More than Markers: Biological Significance of Cancer Stem Cell-Defining Molecules

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Abstract

Small populations within an increasing array of solid tumors, labeled cancer stem cells (CSC) or tumor-initiating cells (TIC), have the ability to differentiate, self-renew, and replicate the original tumor in vivo. To date, these cells have been distinguished from the bulk-tumor population by the expression pattern of cell-surface proteins (e.g., CD24, CD44, CD133) and cellular activities, such as the efflux of Hoechst dye or aldehyde dehydrogenase activity. Recent data have shown that these markers are inducible by exposure to anticancer agents; this finding highlights not only the potential fluidity of the CSC compartment, but also the functionality of these markers. The involvement of CD44 in invasion, adhesion, and metastasis, or the role of CD24 in modulation of src, FAK, and GLI1 are examples of these relevant roles. Instead of looking solely at the marker expression in these populations, we hope to clarify the biologically significant roles these markers and activities play in tumor progression, metastases, and as possible targets for therapy. Mol Cancer Ther; 9(9): 2450–7. ©2010 AACR.

Introduction

The cancer stem cell (CSC) hypothesis has been the focus of hundreds, if not thousands, of journal articles over the past decade. CSCs were originally described in hematologic cancers (1), but more recently have been isolated from solid tumors (2). Characteristics of these tumor-initiating cells have been thoroughly discussed (3, 4), and CSCs have been defined by tumorigenicity in immunocompromised mice and, more importantly, the ability to generate heterogeneous cancer cell populations within the resulting tumors that are phenotypically similar to the original tumor. This ability is attributed to the stem cell (SC)–like behavior of asymmetrical division, in which CSCs are able to replicate themselves and generate progeny that can differentiate into the bulk of the proliferating cancer cells within the tumor. Consistent with the theory, a single CSC isolated by the expression pattern of specific markers can be implanted in mice and serially propagated indefinitely (5). However, several commentators have questioned the existence of these tumor-initiating cells (6, 7).

Investigation of CSCs has been conducted using cancer cell lines, primary cancer cell lines, xenografts, and primary patient tissue samples. Each method has its usefulness and limitations; for example, stable cancer cell lines are simple to use but have been selected to grow in culture, whereas patient samples are the gold standard, but are difficult to obtain regularly. Direct patient xenografts may be the best option because a near endless supply of tissue can be generated in immunocompromised mice and because they have never been under selective pressure in vitro, but commonly maintain histology similar to the original tumor. Admittedly, selection pressures are introduced by transplantation into mice, but xenografts could be used to perfect procedures in preparation of direct patient samples. Also, efficacy of therapeutics on CSC populations is easily studied in vivo when using xenografts.

CSC populations are commonly defined by the presence or absence of various combinations of cell-surface proteins, such as the CD44+/CD24−/low population in breast cancer (2). By staining cells with antibodies against these markers, populations of interest are easily identified and isolated by flow cytometry and/or fluorescence-activated cell sorting (FACS). When used properly, FACS analysis is the most robust tool in the identification of CSCs; by implementing proper controls, false readings are avoided and reproducibility is easily achieved. This accuracy is crucial because many of these errors can be missed during the reviewing process, when only the final histogram image, if any at all, is displayed. Proper calibration of instruments, the use of isotype and compensation controls, and the exclusion of murine cells in preparation of direct patient samples. Also, CSCs are often resistant in vivo and in vitro to common drugs when compared with the majority of the cancer
cell population, which raises the question if traditional therapy only “debuls” tumors, leaving CSCs to repopulate the original tumor or metastasize? CSC drug resistance has been attributed to their relatively slow cycling, active efflux of drugs by ABC transporters, and the upregulation of prosurvival genes (9). Activation of SC-related genes and pathways has been well documented in CSCs, and these genes and pathways are commonly targeted [e.g., hedgehog and epidermal growth factor receptor (EGFR)] with a range of chemotherapeutics (10, 11). In this review, the ties between marker expression and expression of “stemness” genes are discussed. Furthermore, the recent results showing the direct association between these markers and components of these pathways are examined, and although many markers have been used to define CSC populations, here we focus on the most commonly reported markers in the literature for solid tumors [CD24, CD44, CD133, aldehyde dehydrogenase (ALDH) activity and Hoechst efflux]. Finally, although all of the associations between markers and pathways discussed below are not expressly studied in CSCs, it is important to define these relationships in cancer cells, allowing future investigations and development of novel therapeutic targets.

