Cancer Stem Cell:

Review Article

Cancer stem cell: A rogue responsible for tumor development and metastasis

Aditi Kapoor, Sudhir Kumar

School of Biotechnology, International Institute of Information Technology, Pune, Maharshtra, India

Correspondence to: Dr. Sudhir Kumar, E-mail: sudhirk@isquareit.ac.in

Abstract

Cancer stem cells are a small population of cells in a tumor. They have the ability to self-renew and maintain the tumor. The most apt and accepted hypothesis for tumor development is Cancer Stem Cells. This review focuses on this concept of cancer stem cells, serving their purpose and leading to the development of tumor. There are many cell biomarkers which have been described for the identification and characterization of cancer stem cells. The most prominent of the cellular markers for the detection of cancer stem cells; CD133, CD44, ALDH-1 along with some others have been discussed in detail in this review.

Key Words: Clonal evolution, multi-potency, oncogenes, pre-cancerous stem cells, self-renewal, tumor suppressor genes

Introduction

Carcinogenesis is a complex and multi-step process. A normal cell is stressed and transformed into cancer cells.[1] This often requires concordant expression of a number of genes, including multiple genetic and epigenetic changes in oncogenes, tumor-suppressor genes, cell-cycle regulators, cell adhesion molecules, DNA repair genes and genetic instability as well as telomerase activation.[2-12]

Based on the heterogeneity of cancer cells, several models have been proposed to explain cancer development. The stochastic model claims that all cancer cells can reproduce phenotypically heterogeneous cell types in new tumors.[13] However, this model cannot explain why cancer is highly heterogeneous. The cancer stem cell hypothesis may resolve the issue. It emphasizes that only a tiny population of cancer cells has the capability to produce phenotypically heterogeneous cells in new tumors; other cells only have limited proliferative capacity. Accordingly these cells have stem-like properties, having the capability of self-renewal and multi-potency of differentiation, and thus are called Cancer Stem Cells (CSCs).[14-19]

If cancer stem cells are relatively refractory to therapies that have been developed to eradicate the rapidly dividing cells within the tumor that constitute the majority of the non-stem cell component of tumors, then they are unlikely to be curative and relapses would be expected. If correct, the cancer stem cell hypothesis would require that we rethink the way we diagnose and treat tumors, as our objective would have to turn from eliminating the bulk of rapidly dividing but terminally differentiated components of the tumor and be refocused on the minority stem cell population that fuels tumor growth. This explains why the cancer stem cell hypothesis is at the center of a rapidly evolving field that may play a pivotal role in changing how basic cancer researchers, clinical investigators, physicians, and cancer patients view cancer.[20]

Though the idea of cancer stem cells is considered as a new concept in science, it was thought almost 35 years back in 1971 when they were called as leukemic stem cells. A small subset of cancer cells capable of extensive proliferation in leukemia and multiple myeloma were found and named as leukemic stem cells.[21] Two possibilities were proposed: Either all leukemia cells had a low probability of proliferation and therefore all leukemia cells behave as LSC, or only a small subset was clonogenic. The later theory was favored by Dick and colleagues who were able to separate the LSC as $CD34^{+}$ $CD38^{-}$ from patients' samples.[22] Recently, the cancer stem cells were also shown in the solid tumours such as breast cancer and brain tumours.[23,24]

Cancer stem cells identification, isolation and characterization related discoveries and major research developments which have been highlighted in a consolidated form in Table 1.

However, this hypothesis is controversial and has been challenged by recent studies, which argue for a long-standing cancer model, well known as clonal evolution.[37-39] The clonal evolution model claims that normal cells mutate and generate abnormal offspring that also mutate, forming a mass of genetically varied cancer cells.[40] At least two hits of oncogenic mutation may be required.[41,42] Practically, clonal evolution as a mechanism appears to underlie CSC development.[43]

Emerging Concept of pCSCs

It has been identified that a new type of cancer cell from murine lymphoma, represents an early stage of CSC development but similar to pre-cancer in clinical origin, having the potentials of both benign and malignant differentiation. Therefore, it was named as 'pCSCs'.[43,44]

Theoretically, all cells that are hit by carcinogens have the potential to develop into Tumor Initiating Cells (TICs). Practically, the cellular processes of TIC → pCSC → CSC → cancer should parallel the histological process of hyperplasia/metaplasia (TIC) → pre-cancerous lesions (pCSC) → malignant lesions (CSC → cancer) [Figure 1].[43,45-52] While clonal evolution dissects the molecular basis of cancer development, the CSC hypothesis pinpoints the same cellular origin of the primary, metastatic and recurrent cancer.[53,54] The gap between these two models can be resolved with identification of pCSCs. The existence of pCSCs in tumors strongly implies that CSC can be derived from the precursors through a mechanism of clonal evolution, or that the target cells of clonal evolution are the precursors of CSCs. Preliminary studies suggest that the progression of pCSCs to CSCs is associated with

Access this article online

Quick Response Code:

Website: www.indianjcancer.com

DOI: 10.4103/0019-509X.146794

Table 1: Cancer stem cells – First identified and isolated – Time line

Year	Discovery	Reference
1994	First separation of cancer stem cells from the majority of cells in a cancer (Canada) - leukemia.[22,25]	Lapidot *et al.*, 1994 Bonnet *et al.*, 1997
1999	Stem cells discovered and isolated from human brain.[26]	Johansson *et al.*,1999
2003	Successful isolation of cancer stem cells from different phenotypes of brain tumors.[27]	Singh *et al.*, 2003
2003	Breast cancer stem cells discovered at the U-M Comprehensive Cancer Centre.[16]	Al-Hajj *et al.*, 2003
2005	First evidence for human bone cancer stem cells (USA).[26]	Gibbs *et al.*, 2005
2005	Prostate cancer stem cells isolated.[28]	Collins *et al.*, 2005
2005	Melanomas contain cancer-stem-cell-like populations.[29]	Fang *et al.*, 2005
2005	First study on the isolation and identification of stem-like cells in ovarian cancer.[30]	Bapat *et al.*, 2005
2007	First evidence for human colon cancer stem cells (Canada).[31]	Ricci-Vitiani *et al.*, 2007
2007	First evidence of cancer stem cell populations in head and neck squamous cell carcinoma.[32]	Prince *et al.*, 2007
2007	Pancreatic cancer stem cells identified for the first time.[33]	Li *et al.*, 2007
2008	Identification of lung cancer stem cell population.[34]	Eramo *et al.*, 2008
2009	Identification of tumor-initiating cells with stem-lie properties in cervical cancer.[35]	Feng *et al.*, 2009
2011	Two distinct cancer stem cell phenotypes in squamous cell carcinoma.[36]	Biddle *et al.*, 2011

hierarchical genetic alterations, a process resembling clonal evolution.[55] Therefore, the concept of clonal evolution may be integrated into the CSC hypothesis. CSCs are a small population of stem cell-like cancer cells, derived from a precursor undergoing clonal evolutionary pre-cancerous mutations. Whether pCSCs progress to CSCs depends on the effect of environmental cues on the clonal evolution.[43,56] The stem-like property of pCSCs and CSCs does not mean that they are exactly the same as Normal Stem Cells with regard to the capacity of self-renewal and multi-potency of differentiation. Their capacity for self-renewal is impaired

