HHS Public Access

Author manuscript

Cancer Transl Med. Author manuscript; available in PMC 2017 December 20.

Published in final edited form as:

Cancer Transl Med. 2017 ; 3(3): 87–95. doi:10.4103/ctm.ctm_69_16.

Stemness-Related Markers in Cancer

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Abstract

Cancer stem cells (CSCs), with their self-renewal ability and multilineage differentiation potential, are a critical subpopulation of tumor cells that can drive tumor initiation, growth, and resistance to therapy. Like embryonic and adult stem cells, CSCs express markers that are not expressed in normal somatic cells and are thus thought to contribute towards a ‘stemness’ phenotype. This review summarizes the current knowledge of stemness-related markers in human cancers, with a particular focus on important transcription factors, protein surface markers and signaling pathways.

Introduction

Individual tumors consist of a mixed cell population that differ in function, morphology, and molecular signatures. These tumors reside in and interact with their microenvironment, which consists of a wide variety of cell types and cellular structures, such as immune cells, fibroblasts, blood vessels, and the extracellular matrix. Tumor cells themselves can be of multiple clonal populations, each having accumulated unique molecular alterations over the course of tumor development and growth. In addition, tumor cells that are similar at the genetic level may have distinct modes of epigenetic regulation, further increasing the functional heterogeneity.

It has been hypothesized that only a small subset of tumor cells are capable of initiating and sustaining tumor growth; they have been termed cancer stem cells (CSCs) [1]. To date, CSCs have been isolated from many organs and confirmed to have stem cell-like abilities such as self-renewal, multilineage differentiation, and expression of stemness-related markers [2, 3]; some of these features are even confirmed by single cell analysis [4]. These cells may also play a role in disease recurrence after treatment and remission. As such, targeting of CSCs is currently an active area of therapeutic development.

CSCs are classified by the expression of stemness-related markers, which have been identified in embryonic stem cells (ESCs) and adult stem cells, the two main types of human stem cells. Here, we summarize current knowledge about molecular markers and pathways that are not only involved in normal stem cell maintenance and self-renewal, but also regulate the stemness of CSCs. Investigation of these features may help elucidate the mechanism of CSC-driven tumorigenesis and lead to novel approaches for CSC-targeted cancer therapies.

Stemness-Related Transcriptional Factors in Cancers

Yamanaka et al. [5] showed in 2006 that that pluripotent stem cells could be obtained from mouse embryonic fibroblasts by combined expression of four transcriptional factors (TFs) - now named the Yamanaka factors (Oct4, c-Myc, Sox2, and Klf4). Induced pluripotent stem (iPS) cells can now be derived from a wide range of somatic cells via the over-expression of a cocktail of TFs [6] or a combination of TF expression with chemical compounds [7, 8]. Moreover, somatic cells can now be directly reprogrammed into entirely different cell types [9] through the expression of lineage-specific sets of transcription factors. Yamanaka's seminal discovery has introduced the concept that the fate of adult somatic cells can be controlled through TF expression. From another perspective, expression of stem-cell specific TFs can provide a signature for characterizing cell type as well as indicating their functional role.

There are currently approximately 25 TFs that have been reported to be expressed in stem cells. Of them, OCT4, SOX2, KLF4, Nanog, and SALL4 comprise a core regulatory network for embryonic stem cell maintenance and self-renewal. These TFs are highly expressed in embryonic stem cells; in contrast, they are mainly silenced in normal somatic cells, except in small groups of adult stem cell populations. Increasing evidence has shown that embryonic specific TFs are abnormally expressed in human tumor samples [10, 11], suggesting the presence of cancer stem cells. Retrospective studies on patient cohorts have also associated TF expression with survival outcomes in specific tumor types, suggesting that TF expression levels may also be useful for assessing patient prognosis[12]. Thus, detecting the expression level of these TFs, for example by immunohistochemistry staining, can aid in tumor diagnosis, classification, and therapeutic strategies.