**CD44 and Its Variants**

Consistently, CD44+ is reported as at least one characteristic of CSCs across tissues, including breast, pancreas, gastric, prostate, head and neck, ovarian, and colon, whereas other markers (e.g., CD24) are not (2, 8, 12–16). The standard CD44 (CD44s) molecule is an 85- to 90-kDa transmembrane glycoprotein containing 10 standard exons, whereas tissue-specific splice variants (CD44v1-10) contain the standard set and combinations of the 10 variable exons. Specific to the tissue and isoform, CD44 has roles in adhesion, motility, proliferation, and cell survival (17, 18). The CD44 protein contains four major domains, including the conserved extracellular hyaluronan-binding and variably spliced regions, the transmembrane sequence, and the intracellular cytoskeletal-signaling domain (19). Interactions between CD44 and the extracellular matrix glycosaminoglycan hyaluronan (HA) are currently an exciting area of investigation. HA has been shown to be enriched in the SC niche and is also likely to play an integral role in the behavior of CD44 in CSCs (20).

The CSC phenotype commonly includes (uniquely or in part) CD44+, which likely points to important roles for CD44 in tumors, such as in facilitating adhesion, migration, and invasion. However, conflicting results point to possible tissue-specific roles for CD44. In head and neck squamous cell carcinoma (HNSCC) cells, CD44 promotes growth and migration in an HA-dependent manner that is attenuated by small-interfering RNA (siRNA) knockdown of CD44s or CD44v3, 6, 10, or by using blocking antibodies against HA (21, 22). Similarly, CD44s, CD44v3, and CD44v6 levels are increased in invasive breast carcinomas (23), and blocking antibodies against CD44s reduced adhesion, motility, and matrigel invasion, whereas CD44v6 antibodies only inhibited motility in breast cancer cell lines (17). Recently, prostate cancer cells capable of invading matrigel had increased CD44 expression, whereas CD24 was repressed. These cells had also undergone an epithelial-to-mesenchymal transition (EMT; ref. 24). In contrast, others groups have reported that the presence of CD44s or CD44v6 does not differentiate between normal and malignant head and neck epithelia (25), or that CD44s is a marker of disease-free survival in breast carcinoma (26). CD44’s role as a protective protein is supported by results from a mammary tumor mouse model showing that the presence of CD44s reduced metastasis, possibly by blocking the binding of HA by other receptors (e.g., RHAMM), which may be invasion promoting (27). Although the majority of evidence supports the hypothesis that HA-CD44 interactions promote invasion and migration, the exact mechanisms in cancer must still be clarified.

Remarkable headway has been made in understanding the role of CD44 in cell signaling, particularly in SC-related pathways, making CD44 more than just an arbitrary marker. Early results found that invasive CD44+ prostate cells had increased expression of Nanog, BMI1, and SHH, as well as a genetic signature similar to SCs (24). Recently, the HA-CD44 interaction has been tied to pathways closely related to EMT, cancer, and “stemness” in head and neck, breast, and ovarian cancer cells. HA-bound CD44 interacted with EGFR and human epidermal growth factor receptor 2 (HER2), promoting growth through MAP/ERK kinase (MEK), extracellular signal-regulated kinase 1 (ERK1), ERK2, and β-catenin nuclear localization, respectively (21, 28). HA-CD44 also activates the transcription factor Nanog, which, in turn, increases expression of the SC-related genes REST and SOX2 and the ABC-transporter MDR1 (29). The HA-CD44 complex also reportedly activates the p300 acetyltransferase, which, in turn, acetylates β-catenin and nuclear factor κB (NFκB)–p65, resulting in the upregulation of MDR1 and BCL-XL, respectively (30). The HA-CD44 induction of the drug efflux–associated MDR1 and prosurvival BCL-XL could be responsible for the association between CD44 expression and resistance to a range of therapies (21, 29, 31).

