may enable neural stem and progenitor cells to avoid the asymmetric inheritance of the midbody observed for other cells and, by releasing a stem cell membrane microdomain, to potentially influence the balance of their proliferation versus differentiation. Pine et al. [32•] showed that template DNA cosegregation was enhanced by cell-cell contact. Its frequency was density-dependent and modulated by environmental changes, including serum deprivation and hypoxia. Strikingly, during cell division, CD133 cosegregated with the template DNA, whereas the differentiation markers pro-surfactant protein-C and pan-cytokeratins were passed to the opposing daughter cell, demonstrating that segregation of template DNA correlates with lung cancer cell fate [32]. Knockout of CD133 mice did not interestingly affect the regenerative capacity of mammary gland except the branching capacity [33]. A frame shift mutation (R373C) in prominin 1 (PROM1) has been shown to result in retinitis pigmentosa, macular degeneration, and cone-rod dystrophy in human patients possibly due to endothelial dysfunction, leading to impaired adhesion capacity and higher levels of cellular damage. Additionally, patient with this frame shift mutation suffered renal infections, hematua, and recurrent miscarriages possibly reflecting consequences of abnormal tubular modeling.

The lineage tracing models showed that CD133 are found in the transit-amplifying zone of the colonic crypt which is susceptible to malignant transformation [7]. Indeed, CD133 is found on the putative cancer stem cells from a variety of solid tumors including brain [6], prostate [34], pancreas [35], melanoma [36, 37], colorectum [5••, 38], liver and bile duct [39, 40], lung, and ovary, etc. [7, 10, 41]. A number of important regulators and pathways have been implicated in CSC biology and CD133 expression: mTOR, Wnt/β-catenin [42], PI3K-AKT [8, 13], reactive oxygen species-HIF1α pathway [43], Oct4 [9], and CXCR4 [35, 37]. Similar to embryonic stem cells, CD133+ noncancer cells or melanoma expression are mostly found in the G1/G0 portion of the cell cycle [36]. CD133 expression is due to the lack of CpG island methylation [44, 45]. Certain microRNA molecules (eg, miR-200a and miR130b) serve as stemness promoters [46, 47], whereas miR-34 serves as a stemness inhibitor [48]. Sorting and profiling human CD133+ glioblastoma multiforme (GBM) established a 214-gene signature which resembles that of human ES cells, and strongly correlates with histologic grade of GBM as well as breast and bladder cancer and portends poor survival [49••]. Finally, genomic instability plays an important role in the transformation of stem cells [50]. Function still not well understood, CD133 is broadly found among normal tissue stem cells as well as putative CSC population and serves as a marker of asymmetric division, lineage plasticity, tumor cell dormancy, and inherent embryonic gene expression. CD133 expression is under epigenetic regulation subject to microenvironment cues including chemotherapy and radiation (Fig. 1).

Prognostic Values of CD133 Expression in Cancer and in Peripheral Blood

To identify the link between CD133 and prognosis, most researchers had studied CD133 expression in correlation with
clinical and pathological parameters, especially survival, in a variety of tumors. High CD133 expression is associated with poor prognosis in cancers of the colorectum [51, 52, 53], brain [55, 56], liver [57], stomach [55], endometrium [58], ovary [41], and lung [59]. Most of these studies are small in sample size and are further limited by use of immunohistochemistry method, which results in high background noise with the commercial antibody. Some of the studies had utilized CD133 mRNA alone or in combination with other markers. Nevertheless, these studies are limited by relatively small sample size and retrospective study design and thus limit definitive conclusions. In support of the above findings, other work suggests that high CD133 expression in the tumor is due to resistance to cisplatin in lung cancer [11, 60], and drug resistance to 5FU in colorectal cancer [51]. Likewise, the resistance phenotype of colon cancer stem cells may be directly linked to cytokine IL-4, and modulating IL-4 could override the chemoresistance [61]. Similarly, high CD133 expression is also linked to radiation resistance and local relapse in rectal cancer and glioma [62–65]. Collectively, functions still poorly defined, CD133 is a putative CSC marker in a variety of solid tumors due to chemoresistance, and poor survival [42, 54].