A summary of these CSC TFs is shown in Table 1. These TF markers are also classified by tissue type, shown in Table 2. A few examples are listed here:

Oct4—OCT4 expression has been detected in human brain, lung, bladder, ovarian, prostate, renal, testicular tumors, and leukemia, [12] both by RT-PCR and immunohistochemistry. Furthermore, high expression of OCT4 has been associated with poor prognosis in bladder cancer [13, 14], prostate cancer [15], medulloblastoma [16], and esophageal squamous cell carcinoma (ESCC) [17].

Sox2—SOX2 has been found in brain, breast, lung, liver, prostate, and testicular tumors [12, 18, 19]; and its expression has been correlated with poor prognosis in stage I lung adenocarcinoma [18], squamous cell carcinoma [20, 21], gastric carcinoma [22-24], small cell lung cancer [25-28], and ovarian carcinoma [29, 30].

Kfl4—KLF4 has been found to be expressed in brain, breast, head and neck, oral, prostate, and testis tumors, as well as in leukemia and myeloma [12]. Expression of KLF4 can also be as a prognostic predictor for colon cancer [31] and head neck squamous cell carcinoma [24, 32]. In addition, nuclear localization of KLF4 has been associated with the aggressive phenotype of early-stage of breast cancer [33], as well as worse prognosis in nasopharyngeal [34] and oral cancers [35].

Nanog—Nanog has been shown to be expressed in brain, breast, prostate, colon, liver and ovarian tumors [36]. High expression of Nanog promotes the epithelial-mesenchymal transition (EMT) [37], which is an important developmental process for cancer cells to obtain stem cell characteristics. Nanog has also been associated with poor prognosis in breast [38], colorectal [39, 40], gastric [41], lung [42, 43], ovarian [44] and liver cancers [45].

Sall4—SALL4 expression has been detected in breast, liver, colon, ovarian, and testis cancers, and leukemia [46, 47]. The expression of SALL4 has been studied as a poor prognosis marker in hepatocellular carcinoma [48, 49], gliomas [50], and myelodysplastic syndromes [51].

C-myc—C-myc is an important transcriptional factor both in stem cells and cancers. As one of the most studied oncogenes, overexpression of C-myc has been shown to cause tumorigenesis in mouse models. Up to 70% of human cancers exhibit c-myc overexpression, including brain, breast, colon, head and neck, pancreas, prostate, renal, salivary-gland, and testis tumors, as well as leukemia and lymphoma [12, 52, 53]. C-myc expression has also been correlated with poor prognosis in hepatocellular carcinoma [54] and early carcinoma of uterine cervix [55, 56].

Stemness-Related Surface Markers in Cancers

Cell surface proteins provide a feasible way for isolating and studying different cell types by flow cytometry or magnetic sorting. In addition, they are amenable for specific targeting, which is useful for disease monitoring and therapeutic delivery. Similar to stemness-related transcription factors, many surface markers that are highly expressed in stem cells are also expressed in human cancers as TRA-1-60, SSEA-1, EpCam, ALDH1A1, Lgr5, CD13, CD19, CD20, CD24, CD26, CD27, CD34, CD38, CD44, CD45, CD47, CD49f, CD66c, CD90, CD166, TNFRSF16, CD105, CD133, CD117/c-kit, CD138, CD151 and CD166. Table 2 describes most of the stemness-related surface markers and the tumor types they have been found to be expressed in. Among them, CD44 and CD133 are the most widely-used markers in CSC research and are also therapeutic targets in cancers.

CD44 is a transmembrane glycoprotein that plays different roles in cell division, migration, adhesion, and signaling [57]. It is normally expressed in both fetal and adult hematopoietic stem cells; and upon binding to hyaluronic acid, its primary ligand, CD44 mediates cell-cell communication and signal transaction. CD44 is highly expressed in many types of cancers include bladder, breast, colon gastric, glioma, head and neck, osteosarcoma, ovarian, pancreatic, and prostate cancers, as well as leukemia [58][59]. CD44 is being studied as a therapeutic target in metastasizing tumors such as breast and colon cancer [60, 61], and also in leukemia [62].