Recently, p53 has been implicated in the transcriptional regulation of CD44. Repression of CD44 results from the binding of p53 to its promoter region. Suppression of p53 by short hairpin RNA (shRNA) or expression of the papillomavirus E6 oncoprotein drastically increases CD44 levels in breast epithelial cell lines. Also, forced expression of CD44 negated the proapoptotic and antiproliferative effects of p53 by activation of the phosphoinositide 3-kinase (PI3K) pathway and suppression of EGF signaling, respectively, whereas suppression of CD44 decreased sphere and tumor formation (32). Interestingly, the p63 protein shares a homologous DNA-binding domain with p53 and actively promotes the expression of CD44 (33). Combined, these results show the important role of...
CD44 in CSCs, tumor progression, and maintenance, and that CD44-target therapy could be effective in epithelial cancers. These results are promising for the therapeutic targeting of CD44 with monoclonal antibodies and blocking peptides, possibly in conjunction with EGFR.

CD24: Epithelial or Mesenchymal Marker?

The expression of CD24, or lack thereof, is a hallmark of a wide range of epithelial cancers and has recently been used as an indicator for the likelihood of metastasis (34, 35). The presence or absence of CD24 on the cell surface has been used as a marker for putative CSCs. Expression of CD24 in adult nonmalignant tissue is limited to B cells, granulocytes, and the stratum corneum (35, 36). CD24 is a 27–amino-acid single-chain protein that is heavily O- and N-glycosylated (37) and is bound to the extracellular membrane by a glycosylphosphatidylinositol anchor (38). The lack of an inner-membrane domain is interesting because CD24 has been implicated in several cancer-related signaling pathways.

Early results describe increased proliferation, cell adhesion, and migration when CD24+ cell lines are made to express the CD24 protein (36). Cell adhesion and growth are proposed to be increased in CD24-expressing cells by improved interactions between integrins and fibronectin (39). Recently, the function of CD24 in cell signaling has been tied to its possible role as the “gatekeeper” of lipid rafts, and it is involved in the recruitment of integrins to the complex (40). Along with increased cell adhesion, CD24 may have important roles in migration and invasion as measured by several in vitro assays (40) and association with metastasis in vivo (35, 41). However, recent results have called into question the role CD24 plays in migration and invasion in cancer. Breast and prostate CSCs (CD44+/CD24−) were found to have increased adhesion, invasion, and migration characteristics when compared with CD24-expressing cells (42), and prostate cells that were able to migrate through matrigel had suppressed CD24 expression along with decreased levels of E-cadherin (24). Also, recent reports show that breast CSCs have a mesenchymal phenotype (43).

The presence or absence of CD24 as a CSC marker seems to be tissue specific. CSCs have been well-defined populations in breast (CD44+/CD24−/low; ref. 2), prostate (CD44+/CD24−; ref. 14), and pancreatic (CD44+/CD24+/ESA+; ref. 12) cancers. As with other CSC markers, CD24 seems to have conflicting biological roles in tumors and metastasis. Baumann and colleagues (39) showed that CD24 could stabilize the kinase-active form of c-src and FAK in breast cancer cells, increasing proliferation and migration, and hypothesized that CD24− was the phenotype of CSC, whereas CD24+ drove tumor progression. Recently, CD24 has been implicated in playing a part downstream of the developmental hedgehog pathway that is often active in CSCs. Glioblastoma cells were found to express a truncated form of GLI1 (tGLI1), which could bind the promoter of CD24, increasing expression.

Also, tGLI1 induced migration, and invasion was dependent on CD24 expression (44), suggesting that CD24 is representative of a mesenchymal phenotype. However, conflicting results in oral SCC cell lines showed that silencing CD24 expression decreased E-cadherin mRNA, possibly by increasing expression of the EMT-related transcription factors SNAIL and TWIST. Also, the blocking of CD24 with a monoclonal antibody increased expression of E-cadherin as an epithelial marker (45). Furthermore, transformed breast cancer cells were able to transition between the mesenchymal CD44+/CD24− and epithelial CD44+/CD24+ phenotypes, which was dependent of Activin/Nodal signaling (43). Clearly, more work is required to determine the role of CD24 in cancer progression and metastasis, and whether that role is tissue dependent and a viable target for therapy.