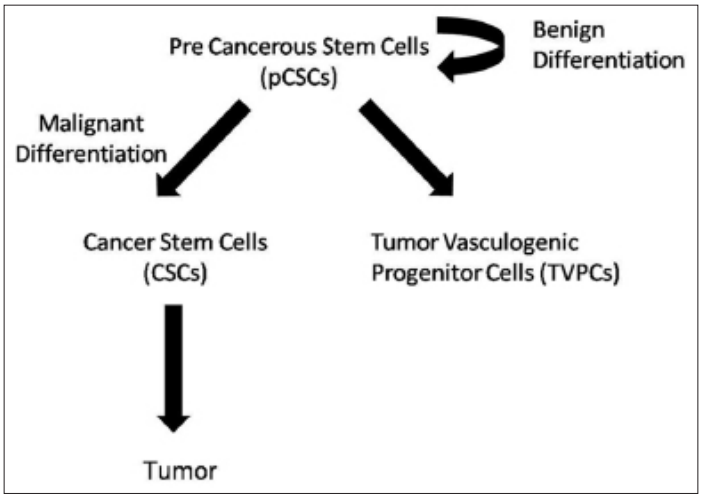

Figure 1: Clonal evolution hypothesis for tumor development

and multi-potency of differentiation is incomplete, compared to Normal Stem Cells.[43,57] While pCSCs are considered as the precursors of CSCs, the ultimate origin of CSCs has not been completely resolved. Based on the limited literature, the origin of CSCs can be adult stem cells, progenitors or actively replenished proliferating cells such as the precursor of epithelial cells.[41,58] This may be true. Since multiple genetic mutations are required for cell transformation, sufficient cell cycles are necessary for accumulating the DNA-damage-induced mutations.[59-62]

The functional definition for pCSCs appears to be reliable, because of successful establishment of a CSC clone (326T) from a mouse with thymoma, which does not have the potential for benign differentiation.[63]

Tumor neo-vascularization is critical for tumor growth, invasion and metastasis, which has been considered to be mediated by a mechanism of angiogenesis.[64] However, histopathological studies have suggested that tumor cells might be the progenitor for tumor vasculature.[65] It has been reported that in the pCSC-derived tumors, most blood vessels were derived from pCSCs.[66] Some pCSCs constitutively expressed vasculogenic receptor, VEGFR-2, which can be up-regulated by hypoxia and angiogenesis-promoting cytokines such as GM-CSF, Flt3 ligand, and IL-13.[67-70] The pCSCs are much more potent in tumor vasculogenesis than the differentiated tumor monocytic cells (TMCs) from the same tumor, which had comparable or even higher capacity to produce some vascular growth factors, suggesting that the potent tumor vasculogenesis of pCSCs is associated with their intrinsic stem-like property.[71] Consistently tumor vasculogenesis was also observed in human cancers such as cervical cancer and breast cancer and xenograft lymphoma. Studies indicate that pCSCs can serve as tumor vasculogenic stem/progenitor cells (TVPCs), and may explain why anti-angiogenic cancer therapy trials are facing challenge.[67]

Cancer Stem Cell Markers

CD133

The novel cell-membrane protein CD133, whose biological function is although not well understood, has been identified

as a marker of a subset of neural stem cells in the adult central nervous system as well as of glioblastoma stem-like cells.[27,72] $CD133^+$ cancer stem cells have a capacity for unlimited self-renewal, as well as the ability to initiate and drive tumor progression in an animal model.[72] Cancer and normal stem cells share the same self-renewal mechanisms, such as the Bmi-1 and Wnt canonical pathways.[73,74] $CD133^+$ cells expressed higher levels of CD90, CD44, Nestin, Msi1, MELK, GLI1 and PTCH. Particularly, Bmi-1, PSP, SHH, OCT4 and Snail were only expressed on $CD133^+$ cells; none of the five genes were detectable on $CD133^-$ tumor cells.[75] $CD133^+$ cancer stem cells are significantly resistant to four tested chemotherapeutic agents, including temozolomide, carboplatin, VP16 and Taxol than autologous $CD133^-$ cells.[75] One of the important mechanisms of drug resistance is the expression of ATP-binding cassette transporter protein, such as BCRP1. $CD133^+$ cells express higher levels of BCRP1, which indicate that BCRP1 may also play an important part in the drug resistance of $CD133^+$ cells.[76] BCRP1 over-expressing tumor cells; however, are only resistant to mitoxantrone, adriamycin, daunorubicin, etoposide, topotecan, and irinotecan. They are not resistant to Taxol and vincristine.[77] Therefore, it has been proposed that both anti-apoptosis factors and BCRP1 contribute the drug resistant property on $CD133^+$ cancer stem cells.[75]

Neural stem cells (NSCs) express nestin and CD133, and differentiate into neurons, astrocytes and oligodendrocytes at a clonal level.[78] An important characteristic of NSCs, not fully understood, is their migratory ability and their tropism to brain pathology. High expression levels of functional chemokine receptor CXCR4 have been found on human neural stem cells.[79] Thus, CXCR4 may play a significant role in directing NSC migration during CNS development. Similar to normal NSCs, $CD133^+$ cancer stem cells showed 337.8 times increase on the expression levels of CXCR4 than did $CD133^-$ cells, which suggests $CD133^+$ cancer stem cells have higher capability of migration and may play an important role in glioma invasion.[75] Cell lines derived from $CD133^+$ CSC showed neurosphere-like growth.[27,72,80-83] However, some cell lines derived from primary glioblastomas grew as adherent spheres within a dense network of differentiated cells and were maintained by $CD133^-$ cells that display infinite potential for self-renewal. Pluri-potency was confirmed by expression of neuronal, astrocytic, and oligodendroglial lineage markers.[83] To confirm that the small subpopulation of $CD133^-$ tumor cells is rightly referred to as CSC, evidence for their selective capability to drive tumor growth *in vivo* is needed. Because there is no surface marker allowing the separation of $CD133^-$ CSC from $CD133^-$ cells lacking stem cell properties, experiments similar to those done with the purified $CD133^+$ CSC subset are not feasible yet.[72] The observation that adherent $CD133^-$ cell cultures are tumorigenic *in vivo*, whereas $CD133^-$ cells from neurosphere-like $CD133^+$ CSC lines do not form tumors in nude mice, is the strongest currently obtainable evidence for the existence of $CD133^-$ CSC consequently referred to as $CD133^-$ CSC. Because only the total number of adherent $CD133^-$ cells injected into immunodeficient mice is known, how many $CD133^-$ CSCs are required to induce tumor formation *in vivo* cannot be determined.[84]