CD133 is another transmembrane glycoprotein, and specifically localizes to cellular protrusions. CD133 is reported to be expressed in hematopoietic stem cells, endothelial progenitor cells, glioblastoma, and neuronal and glial stem cells [63, 64], and it is involved in cell growth and development [65]. Almost all tumor types can be detected with CD133 expression; and CD133+ tumor cells show stem cell-specific characteristics such as self-

renewal, differentiation, and tumor formation in NOD-SCID mouse model [66]. After injection into immune-compromised mice, CD133+ cells also show chemo- and radio-resistance [66]. Studies has been pursued to use CD133 as a potential therapeutic target in colon cancer [67], ovary cancers [68], and metastatic melanoma [69]. CD133 has also been used as a target for drug delivery [70].

There are a number of other CSC surface markers that appear to function in specific types of tumors. For examples, SSEA-1 has been shown to be expressed in human colonic adenocarcinoma and glioblastoma [71, 72]. Similarly, TRA-1-60 has been associated with prostate tumors [73]. Lgr5 has been shown to be expressed in head and neck, colon and gastric tumors [74, 75]. CD90 has been detected in high grade human glioma [76, 77], as well as liver [78] and lung tumors [79, 80]; while CD117 has been used as a CSC marker in leukemia [81, 82] and gastrointestinal stromal tumor [83], as well as oral squamous cell carcinomas [84, 85] and ovarian tumors[86, 87]. CD117 has been shown to be overexpressed in hepatocellular [88] and pancreatic carcinoma[89]. CD24 has been used in combination with CD44 in breast cancer cell lines to show that CD44+/CD24- cancer cells exhibit drug resistance and invasive properties [90-92]. Studies have also shown that CD24 can be used as an independent prognostic marker non-small cell lung cancer [93, 94] and ovarian cancer [95].

Other Important Stemness-Related Markers

There are a number of stemness-related markers that are neither TFs nor cell surface proteins, which include ALDH, Bmi-1, Nestin, Musashi-1, TIM-3 and CXCR. The ubiquitous family of aldehyde dehydrogenase (ALDH) enzymes catalyzes the irreversible oxidation of cellular aldehydes in the cytoplasm. High activity of ALDH enzymes have been found in ESCs, adult hematopoietic and neural stem cells, as well as CSCs. ALDH activity in CSCs has been attributed to ALDH1A1 expression, which can regulate stem cell self-protection, differentiation, and population expansion. ALDH has been reported to have prognostic significance in head and neck squamous cell [96] and esophageal squamous cell carcinomas [97]. It is also being pursued as a therapeutic target in ovarian [98, 99] and non-small cell lung cancers [100].

BMI1 is a protein required for hematopoietic stem cell self-renewal [101] and neural stem cells [102]. Drug-induced expression of BMI1 has been shown to enhance stem cell populations in head and neck cancer models [103]. BMI1 has been reported as a marker for poor prognosis in oligodendroglial tumors [104] and breast cancer [105, 106]. Nestin and Musashi-1 have been detected in neural stem cells [107], where they both play an important role in stem cell self-renewal and maintenance. Nestin expression has been shown in transformed cells of various human malignancies, correlating with the clinical course of some diseases [108]. Furthermore, co-expression of Nestin with other stem cell markers was described as a CSC phenotype [109]. Nestin was reported as a potential target for tumor angiogenesis [110, 111]. Musashi-1 signaling was also detected in hematopoietic stem cells and it is being investigated as a potential therapeutic target and diagnostic marker for lung cancer [112].