CD133

The discovery of CD133 and its use as a marker of CSCs has recently been discussed in depth (46, 47). Briefly, human CD133 (Prominin-1) was discovered as the target of the AC133 monoclonal antibody, specific for the CD44+ population of hematopoietic SCs (HSC). CD133 is a glycosylated, ∼120-kDa protein with five transmembrane domains and two large extracellular loops (48, 49). Best known for being expressed on the tumor-initiating population of brain neoplasms (50), the CD133+ phenotype has recently been used to define the CSC populations in lung, pancreatic, liver, prostate, gastric, colorectal, and head and neck cancers, and CD133+ clearly generated tumors in immunocompromised mice more efficiently than CD133− populations (51–56). Recent findings in colon suggest that CD133 expression does not change upon differentiation, but tertiary conformational changes in differentiated colon cancer cells block the binding of the commonly used AC133 antibody (57). Unlike CD44, the biological role of CD133 has yet to be clarified. However, the properties and gene expression of cancer cells expressing CD133 have been carefully examined.

Along with the ability to generate tumors, CSCs have also been defined by resistance to traditional chemotherapies. Across tissues, CD133+ cells have had increased survival in vitro and have been enriched in vivo after treatment with cisplatin, etoposide, doxorubicin, and paclitaxel (51, 55). Not surprisingly, resistance to therapy has been tied to expression of genes known to be markers of “stemness.” Increased survival of the CD133+ population after cisplatin treatment has been coupled with the expression of ABC transporters, and more specifically, the CD133+/ABCG2+ subpopulation was enriched in lung xenografts (58). Also, radioreistance has been attributed to increased DNA-damage checkpoint activation by Chk1 and Chk2 in CD133+ glioma cells (59). Although actual interactions between expression of ABC transporters and DNA repair pathways have not been reported, it will be fascinating to discover if such a connection exists.
The expression of genes known to play important roles in the maintenance of SC populations has been investigated in putative CD133+ CSC populations of multiple tissues. Common “stemness” genes like Nestin, BMI1, Olig2, and Nanog are upregulated in CD133+ populations of brain, lung, liver, and prostate cancers (53, 54, 58, 60). Recently, OCT4 was identified as crucial in the maintenance of lung CSCs, and silencing of OCT4 led to loss of sphere formation, differentiation, and sensitization to chemotherapy (51). Also, the CXCR4 protein that is important for homing of SCs, and possibly metastasis in CSCs, is expressed in a subpopulation of CD133+ prostate cancer cells that showed increased migration (54).

Recently, connections between the CD133+ phenotype to EGFR signaling have been reported. The ability of glioma CSC lines to form spheres in culture requires EGF. EGFR signaling through Akt and ERK1/2 led to increased CSC characteristics, including sphere formation and expansion of the CD133+ population (61). Interestingly, CD133+ liver cell survival after treatment with chemotherapeutics was dependent on the upregulation of prosurvival Bcl-2 through Akt/PKB signaling (62), and lower levels of phosphorylated Akt after Notch inhibition increased apoptosis in glioblastoma cells (60). Hypoxic induction of HIF-1α by mammalian target of rapamycin (mTOR) downstream of PI3K led to the expansion of CD133+ glioma CSCs, which was enhanced by EGFR signaling, showing possible crosstalk between the two pathways (63). However, conflicting results in gastric cancer cells show decreased CD133 expression caused by upregulation of HIF-1α (56), pointing to a possible tissue-specific response to hypoxia. Although far from clear, hypoxia and EGFR signaling seem to be important to CD133+ CSC maintenance.

The developmental and SC-related hedgehog pathway is commonly upregulated in various cancers (64). In primary glioma cells, SHH was found to be highly expressed in CD133+ cells compared with CD133- cells. When treated with the SMO inhibitor cyclopamine, GLI1, PTCH1, NANOG, SOX2, and OCT4 were significantly downregulated in CD133+. Expression levels in CD133- were unaffected, and CD133+ cells were unable to form spheres (65). Similarly, in glioma xenographs, PTCH+ cells were enriched in the CD133+ population that highly expressed PTCH and GLI1 compared with the unsorted population. Interestingly, xenographs that didn’t express PTCH were unresponsive to cyclopamine treatment (66). Surely, more reports on hedgehog signaling in CD133+ CSCs of gliomas and other tissues will be forthcoming, including possible crosstalk with the EGFR pathway (67).