CD133 has been identified as a stem cell maker for human leukemia, brain tumors, and prostate cancer. Also, only a small proportion (<5%) of cells in the Hep-2 cell line expressed CD133. $CD133^+$ cells possess a marked capacity for self renewal, extensive proliferation, and multi-lineage differentiation potency *in vitro*. Thus, CD133 is one of the markers for cancer stem cells in human laryngeal tumors.[85] Colon cancer stem cells are believed to originate from a rare population of putative $CD133^+$ intestinal stem cells. A small subset of colon cancer cells express CD133, and only these $CD133^+$ cancer cells are capable of tumor initiation.[86] $CD133^+$ colonic tumor cells express epithelial cell adhesion molecule (EpCAM). Similarly, $CD133^+$ is widely expressed by human primary colon cancer epithelial cells, whereas the $CD133^-$ population is composed mostly of stromal and inflammatory cells. Conversely, CD133 expression does not identify the entire population of epithelial and tumor-initiating cells in human metastatic colon cancer. Indeed, both $CD133^+$ and $CD133^-$ metastatic tumor subpopulations formed colonospheres in '*in vitro*' cultures and were capable of long-term tumorigenesis in a NOD/SCID serial xenotransplantation model. Moreover, metastatic $CD133^-$ cells form more aggressive tumors and express typical phenotypic markers of cancer-initiating cells, including CD44 ($CD44^+CD24^-$), whereas the $CD133^+$ fraction is composed of $CD44^{low}CD24^+$ cells. CD133 expression is not restricted to intestinal stem or cancer-initiating cells, and during the metastatic transition, $CD133^+$ tumor cells might give rise to the more aggressive $CD133^-$ subset, which is also capable of tumor initiation in NOD/SCID mice.[86]

Prospectively isolated $CD133^+$ cells and/or side population (SP) cells in endometrial cancer were capable of initiating tumor formation and of recapitulating the phenotype of the original tumor, and therefore are candidate for endometrial cancer stem cells.[87] High expression of CD 133 has also been reported in 4T1 mouse breast cancer cells.[88] Identification of a cancer stem cell population has been reported in Hepatocellular Carcinoma characterized by their CD133 phenotype.[89] Human pancreatic cancer tissue contains cancer stem cells defined by CD133 expression that are exclusively tumorigenic and highly resistant to standard chemotherapy. In the invasive front of pancreatic tumors, a distinct subpopulation of $CD133^+$ $CXCR4^+$ cancer stem cells was identified that determines the metastatic phenotype of the individual tumor.[90] CD133 expression defines a NOD/SCID tumor initiating subpopulation of cells in human ovarian cancer that may be an important target for new chemotherapeutic strategies aimed at eliminating ovarian cancer.[91] CD133 has also been used to identify normal and cancer stem cells from several different tissues, such as renal epithelial or kidney cancer cells [Figure 2].[92]

CD200

Recently the glycoprotein CD200, expressed within the innate immune system and other tissues and cells, was shown

to be involved in tolerance. CD200 co-expression with stem cell markers found on prostate, breast, brain, and colon cancers has been described. This is the first report describing an immunomodulatory molecule on epithelial cancer stem cells. This important finding suggests a mechanism by which a tumor might evade immune system detection [Figure 3].[93]

CD117

Gastrointestinal stromal tumors (GISTs) represent a distinct and the most important subset of mesenchymal tumors of the GI tract. These tumors are both phenotypically and genotypically different from true leiomyomas and usually express CD34, a hematopoietic progenitor cell antigen. CD34 however, is also present in a wide variety of fibroblastic and endothelial cell tumors. CD117, the c-kit proto-oncogene product is expressed in subsets of hematopoietic stem cells, mast cells, melanocytes, and interstitial cells of Cajal of the GI tract. CD117 was almost always (85%) expressed in both benign and malignant GISTs. CD117 was observed both in the spindle cell and epithelioid subtypes of GISTs in all locations. In addition to reacting with the $CD34^+$ GISTs, CD117 was positive in some $CD34^-$ cases. These results indicate that CD117 is a specific marker for GIST among tumors that occur in the GI tract and adjacent regions. CD117 expression also separates GISTs from true leiomyomas and gastric schwannomas.[94] The sphere-forming cells isolated from primary ovarian cancer tissues have the characterization of cancer stem cell as they had the properties of self-renewal, over expression of stem cell marker genes Nanog, Oct-4, Sox-2, nestin, ABCG2, CD (133) and CD (117) [Figure 4].[95]

CD90

CD90 is a potential marker of liver CSCs, and the concomitantly expressed CD44 modulates the biological activity of the $CD90^+$ CSCs. The presence of local and circulating CSCs implies the aggressive phenotype of liver malignancy, in which the $CD90^+$ $CD44^+$ cells contribute prominently to its aggressiveness and metastasis. The prevention of local and systemic tumor formation by CD44 blockade highlights the potential of CD44 as a therapeutic target for $CD90^+$ CSCs. The differential gene expression profiles of CSCs and normal stem cells suggest the importance of these genes in hepatocarcinogenesis. The identification of local and circulating CSCs provides a cellular basis of liver cancer development, recurrence, and metastasis and will favor the design of future therapeutic strategies [Figure 5]. [96]

ALDH-1

ALDH is a detoxifying enzyme responsible for the oxidation of intracellular aldehydes, thereby mediating self-protection and resistance to some alkylating agents used in cancer therapy.[97] Besides, ALDH is implicated in the biology of normal stem cells through its role in metabolism of retinol to retinoic acid, which initiates a program of cellular differentiation.[98] Therefore, ALDH has been suggested as a marker for isolating normal stem cells and lately also CSCs from several tumor types.[99] $ALDH1^+$ cells displayed radio resistance and represented a reservoir for generating tumors. $ALDH1^+$-lineage cells showed evidence of having epithelial-mesenchymal transition (EMT) shifting and endogenously co-expressed Snail. Furthermore, the knockdown of Snail expression significantly decreased the expression of ALDH1, inhibited cancer stem-like properties, and blocked the tumorigenic abilities of $CD44^+$ $CD24^-$ $ALDH1^+$ cells. Finally, in a xenotransplanted tumorigenicity study, it was confirmed that the treatment effect of chemoradiotherapy for $ALDH1^+$

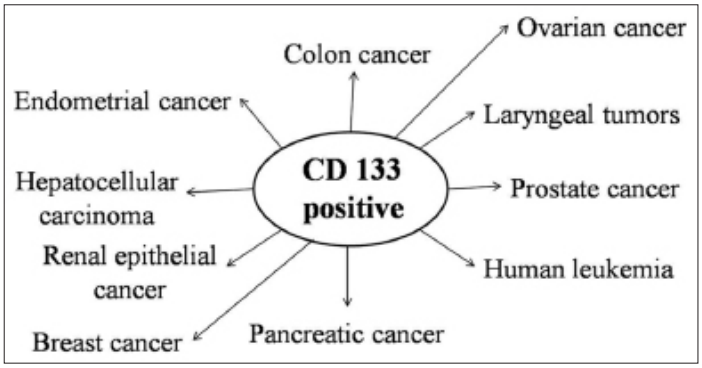

Figure 2: CD133: A marker of solid and liquid cancer stem cells

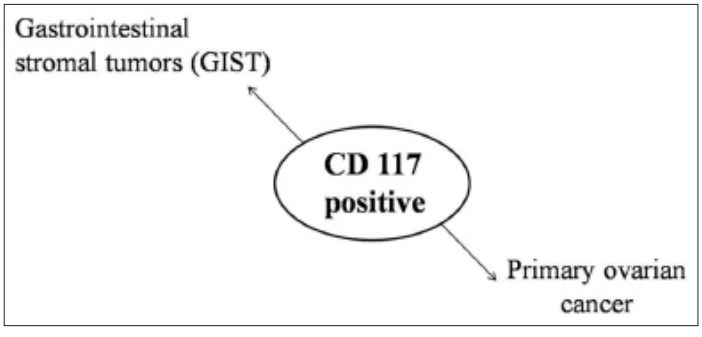

Figure 4: CD117: A marker of gastrointestinal stromal and ovarian cancer stem cells