Chemokines are small peptide molecules secreted by cells that affect the movement of neighboring cells, thus mediating cellular homing and migration. They are crucial for normal physiological functions, and are found to be dysregulated in cancers. The chemokine CXCL12 (SDF-1) and its receptor CXCR4 regulate cellular chemotaxis, cell adhesion, survival, proliferation, and gene transcription through multiple divergent pathways. CXCL12/CXCR4 interactions were shown to play an important role in the migration of hematopoietic stem cells [113]. CXCR4 is overexpressed in more than twenty cancer types, with discovered roles in tumor growth, invasion, angiogenesis, metastasis, relapse, and therapeutic resistance [114]. CXCR4 antagonists have been shown to disrupt tumor–stromal cell interactions, sensitize cancer cells to cytotoxic drugs, and reduce tumor growth and metastasis. Therefore CXCR4 is considered as a target for therapeutic intervention of lung [115][116] and breast cancer [117, 118]. It has also been used for noninvasive monitoring of disease progression and therapeutic guidance [114].

Stemness-Related Pathways

Stem cell maintenance, self-renewal, and differentiation pathways are involved in embryonic development and adult tissue homeostasis. Cancers commonly display aberrant activities within these pathways, often in a cell-context dependent manner. Here we discuss current evidence for Hedgehog (HH), Notch, JAK/STAT, PI3K/Akt/mTOR and Wnt/β-catenin pathway regulation in CSCs.

Hedgehog (Hh) pathway—The Hedgehog (Hh) pathway is a major regulator in vertebrate embryonic development, playing critical roles in stem cell maintenance, cell differentiation, tissue polarity, and cell proliferation, as well as EMT [119]. Hedgehog ligands (Desert Hedgehog, Sonic Hedgehog and Indian Hedgehog) bind to Ptch, activating a cascade of downstream signals that lead to the activation and nuclear localization of TFs, consequently followed by expression of genes that are involved in survival, proliferation, and angiogenesis [120]. Hedgehog signaling has been widely implicated in CSC self-renewal and cell fate determination [120], and is considered a potential therapeutic target in breast cancer and pancreatic cancer [121-123],

Notch pathway—Notch signaling is a critical part of stem cell fate determination and angiogenesis. Notch signaling is predominantly involved in cell-cell communication between adjacent cells through transmembrane receptors and ligands. In human ESCs, Notch signaling governs cell-fate determination in the developing embryo and is required for undifferentiated ESCs to develop all three embryonic germ layers [124]. In CSCs, it controls tumor immunity and CSC population maintenance [125, 126]. Notch signaling is frequently dysregulated in cancers, providing a survival advantage for tumors. In certain tumor types, activation of Notch signaling aids CSCs in maintaining their population in tumors, inducing EMT, and acquiring chemoresistance [127] Notch signalling is potential target for cancers [128, 129].

JAK/STAT pathway—The JAK-STAT signaling pathway is important in cytokine-mediated immune responses and known to be involved in many biological processes such as proliferation, apoptosis, and migration, as well as the regulation of stem cells. Cancer cells

also show frequent dysregulation of the JAK/STAT. Studies in *Drosophila* first implicated JAK-STAT signaling in the control of stem cell maintenance in the male germline stem cell microenvironment [130][131]. Tightly controlled JAK-STAT signaling is required for stem cell maintenance and self-renewal. Furthermore, JAK-STAT activity is essential for anchoring the stem cells in their respective niches by regulating different adhesion molecules.

PI3K/Akt/mTOR pathway—The phosphatidylinositol-3-kinase (PI3K)/Akt and the mammalian target of rapamycin (mTOR) signaling pathways are crucial to stem cell proliferation, metabolism and differentiation. This pathway is frequently improperly regulated in human cancers [132]. Over 70% of ovarian cancers have active PI3K/Akt/mTOR pathway, making it a therapeutic target in this cancer type [133, 134], it is also a therapeutic target for neuroblastoma [135], endometrial cancer [136], and acute myeloid leukemia [137].

Wnt/β-catenin pathway—Pathways induced by Wnt ligands are highly evolutionarily conserved. Given their strong conservation in phylogeny, it is not surprising that Wnt pathways also play key roles in regulating stem cell differentiation and pluripotency. Consistently in many tissue types, dysregulation of Wnt pathway has been strongly associated with expansion of stem and/progenitor cell lineages, as well as carcinogenesis [138]. Hence, therapies targeting Wnt pathway may lead to treatment options in hematological malignancies [139], liver cancer [140], and other type of tumors [141].