**Aldehyde Dehydrogenase Activity as a Marker of “Stemness”**

HSCs are partially distinguished by expressing high levels of ALDH genes, particularly ALDH1. With the generation of the CSC hypothesis, ALDH expression was investigated as a marker, and leukemia CSCs were determined to be highly ALDH positive (68-70). ALDH activity in normal and malignant SCs converts retinol to retinoic acid, which is crucial for differentiation pathways (71, 72). Traditional methods such as immunohistochemistry and blotting are used to detect levels of ALDH present in tissues and cells, but the method of choice to measure ALDH activity is by using BIODIPY aminoacetaldehyde (BAAA), commonly known as Aldefluor (73). Aldefluor consists of a BIODIPY fluorochrome attached to an aminoacetaldehyde moiety, which is a substrate of ALDH, and when cleaved, fluoresces and remains within the cell. In the past 4 years Aldefluor has been used to characterize CSCs in breast, lung, head and neck, colon, and liver tumors and cell lines (42, 53, 74-77).

Populations of CSCs in several solid cancers have already been well established and characterized by the presence and/or absence of cell-surface markers like the CD44+/CD24- cells with low expression, were found to be resistant than CD44+/CD24- cells, and one report shows CD44+/CD24-/ALDH+ cells are unable to form tumors at all (78, 79). In colon, ALDH activity enriched CSC populations defined by CD44+, CD133+, and CD44+/CD166+ (77, 80). Also, in liver and pancreatic cancers, ALDH expression enriches CD133+ and CD24+ CSC populations, respectively (53, 81).

In addition to important responsibilities in cell-signaling pathways, ALDHs play a special role in the oxidation of toxic aldehydes such as acetaldehyde during alcohol metabolism. This cellular function is likely crucial for SC longevity and probably a key explanation for the reported resistance of CSCs to chemotherapies, especially those that generate toxic aldehyde intermediates. HNSCC cells expressing high levels of ALDH1, compared with cells with low expression, were found to be resistant to cisplatin and cyclophosphamide (CPA), which are both converted into toxic aldehyde intermediates (75). Separate groups have found that shRNA and siRNA knockdown of ALDH1 in colorectal xenographs and lung cells, respectively, sensitized ALDH+ CSCs to CPA and 4-hydroperoxycyclophosphamide treatment (82, 83). Showing that resistance to therapy relies on more than one mechanism, Dylla and colleagues (82) determined that colorectal xenograft CSCs were resistant to irinotecan, but sensitivity was not enhanced by silencing ALDH1. Also, ALDH+ breast cancer cells are resistant to paclitaxel and epirubicin, and, interestingly, ALDH+ HNSCC cells are less sensitive to radiation than ALDH- cells (76, 78). Reduced sensitivity to radiation may be due...
more in part to the SC phenotype than to the expression of ALDH.

Although CSCs are enriched in ALDH\(^+\) populations in several tissues, it is important to acknowledge possible limitations, especially when used as a single marker. Enzymatic activity measured by Aldefluor is much more transient than the expression of traditional surface markers and may be altered by treatment of tumors or cells. Treating tumors and/or cells with chemotherapeutics and/or radiation to enrich for CSCs may induce ALDH activity in CSCs, as well as bulk tumor cells as a defense against toxicity, decreasing the usefulness of ALDH activity as a CSC marker. This activity could be avoided by simultaneously staining cells for ALDH activity, as well as for more stable markers (e.g., CD44, CD133). However, targeted suppression of ALDH1A1 activity by siRNA and/or shRNA could sensitize cells to traditional therapy.

**Side-Population Enrichment of CSC**

Hoechst 33342 is a DNA dye historically used for flow cytometric analysis of the DNA content of live cells (84). Although Hoechst is able to penetrate intact cell membranes, it is actively transported out of cells by ATP-dependent ABC transporters (85). More than a decade ago, Goodell and colleagues (86) established that a small fraction of cells isolated from bone marrow rapidly expressed the dye and were characterized by the lack of fluorescence when analyzed by flow cytometry. This fraction was highly enriched in HSCs, as measured by the ability to repopulate mouse bone marrow. These cells were also enriched for SCs when other tissues were analyzed (87). More recently, Hoechst has also been used to define CSC populations (88). These low-staining fractions of cells are now commonly known as the side population (SP).