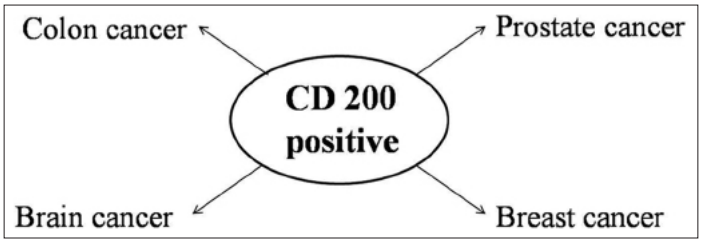

Figure 3: CD200: A marker of brain, breast, colon and prostrate cancer stem cells

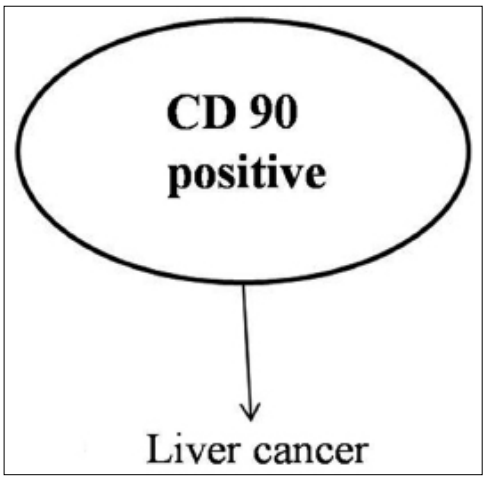

Figure 5: CD90: A marker of cancer stem cells of liver

could be improved by Snail siRNA. Therefore, it is likely that ALDH1 is a specific marker for the cancer stem-like cells of head and neck squamous cell carcinoma.[100]

Stem-like ALDH (hi) CD44 (+) CD24 (-) and ALDH (hi) CD44 (+) CD133 (+) cells may be important mediators of breast cancer metastasis.[101] Breast cancer stem cells identified as ALDH1+, but not CD44+/CD24-, play a significant role in resistance to chemotherapy. Thus, ALDH1 seems to be a more significantly predictive marker than CD44+/CD24- for the identification of breast cancer stem cells in terms of resistance to chemotherapy.[102] The metastatic behavior of inflammatory breast cancer may be mediated by a cancer stem cell component that displays ALDH enzymatic activity. ALDH1 expression represents the first independent prognostic marker to predict metastasis and poor patient outcome in inflammatory breast cancer.[103]

ALDH1 is a tumor stem cell-associated marker in lung cancer.[104] The existence of a hierarchical organization in hepatocellular carcinoma bearing tumorigenic potential revealed in the order of CD133+ ALDH+ >CD133+ ALDH->CD133- ALDH-. ALDH, expressed along CD133, can more specifically characterize the tumorigenic liver CSC population [Figure 6].[105]

CD44

Al Hajj and his group made experiments using a model in which human breast cancer cells were grown in immunocompromised mice, they found that only a minority of breast cancer cells had the ability to form new tumors. They prospectively identified and isolated the tumorigenic cells as CD44+ CD24-/low Lineage- in eight of nine patients. As few as 100 cells with this phenotype were able to form tumors in mice, whereas tens of thousands of cells with alternate phenotypes failed to form tumors. The tumorigenic subpopulation could be serially passaged: Each time cells within this population generated new tumors containing additional CD44+ CD24-/low Lineage- tumorigenic cells as well as the phenotypically diverse mixed populations of non-tumorigenic cells present in the initial tumor.[16]

Breast cancer cells with CD44+/CD24- subpopulation express higher levels of pro-invasive genes and have highly invasive properties.[106] The prevalence of CD44+/CD24-/low tumor cells in breast cancer may not be associated with clinical outcome and survival but may favor distant metastasis.[107] Role of CD 44 in colon cancer has also been established as it has been found out that ESA (+) -CD44 (+) is one of the surface markers for colonic cancer stem cells, and CD133 (+) -CD44 (+) –ESA (+) cells are SW480-colon cancer-like cancer stem cells.[108] In prostate cancer stem cells have a CD44+/$\alpha_2\beta_1^{hi}$/CD133+ phenotype. Approximately 0.1% of cells in any tumor expressed this phenotype, and there was no correlation between the number of CD44+/$\alpha_2\beta_1^{hi}$/CD133+ cells and tumor grade.[28] A minority population of CD44+ cancer cells, which typically comprise <10% of the cells in a head and neck squamous cell carcinoma tumor, but not the CD44- cancer cells, gave rise to new tumors *in vivo*. Immunohistochemistry revealed that the CD44+ cancer cells have a primitive cellular morphology and costain with the basal cell marker Cytokeratin 5/14, whereas the CD44- cancer cells resemble differentiated squamous epithelium and express the differentiation marker Involucrin.[109] Furthermore, the tumorigenic CD44+ cells differentially express the *BMI1* gene, at both the RNA and protein levels. By immunohistochemical analysis, the CD44+ cells in the tumor express high levels of nuclear *BMI1*, and are arrayed in characteristic tumor microdomains.[32] *BMI1* has been demonstrated to play a role in self-renewal in other stem cell types and to be involved in tumorigenesis.[73] Therefore, cells within the CD44+ population of human HNSCC possess the unique properties of cancer stem cells in functional assays for cancer stem cell self-renewal and differentiation and form unique histological micro domains that may aid in cancer diagnosis.[32]

CD44+, CD133+, and CD24+ cells have some biological properties of cancer stem-like cells or are highly similar to the characteristics of cancer stem cells (CSC). These results provide an important method for identifying cancer stem-like cells in B16F10 cells and for further cancer target therapy.[110] CD44 (+) gastric cancer cells showed increased resistance for chemotherapy-or radiation-induced cell death. These results support the existence of gastric CSCs and may provide novel approaches to the diagnosis and treatment of gastric cancer [Figure 7].[111]

Conclusion

At present, the shrinkage in the size of a tumor is considered as a response to the treatment. But, CSCs are