Conclusion

A primary goal in cancer research is to identify mechanisms driving drug resistance, and recent studies have implicated CSCs in intrinsic resistance models. Similar to normal stem cells, the abilities of self-renewal, maintenance, and differentiation of CSCs serve as a core reservoir for cancer initiation, development, and growth. The overexpression of stem cell specific TFs may contribute to the pathologic self-renewal characteristics of cancer stem cells while the surface molecules mediate interactions between cells and their microenvironment. Other stemness-related markers and pathways may promote cancer cell proliferation, progression, and metastasis. Our summary of stem cell markers by tissue types and cellular locations in Table 2 and Figure 1 highlights the complex nature of CSC regulation, which appears utilize different pathways in different cell or tissue types. This context-dependency makes it hard to find overarching CSC pathways and makers. Understanding the stemness-related features in cancers will not only provide important knowledge on molecular mechanisms for cancer pathogenesis, but also shed new light on development of effective therapeutic approaches specifically targeting these stemness-related features.

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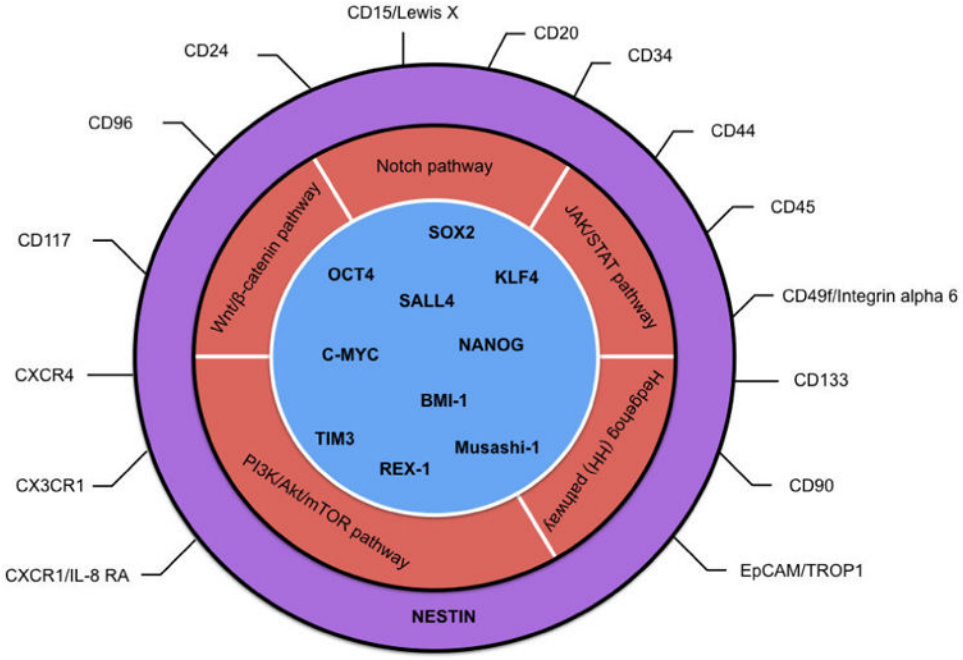

Figure 1.
Categories of cancer stem cell markers.

Cancer Transl Med. Author manuscript; available in PMC 2017 December 20.