The ability to efflux dye has been closely tied to the ABC family of transporters, but narrowing down the specific member has proven to be more difficult. ABCG2 has commonly been referenced as the SP generator, although in a range of cancer-cell lines only a fraction of SP cells were ABCG2\(^+\) (89). More likely, the SP is generated by activation of a range of transporters including ABCC1 (MDR1), ABCF2, ABCB2, ABCC7, and ABCA5, which are upregulated in the SP of various cells and may vary from tumor to tumor (90–92). However defined, the SP has been used to enrich putative CSCs in prostate, breast, glioma, ovarian, head and neck, liver, and thyroid cancers with the common characteristics of increased proliferation, clonogenicity, tumorigenicity, and drug resistance to doxorubicin, mitoxantrone, topotecan, SN-38, and methotrexate (89–91, 93, 94).

Evidence is growing that the SP is enriched in CSCs because of the upregulation of "stemness" genes when compared with the main population. In the SP of liver cancer cell lines, the Wnt pathway is highly expressed (90), whereas Notch-1 and \(\beta\)-catenin were found to be increased in MCF-7 cells (89). More recently, the SP phenotype has been more closely tied to signaling pathways. BMI1 was found to directly maintain the SP in liver cancer cells, whereas forced expression increased the population eightfold, and silencing of the protein led to differentiation (95). In breast cancer cells, transforming growth factor-\(\beta\) (TGF-\(\beta\))-induced EMT reduces the SP, along with reduced ABCG2 mRNA and surface-protein levels. However, silencing of E-cadherin decreased ABCG2 protein levels but not mRNA, leading to the conclusion that E-cadherin regulated ABCG2 at the post-translational level (92). Furthermore, TGF-\(\beta\)–EMT in pancreatic cancer cells occurs readily in SP cells but not in the main population (96), which could be a possible mechanism for CSC migration resulting in metastasis (97). Similarly, Akt inhibition in HNSCC and breast cancer cells resulted in the loss of ABCG2 from the cell surface, decreased SP, reduced doxorubicin efflux, and increased efficacy and/or apoptosis (98, 99). Although CSCs may not compose 100% of the SP, Hoechst efflux is a useful tool for the characterization of these cells.

**Conclusions**

Investigation of tumorigenic cells should be conducted given recent results showing that the populations responsible for driving tumor progression are actually in a transient phase of altered cell cycling, gene expression, and drug sensitivity, likely because of chromatin structure (100, 101). Alterations in chromatin and the resulting changes in gene expression highlight that CSC-marker expression is not static, but consistently shifting, be it during differentiation or continuously as an environmental response. Although the definition and origin of these CSC populations are constantly shifting with each breakthrough, the usefulness of targeting markers specific for these cells cannot be denied.

The SC-like properties of CSCs have been examined in more than a dozen tissues sharing common characteristics. These distinguishing markers are more frequently being connected to the CSC properties of drug resistance, proliferation, self-renewal, and metastasis. In the case of CD44, upregulated expression increases growth and has an anti-apoptotic effect, whereas CD24 is associated with the mesenchymal phenotype and invasiveness. Resistant CSCs may arise from increased expression of ABC transporters that can actively efflux drugs and increased ALDH enzymes that can destroy toxic intermediates. Not only are these markers important for defining aggressive and resistant populations, but targeting of these surface proteins with blocking antibodies and inhibition of ABC transporters and ALDH enzymes with small molecules may also prove useful in inhibiting tumor progression. At the present, CSC markers must be clearly defined for each tissue, and investigation is needed to determine whether
variations between tumors can be used as indicators of sensitivity to therapy. Finally, clarifying cellular and signaling functions of markers themselves will lead to more therapeutic options to destroy tumor cells that have the ability to repopulate.

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is specific and reveals that each contributes equally to the resistance against 4-hydroperoxycyclophosphamide. Cancer Chemother Pharmacol 2007;59:127–36.


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