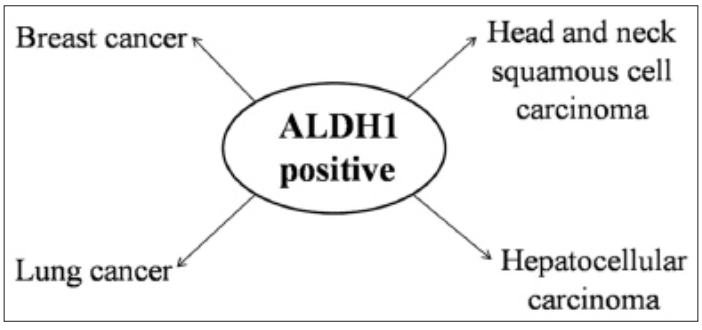

Figure 6: ALDH-1 positive cells as cancer stem cells

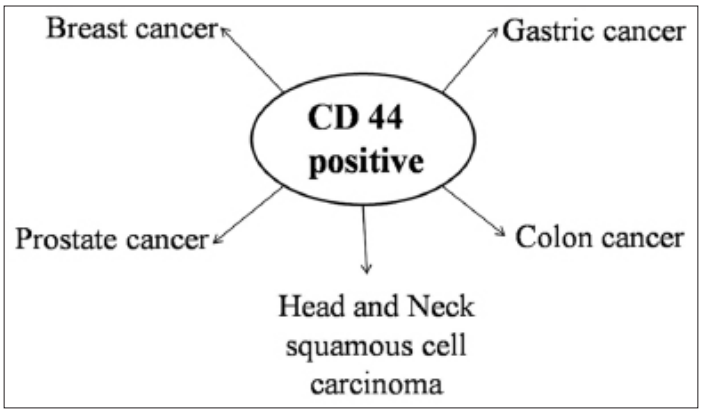

Figure 7: CD44 positive cells as cancer stem cells in breast, colon, gastric, head and neck and prostate cancer

resistant to treatment, therefore the identification of CSCs is necessary for better treatment. In this review we bring to light that CD133, CD44 and ALDH-1 altogether can be used for the identification and characterization of cancer stem cells in tumors.

Integrating the hypothesis of cancer stem cells with the concept of clonal evolution hypothesis, by far looks the most appropriate. Benign differentiation leads to the pre-cancerous stem cells to maintain their howsoever small population, while differentiation on the malignant lines, leads to the formation of CSCs. From the concept of CSCs, now cancer may be considered as a cancer stem cell disorder rather than lump of undifferentiated cells. Although the origin of the cancer stem cells is yet to be defined, the concept of the pre-cancer stem cells (pCSCs) may allow new treatment options in the possible cure of the cancer.

Further research is required to be more focused, so as to identify and separate the cancer stem cells in various cancers other than what have been identified to date, from normal stem cells and other cancer cells. Also, there is a need to identify the differences between gene expression and pathways involved normal stem cells and CSCs, with the eventual goal of eliminating the residual disease and recurrence.

Acknowledgment

We thank School of Biotechnology and International Institute of Information Technology for their support.

References

1. Weinstein IB, Arcoleo J, Backer J, Jeffrey A, Hsiao WL, Gattoni-Celli S, *et al.* Molecular mechanisms of tumor promotion and multistage carcinogenesis. Princess Takamatsu Symp 1983;14:59-74.
2. Hardwick JP, Schlenker RA, Huberman E. Alteration of the c-mos locus in "normal" tissues from humans exposed to radium. Cancer Res 1989;49:2668-73.
3. Wrzeszczynski KO, Varadan V, Byrnes J, Lum E, Kamalakaran S, Levine DA, *et al.* Identification of tumor suppressors and oncogenes from genomic and epigenetic features in ovarian cancer. PLoS One 2011;6:e28503.
4. Greger V, Passarge E, Hopping W, Messmer E, Horsthemke B. Epigenetic changes may contribute to the formation and spontaneous regression of retinoblastoma. Hum Genet 1989;83:155-8.
5. Leśniak W. Epigenetic regulation of S100 protein expression. Clin Epigenetics 2011;2:77-83.
6. Liu Z, Yang X, Li Z, McMahon C, Sizer C, Barenboim-Stapleton L, *et al.* CASZ1, a candidate tumor-suppressor gene, suppresses neuroblastoma tumor growth through reprogramming gene expression. Cell Death Differ 2011;18:1174-83.
7. Liu WB, Ao L, Cui ZH, Zhou ZY, Zhou YH, Yuan XY, *et al.* Molecular analysis of DNA repair gene methylation and protein expression during chemical-induced rat lung carcinogenesis. Biochem Biophys Res Commun 2011;408:595-601.
8. Singh KP, Treas J, Tyagi T, Gao W. DNA demethylation by 5-aza-2-deoxycytidine treatment abrogates 17 beta-estradiol-induced cell growth and restores expression of DNA repair genes in human breast cancer cells. Cancer Lett 2012;316:62-9.
9. Harnden DG. Cellular instability and susceptibility to malignancy. Proc R Soc Med 1974;67:101-2.
10. Collins SL, Herve R, Keevil CW, Blaydes JP, Webb JS. Down-regulation of DNA mismatch repair enhances initiation and growth of neuroblastoma and brain tumor multicellular spheroids. PLoS One 2011;6:e28123.
11. Mehle C, Ljungberg B, Roos G. Telomere shortening in renal cell carcinoma. Cancer Res 1994;54:236-41.
12. Shay JW, Wright WE. Role of telomeres and telomerase in cancer. Semin Cancer Biol 2011;21:349-53.
13. Wheldon EG, Lindsay KA, Wheldon TE, Mao JH. A two-stage model for childhood acute lymphoblastic leukemia: Application to hereditary and nonhereditary leukemogenesis. Math Biosci 1997;139:1-24.
14. Wang JC, Lapidot T, Cashman JD, Doedens M, Addy L, Sutherland DR, *et al.* High level engraftment of NOD/SCID mice by primitive normal and leukemic hematopoietic cells from patients with chronic myeloid leukemia in chronic phase. Blood 1998;91:2406-14.
15. Al-Hajj M, Clarke MF. Self-renewal and solid tumor stem cells. Oncogene 2004;23:7274-82.
16. Al-Hajj M, Wicha MS, Benito-Hernandez A, Morrison SJ, Clarke MF. Prospective identification of tumorigenic breast cancer cells. Proc Natl Acad Sci U S A 2003;100:3983-8.
17. Wang JC, Dick JE. Cancer stem cells: Lessons from leukemia. Trends Cell Biol 2005;15:494-501.
18. Clarke MF, Fuller M. Stem cells and cancer: Two faces of eve. Cell 2006;124:1111-5.
19. Wicha MS, Liu S, Dontu G. Cancer stem cells: An old idea-A paradigm shift. Cancer Res 2006;66:1883-90; discussion 95-6.
20. Clarke MF, Dick JE, Dirks PB, Eaves CJ, Jamieson CH, Jones DL, *et al.* Cancer stem cells-perspectives on current status and future directions: AACR Workshop on cancer stem cells. Cancer Re 2006;66:9339-44.
21. Park CH, Bergsagel DE, McCulloch EA. Mouse myeloma tumor stem cells: A primary cell culture assay. J Natl Cancer Inst 1971;46:411-22.
22. Bonnet D, Dick JE. Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell. Nat Med 1997;3:730-7.
23. Dick JE. Breast cancer stem cells revealed. Proc Natl Acad Sci U S A 2003;100:3547-9.
24. Galderisi U, Cipollaro M, Giordano A. Stem cells and brain cancer. Cell Death Differ 2006;13:5-11.
25. Lapidot T, Sirard C, Vormoor J, Murdoch B, Hoang T, Caceres-Cortes J, *et al.* A cell initiating human acute myeloid leukaemia after transplantation into SCID mice. Nature 1994;367:645-8.
26. Johansson CB, Svensson M, Wallstedt L, Janson AM, Frisen J. Neural stem cells in the adult human brain. Exp Cell Res 1999;253:733-6.
27. Singh SK, Clarke ID, Terasaki M, Bonn VE, Hawkins C, Squire J, *et al.* Identification of a cancer stem cell in human brain tumors. Cancer Res 2003;63:5821-8.
28. Collins AT, Berry PA, Hyde C, Stower MJ, Maitland NJ. Prospective identification of tumorigenic prostate cancer stem cells. Cancer Res 2005;65:10946-51.
29. Fang D, Nguyen TK, Leishear K, Finko R, Kulp AN, Hotz S, *et al.* A tumorigenic subpopulation with stem cell properties in melanomas. Cancer Res 2005;65:9328-37.
30. Bapat SA, Mali AM, Koppikar CB, Kurrey NK. Stem and progenitor-like cells contribute to the aggressive behavior of human epithelial ovarian cancer. Cancer Res 2005;65:3025-9.
31. Ricci-Vitiani L, Lombardi DG, Pilozzi E, Biffoni M, Todaro M, Peschle C, *et al.* Identification and expansion of human colon-cancer-initiating cells. Nature 2007;445:111-5.
32. Prince ME, Sivanandan R, Kaczorowski A, Wolf GT, Kaplan MJ, Dalerba P, *et al.* Identification of a subpopulation of cells with cancer stem cell properties in head and neck squamous cell carcinoma. Proc Natl Acad Sci U S A 2007;104:973-8.
33. Li C, Lee CJ, Simeone DM. Identification of human pancreatic cancer stem cells. Methods Mol Biol 2009;568:161-73.
34. Eramo A, Lotti F, Sette G, Pilozzi E, Biffoni M, Di Virgilio A, *et al.* Identification and expansion of the tumorigenic lung cancer stem cell population. Cell Death Differ 2008;15:504-14.
35. Feng D, Peng C, Li C, Zhou Y, Li M, Ling B, *et al.* Identification and characterization of cancer stem-like cells from primary carcinoma of the cervix uteri. Oncol Rep 2009;22:1129-34.
36. Biddle A, Liang X, Gammon L, Fazil B, Harper LJ, Emich H, *et al.* Cancer stem cells in squamous cell carcinoma switch between two distinct phenotypes that are preferentially migratory or proliferative. Cancer Res 2011;71:5317-26.
37. Shipitsin M, Campbell LL, Argani P, Weremowicz S, Bloushtain-Qimron N, Yao J, *et al.* Molecular definition of breast tumor heterogeneity. Cancer Cell 2007;11:259-73.
38. Nowell PC. The clonal evolution of tumor cell populations. Science 1976;194:23-8.
39. Kuukasjarvi T, Karhu R, Tanner M, Kahkonen M, Schaffer A, Nupponen N, *et al.* Genetic heterogeneity and clonal evolution underlying development of asynchronous metastasis in human breast cancer. Cancer Res 1997;57:1597-604.
40. Sakai K, Ishikawa Y, Mori Y, Kobayashi M, Iriyama C, Ozawa Y, *et al.* A novel insertion mutation of K294RGG within BCR-ABL kinase domain confers imatinib resistance: Sequential analysis of the clonal evolution in a patient with chronic myeloid leukemia in blast crisis. Int J Hematol 2011;93:237-42.

41. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell 1990;61:759-67.
42. Knudson AG. Hereditary cancer: Two hits revisited. J Cancer Res Clin Oncol 1996;122:135-40.
43. Chen L, Shen R, Ye Y, Pu XA, Liu X, Duan W, *et al.* Precancerous stem cells have the potential for both benign and malignant differentiation. PLoS One 2007;2:e293.
44. Gao JX, Liu X, Wen J, Zhang H, Durbin J, Liu Y, *et al.* Differentiation of monocytic cell clones into CD8 alpha+ dendritic cells (DC) suggests that monocytes can be direct precursors for both CD8 alpha+ and CD8 alpha- DC in the mouse. J Immunol 2003;170:5927-35.
45. Berman JJ, Albores-Saavedra J, Bostwick D, Delellis R, Eble J, Hamilton SR, *et al.* Precancer: A conceptual working definition-results of a Consensus Conference. Cancer Detect Prev 2006;30:387-94.
46. Bond JH. Colon polyps and cancer. Endoscopy 2003;35:27-35.
47. Cardiff RD, Anver MR, Boivin GP, Bosenberg MW, Maronpot RR, Molinolo AA, *et al.* Precancer in mice: Animal models used to understand, prevent, and treat human precancers. Toxicol Pathol 2006;34:699-707.
48. He XC, Yin T, Grindley JC, Tian Q, Sato T, Tao WA, *et al.* PTEN-deficient intestinal stem cells initiate intestinal polyposis. Nat Genet 2007;39:189-98.
49. Maglione JE, Moghanaki D, Young LJ, Manner CK, Ellies LG, Joseph SO, *et al.* Transgenic Polyoma middle-T mice model premalignant mammary disease. Cancer Res 2001;61:8298-305.
50. Namba R, Maglione JE, Davis RR, Baron CA, Liu S, Carmack CE, *et al.* Heterogeneity of mammary lesions represent molecular differences. BMC Cancer 2006;6:275.
51. Sternlicht M, Mirell C, Safarians S, Barsky SH. A novel strategy for the investigation of clonality in precancerous disease states and early stages of tumor progression. Biochem Biophys Res Commun 1994;199:511-8.
52. Wistuba, II. Genetics of preneoplasia: Lessons from lung cancer. Curr Mol Med 2007;7:3-14.
53. Geyer FC, Weigelt B, Natrajan R, Lambros MB, de Biase D, Vatcheva R, *et al.* Molecular analysis reveals a genetic basis for the phenotypic diversity of metaplastic breast carcinomas. J Pathol 2010;220:562-73.
54. Hansford LM, McKee AE, Zhang L, George RE, Gerstle JT, Thorner PS, *et al.* Neuroblastoma cells isolated from bone marrow metastases contain a naturally enriched tumor-initiating cell. Cancer Res 2007;67:11234-43.
55. Shen R, Tao L, Xu Y, Chang S, Van Brocklyn J, Gao JX. Reversibility of aberrant global DNA and estrogen receptor-alpha gene methylation distinguishes colorectal precancer from cancer. Int J Clin Exp Pathol 2009;2:21-33.
56. Klein AM, Brash DE, Jones PH, Simons BD. Stochastic fate of p53-mutant epidermal progenitor cells is tilted toward proliferation by UV B during preneoplasia. Proc Natl Acad Sci U S A 2010;107:270-5.
57. Covello KL, Kehler J, Yu H, Gordan JD, Arsham AM, Hu CJ, *et al.* HIF-2alpha regulates Oct-4: Effects of hypoxia on stem cell function, embryonic development, and tumor growth. Genes Dev 2006;20:557-70.
58. D'Andrea FP, Horsman MR, Kassem M, Overgaard J, Safwat A. Tumourigenicity and radiation resistance of mesenchymal stem cells. Acta Oncol 2012;51:669-79.
59. Compagno M, Lim WK, Grunn A, Nandula SV, Brahmachary M, Shen Q, *et al.* Mutations of multiple genes cause deregulation of NF-kappaB in diffuse large B-cell lymphoma. Nature 2009;459:717-21.
60. Sotiropoulou PA, Candi A, Mascre G, De Clercq S, Youssef KK, Lapouge G, *et al.* Bcl-2 and accelerated DNA repair mediates resistance of hair follicle bulge stem cells to DNA-damage-induced cell death. Nat Cell Biol 2010;12:572-82.
61. Reya T, Morrison SJ, Clarke MF, Weissman IL. Stem cells, cancer, and cancer stem cells. Nature 2001;414:105-11.
62. Pardal R, Clarke MF, Morrison SJ. Applying the principles of stem-cell biology to cancer. Nat Rev Cancer 2003;3:895-902.
63. Gao JX. Cancer stem cells: The lessons from pre-cancerous stem cells. J Cell Mol Med 2008;12:67-96.
64. Zhao C, Wang X, Zhao Y, Li Z, Lin S, Wei Y, *et al.* A novel xenograft model in zebrafish for high-resolution investigating dynamics of neovascularization in tumors. PLoS One 2011;6:e21768.
65. Ping YF, Bian XW. Cancer stem cells switch on tumor neovascularization. Curr Mol Med 2011;11:69-75.
66. Liu HG, Chen C, Yang H, Pan YF, Zhang XH. Cancer stem cell subsets and their relationships. J Transl Med 2011;9:50.
67. Shen R, Ye Y, Chen L, Yan Q, Barsky SH, Gao JX. Precancerous stem cells can serve as tumor vasculogenic progenitors. PLoS One 2008;3:e1652.
68. Valdembri D, Serini G, Vacca A, Ribatti D, Bussolino F. *In vivo* activation of JAK2/STAT-3 pathway during angiogenesis induced by GM-CSF. FASEB J 2002;16:225-7.
69. O'Farrell AM, Abrams TJ, Yuen HA, Ngai TJ, Louie SG, Yee KW, *et al.* SU11248 is a novel FLT3 tyrosine kinase inhibitor with potent activity *in vitro* and *in vivo*. Blood 2003;101:3597-605.
70. Fukushi J, Ono M, Morikawa W, Iwamoto Y, Kuwano M. The activity of soluble VCAM-1 in angiogenesis stimulated by IL-4 and IL-13. J Immunol 2000;165:2818-23.
71. Kondo T, Setoguchi T, Taga T. Persistence of a small subpopulation of cancer stem-like cells in the C6 glioma cell line. Proc Natl Acad Sci U S A 2004;101:781-6.
72. Singh SK, Hawkins C, Clarke ID, Squire JA, Bayani J, Hide T, *et al.* Identification of human brain tumor initiating cells. Nature 2004;432:396-401.
73. Lessard J, Sauvageau G. Bmi-1 determines the proliferative capacity of normal and leukaemic stem cells. Nature 2003;423:255-60.
74. Reya T, Duncan AW, Ailles L, Domen J, Scherer DC, Willert K, *et al.* A role for Wnt signalling in self-renewal of haematopoietic stem cells. Nature 2003;423:409-14.
75. Liu G, Yuan X, Zeng Z, Tunici P, Ng H, Abdulkadir IR, *et al.* Analysis of gene expression and chemoresistance of CD133+ cancer stem cells in glioblastoma. Mol Cancer 2006;5:67.
76. Zhou S, Schuetz JD, Bunting KD, Colapietro AM, Sampath J, Morris JJ, *et al.* The ABC transporter Bcrp1/ABCG2 is expressed in a wide variety of stem cells and is a molecular determinant of the side-population phenotype. Nat Med 2001;7:1028-34.
77. Ejendal KF, Hrycyna CA. Multidrug resistance and cancer: The role of the human ABC transporter ABCG2. Curr Protein Pept Sci 2002;3:503-11.
78. Lee A, Kessler JD, Read TA, Kaiser C, Corbeil D, Huttner WB, *et al.* Isolation of neural stem cells from the postnatal cerebellum. Nat Neurosci 2005;8:723-9.
79. Ehtesham M, Yuan X, Kabos P, Chung NH, Liu G, Akasaki Y, *et al.* Glioma tropic neural stem cells consist of astrocytic precursors and their migratory capacity is mediated by CXCR4. Neoplasia 2004;6:287-93.
80. Galli R, Binda E, Orfanelli U, Cipelletti B, Gritti A, De Vitis S, *et al.* Isolation and characterization of tumorigenic, stem-like neural precursors from human glioblastoma. Cancer Res 2004;64:7011-21.
81. Hemmati HD, Nakano I, Lazareff JA, Masterman-Smith M, Geschwind DH, Bronner-Fraser M, *et al.* Cancerous stem cells can arise from pediatric brain tumors. Proc Natl Acad Sci U S A 2003;100:15178-83.
82. Yuan X, Curtin J, Xiong Y, Liu G, Waschsmann-Hogiu S, Farkas DL, *et al.* Isolation of cancer stem cells from adult glioblastoma multiforme. Oncogene 2004;23:9392-400.
83. Ignatova TN, Kukekov VG, Laywell ED, Suslov ON, Vrionis FD, Steindler DA. Human cortical glial tumors contain neural stem-like cells expressing astroglial and neuronal markers *in vitro*. Glia 2002;39:193-206.
84. Beier D, Hau P, Proescholdt M, Lohmeier A, Wischhusen J, Oefner PJ, *et al.* CD133 (+) and CD133(-) glioblastoma-derived cancer stem cells show differential growth characteristics and molecular profiles. Cancer Res 2007;67:4010-5.
85. Zhou L, Wei X, Cheng L, Tian J, Jiang JJ. CD133, one of the markers of cancer stem cells in Hep-2 cell line. Laryngoscope 2007;117:455-60.
86. Shmelkov SV, Butler JM, Hooper AT, Hormigo A, Kushner J, Milde T, *et al.* CD133 expression is not restricted to stem cells, and both CD133+ and CD133- metastatic colon cancer cells initiate tumors. J Clin Invest 2008;118:2111-20.
87. Kyo S, Maida Y, Inoue M. Stem cells in endometrium and endometrial cancer: Accumulating evidence and unresolved questions. Cancer Lett 2011;308:123-33.
88. Kim RJ, Nam JS. OCT4 expression enhances features of cancer stem cells in a mouse model of breast cancer. Lab Anim Res 2011;27:147-52.
89. Marzban H, Chung S, Watanabe M, Hawkes R. Phospholipase Cbeta4 expression reveals the continuity of cerebellar topography through development. J Comp Neurol 2007;502:857-71.
90. Hermann PC, Huber SL, Herrler T, Aicher A, Ellwart JW, Guba M, *et al.* Distinct populations of cancer stem cells determine tumor growth and metastatic activity in human pancreatic cancer. Cell Stem Cell 2007;1:313-23.
91. Curley MD, Therrien VA, Cummings CL, Sergent PA, Koulouris CR, Friel AM, *et al.* CD133 expression defines a tumor initiating cell population in primary human ovarian cancer. Stem Cells 2009;27:2875-83.
92. Bussolati B, Bruno S, Grange C, Buttiglieri S, Deregibus MC, Cantino D, *et al.* Isolation of renal progenitor cells from adult human kidney. Am J Pathol 2005;166:545-55.
93. Kawasaki BT, Mistree T, Hurt EM, Kalathur M, Farrar WL. Co-expression of the toleragenic glycoprotein, CD200, with markers for cancer stem cells. Biochem Biophys Res Commun 2007;364:778-82.
94. Sarlomo-Rikala M, Kovatich AJ, Barusevicius A, Miettinen M. CD117: A sensitive marker for gastrointestinal stromal tumors that is more specific than CD34. Mod Pathol 1998;11:728-34.