Table 1

Stemness-Related Transcriptional Factor (TF) Markers in Cancer

Marker	Other names	Function in stem cell	Characteristics	Expressed in Tumor types	Poor prognosis for tumor types	Selected Refs
OCT4	Oct3/4 or POU5F1	Stem cell self-renew and poluropotency maintenance	Oct family of POU transcription factor.	Leukemia, Brain, Lung, Bladder, Ovarian, Pancreas, Prostate, Renal, Seminoma, Testis	• Esophageal squamous cell carcinoma • Medulloblastoma • Prostate cancer • Blader cancer	[11-16]
SOX2		Stem cell self-renew and poluropotency maintenance	POU family binder transcription factor	Brain, Breast, Lung, Liver, Prostate, Seminoma, Testis	• Stage I lung adenocarcinoma • Squamous cell carcinoma • Gastric carcinoma • Small cell lung cancer • Ovarian carcinoma	[11],[17-29]
KLF4		Stem cell self-renew and poluropotency maintenance	Zinc-finger transcription factor	Leukemia, Myeloma, Brain, Breast, Head and neck, Oral, Prostate, Testis	• Breast cancer • Nasopharyngeal carcinoma • Colon cancer • Head and neck squamous cell carcinoma • Oral cancer	[27],[30-34]
C-MYC		Stem cell self-renewal	Transcription factor and an oncogene	Leukemia, Lymphoma, Myoloma, Brain, Breast, Colon, Head and Neck, Pancreas, Prostate, Renal, Salivary-gland, testis	• Hepatocellular carcinoma • Early carcinoma of uterine cervix	[11],[51-55]
Nanog		Stem cell self-renew and poluropotency maintenance	Transcription factor	Brain, Breast, Prostate, colon, liver, Ovarian,	• Breast cancer • Colorectal cancer • Gastric adenocarcinoma • Non-small cell lung cancer • Ovarian Serous Carcinoma • Liver cancer	[36-44]

Marker	Other names	Function in stem cell	Characteristics	Expressed in Tumor types	Poor prognosis for tumor types	Selected Refs
SALL4		Stem cell self-renew and poluropotency maintenance Differentiation regulation	Zinc finger transcription factor and an oncogene	Leukemia, Breast, Liver, Colon, Ovarian, testis	• Hepatocellular carcinoma • Gliomas • Myelodysplastic syndromes	[47-50]

Table 2

Stemness-Related Markers in Different Cancer Types

Leukemia	Bladder	Breast	Colon	Gastric	Glioma/Medulloblastoma	Head and Neck	Liver	Lung	Melanoma	Myeloma	Osteosarcoma	Ovarian	Pancreatic	Prostate
	ALDH1A1	ALDH1A1	ALDH1A1	ALDH1A1		ALDH1A1		ALDH1A1					ALDH1A1	ALDH1A1
CD34	CD47	CD49f/Integrin alpha 6	CD166		CD49f/Integrin alpha 6		CD45		TNFRSF16	CD27/TNFRSF7		Endoglin/CD105	CD24	CD49f/Integrin alpha 6
CD38		CD24	CD24				CD24			CD38		CD24	CD24	CD151
CD44	CD44	CD44	CD44	CD44	CD44	CD44					CD44	CD44	CD44	CD44
		CD133	CD133		CD133		CD133	CD133	CD133			CD133	CD133	CD133
CD47		CD90	CD26	CD15/Lewis X	CD15/Lewis X		CD13			CD20/MS4A1				CD166
CD96			CD29		CD90/Thy1		CD90/Thy1	CD90/Thy1		CD19				TRA-1-60(R)
CD117/c-kit								CD117/c-kit				CD117/c-kit		
CD123/IL-3 R alpha	CEACAM-6/CD66c						Aminopeptidase N/CD13		CD166/ALCAM	CD138Syndecan-1				ALCAM/CD166
			Lgr5/GPR49	Lgr5/GPR49		Lgr5/GPR49								
		EpCAM/TROP1	EpCAM/TROP1					EpCAM/TROP1					EpCAM/TROP1	
		CXCR4			CXCR4								CXCR4	
		CXCR1/IL-8 RA			CX3CR1									
BMI-1		BMI-1	BMI-1			BMI-1							BMI-1	BMI-1
					Nestin				Nestin		Nestin		Nestin	
			Musashi-1		Musashi-1									
c-Myc		c-Myc	c-Myc		c-Myc								c-Myc	c-Myc
		SOX2			SOX2		SOX2	SOX2						SOX2
OCT4	OCT4											OCT4	OCT4	OCT4
KLF4		KLF4												KLF4
		Nanog	Nanog				Nanog					Nanog		Nanog
SALL4		SALL4	SALL4				SALL4					SALL4		SALL4
TIM3														Rex1