CD133 also marks the circulating bone marrow–derived endothelial progenitor cells (CEP), which directly participate in tumor angiogenesis and form pre-metastatic niche [66, 67]. A number of assays had been developed to quantify CEP via flow cytometry, colony assay, and qRT-PCR [68]. When interpreting these results, one needs to consider the fact that elevated CD133 mRNA or CD133+ cells may also reflect circulating CD133+ CSC as well. Furthermore, a recent study showed that CD133+ glioblastoma cells were even capable of direct endothelial differentiation through CD133+ transit-amplifying progenitor [14]. One study measured VEGFR2, CD133, CD34, and VE-cadherin mRNA in the peripheral blood samples and in lung cancer tissues. With confocal microscopy, putative CD133+ “EPCs” are found in 9 of 22 non–small cell lung cancer (NSCLC) tissues. Also, circulating EPC levels before therapeutic intervention were increased in NSCLC patients (P<0.002, vs healthy controls), and high pretreatment circulating EPC numbers correlated with poor overall survival (P<0.001) [69]. Hermann and colleagues [35] identified the subset of CD133 + CXCR4+ cancer stem cells relates to the tumor metastasis in the pancreatic cancer model. We first showed that elevated CD133 mRNA levels

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**Fig. 1** A view of CD133 expression as it relates to variety of normal tissue and cancer stem cells. CD133 expression is due to the lack of CpG island methylation and is regulated by several important pathways, including miR-200a, which serves as stemness promoter through the canonical Wnt/β-catenin pathway. There are three reported isoforms, CD133-1, CD133-2, and CD133-3, which are detected in different tissue stem cells, niche, and normal tissues.
in peripheral blood predict colon cancer recurrence independent of tumor stage and serum CEA [68]. Mehra et al. [70] also showed that elevated CD133 mRNA levels in peripheral blood were associated with bone metastasis and poor overall survival in a variety of solid tumors including colorectal cancer. Iinuma showed that peripheral blood CD133 mRNA was the most prognostic when combined with CK and CEA via RT-PCR in 735 stage II and III colorectal cancer patients. Interestingly, CD133 mRNA alone was reportedly not prognostic by Iinuma in stage II and III colorectal cancer, but was prognostic in two other studies that included stage IV patients [71, 72, 73]. Earlier-stage diseases, small sample size, possibly technical difference, and timing of CD133 mRNA acquisition (preoperative vs postoperative) may explain the differences why CD133 mRNA was not prognostic in the current study. Our study included stage IV colorectal cancer patients who may shed more CD133+ circulating tumor cells [74]. Quantification of CD133+ cells using with flow cytometry or RT-PCR alone or in conjunction with other biomarkers may be useful to monitor treatment response to antiangiogenic agents including sorafenib plus erlotinib [75], and bevacizumab [76], and chemotherapy plus antiangiogenic agents [77].

Given its association with drug and radiation resistance and relationship to tumor angiogenesis, CD133 is considered to be a valid therapeutic target despite the lack of understanding on its function. A number of strategies have been tested: 1) A CD133 antibody conjugated to a potent cytotoxic drug, monomethyl auristatin F (MMAF), effectively inhibited the growth of Hep3B hepatocellular and KATO III gastric cancer cells in vitro and in vivo [78]. 2) Immunotherapy including adoptive immunotherapy targeting testicular antigen was also proposed [79]. CD133 is considered to be a target for melanoma immunotherapy [80]. 3) Using high-throughput CSC assays that undergo epithelial mesenchymal transition, Gupta et al. [81] had already yielded active small molecules of salinomycin that target breast CSC. Large pharmaceutical companies had put in greater resources of coming up with designer small molecules targeting its relevant pathways including sonic hedgehog, stat pathways, wnt pathway, etc. Some of these agents had entered into clinical trials (eg, anti-DLL4, MT110, IPJ925, DI-Leu16-IL2, AZD7762) [82]. 4) Given that CSC is a functional definition and likely exists in a dynamic state and adapts to a functionally defining microenvironment including hypoxia etc., we proposed activation-depletion strategies targeting colon CSC in the clinic, which resulted in long-term survival outcomes in colorectal cancer [83].

## Conclusions

The link between CD133 and normal and cancer stem cells is now firmly established. While not specific and function still is not clearly defined, CD133 is an important stemness biomarker in normal tissue stem cells as well as cancer stem cells. First used in colorectal cancer, CD133 can enrich the putative CSC from a variety of solid tumors and is associated with a set of embryonic gene signatures shared across many tumor types. High CD133 expression is associated with treatment resistance, relapse, and decreased survival in a variety of solid tumors, including colorectal cancer. More importantly, the prognostic value of circulating CD133 mRNA levels in advanced and locally advanced colorectal cancer is beginning to emerge. Given that CD133+ CEP and CSC may even overlap functionally through stem cell plasticity and inherent embryonic machinery, we will need to integrate strategies that will target the tumor bulk, CSC fraction, as well as the tumor microenvironment. Targeting and monitoring CD133 may lead to significant advances in outcome prediction and cancer therapy Table 1.

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•• Of major importance

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