95. Lai DM, Liu T, Huang Y, Wang LH, Zhang J, Cheng WW. Identification and characterization of ovarian cancer stem-like cells from primary tumor. Zhonghua Fu Chan Ke Za Zhi 2009;44:936-40.
96. Yang ZF, Ho DW, Ng MN, Lau CK, Yu WC, Ngai P, *et al.* Significance of CD90+ cancer stem cells in human liver cancer. Cancer Cell 2008;13:153-66.
97. Sladek NE. Human aldehyde dehydrogenases: Potential pathological, pharmacological, and toxicological impact. J Biochem Mol Toxicol 2003;17:7-23.
98. Chute JP, Muramoto GG, Whitesides J, Colvin M, Safi R, Chao NJ, *et al.* Inhibition of aldehyde dehydrogenase and retinoid signaling induces the expansion of human hematopoietic stem cells. Proc Natl Acad Sci U S A 2006;103:11707-12.
99. Douville J, Beaulieu R, Balicki D. ALDH1 as a functional marker of cancer stem and progenitor cells. Stem Cells Dev 2009;18:17-25.
100. Chen YC, Chen YW, Hsu HS, Tseng LM, Huang PI, Lu KH, *et al.* Aldehyde dehydrogenase 1 is a putative marker for cancer stem cells in head and neck squamous cancer. Biochem Biophys Res Commun 2009;385:307-13.
101. Croker AK, Goodale D, Chu J, Postenka C, Hedley BD, Hess DA, *et al.* High aldehyde dehydrogenase and expression of cancer stem cell markers selects for breast cancer cells with enhanced malignant and metastatic ability. J Cell Mol Med 2009;13:2236-52.
102. Tanei T, Morimoto K, Shimazu K, Kim SJ, Tanji Y, Taguchi T, *et al.* Association of breast cancer stem cells identified by aldehyde dehydrogenase 1 expression with resistance to sequential Paclitaxel and epirubicin-based chemotherapy for breast cancers. Clin Cancer Res 2009;15:4234-41.
103. Charafe-Jauffret E, Ginestier C, Iovino F, Tarpin C, Diebel M, Esterni B, *et al.* Aldehyde dehydrogenase 1-positive cancer stem cells mediate metastasis and poor clinical outcome in inflammatory breast cancer. Clin Cancer Res 2010;16:45-55.
104. Jiang F, Qiu Q, Khanna A, Todd NW, Deepak J, Xing L, *et al.* Aldehyde dehydrogenase 1 is a tumor stem cell-associated marker in lung cancer. Mol Cancer Res 2009;7:330-8.
105. Ma S, Chan KW, Lee TK, Tang KH, Wo JY, Zheng BJ, *et al.* Aldehyde dehydrogenase discriminates the CD133 liver cancer stem cell populations. Mol Cancer Res 2008;6:1146-53.
106. Sheridan C, Kishimoto H, Fuchs RK, Mehrotra S, Bhat-Nakshatri P, Turner CH, *et al.* CD44+/CD24- breast cancer cells exhibit enhanced invasive properties: An early step necessary for metastasis. Breast Cancer Res 2006;8:R59.
107. Abraham BK, Fritz P, McClellan M, Hauptvogel P, Athelogou M, Brauch H. Prevalence of CD44+/CD24-/low cells in breast cancer may not be associated with clinical outcome but may favor distant metastasis. Clin Cancer Res 2005;11:1154-9.
108. Xue FQ, Yang GH, Huang RL. Role of CD44(+)/ESA(+) in sorting colonic cancer stem cells. Zhonghua Wei Chang Wai Ke Za Zhi 2011;14:896-8.
109. Walts AE, Said JW, Siegel MB, Banks-Schlegel S. Involucrin, a marker of squamous and urothelial differentiation. An immunohistochemical study on its distribution in normal and neoplastic tissues. J Pathol 1985;145:329-40.
110. Dou J, Pan M, Wen P, Li Y, Tang Q, Chu L, *et al.* Isolation and identification of cancer stem-like cells from murine melanoma cell lines. Cell Mol Immunol 2007;4:467-72.
111. Takaishi S, Okumura T, Tu S, Wang SS, Shibata W, Vigneshwaran R, *et al.* Identification of gastric cancer stem cells using the cell surface marker

How to site this article: Kapoor A, Kumar S. Cancer stem cell: A rogue responsible for tumor development and metastasis. Indian J Cancer 2014;51:282-9.
Source of Support: School of Biotechnology and International Institute of Information Technology. **Conflict of Interest:** None declared.

News

9th SFO (SAARC Federation of Oncologists), conference 2014
Organizing Chairman : Dr. Ashok Vaid
Web: www.sfo2014.com
Mail: saarconcology14@gmail.com

News

Congratulations
Padamshree Awardee

Dr. Ramakant Deshpande: He is presently the chief of thoracic surgical oncology and Executive Vice Chairman at the Asian Institute of Oncology, Mumbai. He graduated from Karnataka Medical College, Hubli and completed his post-graduation at the Tata Memorial Hospital, Mumbai. He was later trained at the Memorial Sloan Kettering Cancer Centre (USA) and began his surgical oncology career at the Bangalore Kidwai Cancer Centre in 1982. He worked in the capacity of chief of thoracic services at the Tata Memorial Hospital, Mumbai from 1985 till 2002. He was the first person to introduce thoracoscopic surgery at the Tata Memorial Hospital and many enthusiastic surgeons have trained under him. He is an ardent speaker, is multilinguistic and an eminent scholar. He has over 50 publications to his credit in national and international journals including chapters on management of cancer in lung in the Textbook of Cancer published by the National Book Trust of India.

News

Congratulations
First rank at ESMO Examination:

Dr. Manish K Singhal, MD, DM: A leading medical oncologist working at Noida (NCR), he is a graduate of AIIMS (All India Institute of Medical Sciences), New Delhi where he did post-doctoral training in Medical Oncology. He learned bone marrow transplant at Barabara Ann Karmanos Cancer Institute, Michigan University, Detroit, USA. He visited Oxford University regarding randomized controlled clinical trials. He is presently in charge of the department of Medical Oncology at, Fortis hospital, Noida under the aegis of International Oncology Group.
He has made us proud by scoring the highest marks in the prestigious ESMO (European Society of Medical Oncology) Examination 2013, the first Indian to do so. He will be presented with the Best exam Award at the forthcoming ESMO meeting in Sept 2014 at Spain, Madrid.