Ali *et al*., 2020. Journal of Genes and Cells, 6(2): p, 21-29
doi: 10.15562/gnc.74

www.imaqpress.com

REVIEW ARTICLE

Role of Organ Specific Cancer Stem Cells in Localized Cancer Progression

Muhammad Ali*[1], Fatima Ali[1] and NadiaWajid[1]
1. Institute of Molecular Biology and Biotechnology, University of Lahore, Pakistan

ABSTRACT

Since the cancer stem cells (CSC) have been identified in 1997 by Bonnet and Dick, more than 100,000 papers have been published describing their characteristics. This mountain research on cancer stem cells helped the scientists to rethink about the cancer therapeutics because classic chemotherapy failed to stop the cancer relapse. The cancer theory of stem cells is one of the most trending theory in stem cells now a days and cancer biology focusing on the understanding of biology of cancer cells for an enhanced and improved therapeutic approaches is being applied while developing strategies to cure the cancer. This mini-review is a short overview on the role of organ specific cancer stem cells in the localized cancer progression.

Keywords: Cancer Stem Cells, Cancer Progression, Cancer biology, stem cells, cancer therapeutics

Evidence states that in cancer, leukemia growth and propagation are determined by leukemia cells, which have the potential for self-renewal and are known as cancer stem cells (CSC) (1). Shortly hereafter, this phenomenon was identified that leukemia cells are composed of many immature undifferentiated cells to more specialized cells having limited ability to self-renew. With the passage of time and more research on CSCs, it was observed that these cells are not located in blood only because these cells were isolated and characterized from various tumors such as breast (1), brain (2), colon (3), pancreas (4), prostate (5), lung (6), neck & head tumor (7). Lately, researchers suggested that CSCs presence is the main reason for relapse of disease (8, 9). Chemotherapies can wipe out bulk of cancer cells, while fails to target CSCs. Moreover, early treatment increases the quantity of drug resistant CSCs which results in recurrence of the disease (10). Hence, the cancer theory of stem cell suggest that small groups of CSCs are present in tumors which promote and maintain tumor growth (11, 12). For example, breast cancer stem cells (BCSCs) progressively play a vital function in growth of BC and are involved in metastasis. CSCs have potential to self-renew and yield daughter cells which result in bulk tumor cells formation, while maintaining a self-replicating potential. The long lasting life time of stem cells makes them able to cause mutations in DNA. The cells ability to replicate also makes them candidates for origin of

* **Correspondence**:
Email: mali855@yahoo.com

tumor cells (13). Here, we tried to discuss the role of organ specific CSCs in the localized cancer progression and metastasis.

BREAST CANCER STEM CELLS (BCSCS)

According to the CSC studies, cancer arises from normal stem cells, in the breast and in other tissues which undergo oncogenic transformation (14). CSC display characteristics that can have fundamental importance for detection of breast cancer, prevention as well as treatment. CSC promote formation of cell motility, growth of blood vessel and therapy resistance (15) and also involved in metastasis of breast (16, 17). Breast CSCs progressively play a vital role in growth of BC and are involved in metastasis.

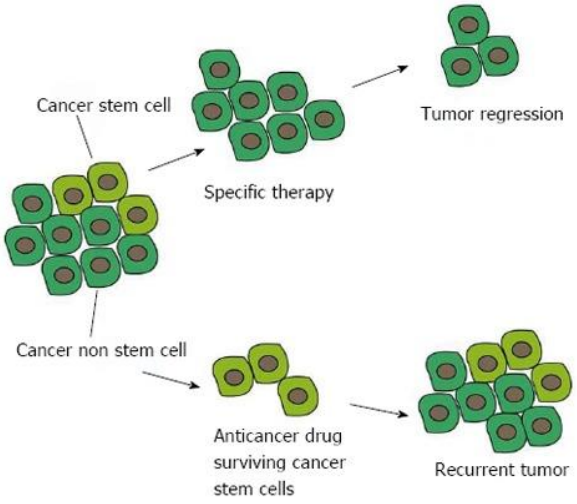

Fig. 1. Diagrammatic representation of cancer stem cells therapy. Figure adapted from (18)

Tumor suppressor gene, BRCA1, is strongly associated to breast cancer, the risk to develop breast cancer increases as soon as this gene mutated. BRCA1 is involved in the regulation of self-renewal of CSCs. BRCA1 plays a vital part in the fixing double stranded DNA within the breast, so that maintaining chromosomal structure (19).

Breast CSCs are mainly composed of cells expressing the cancer stem cell surface protein marker $CD44^+$ ((20). BCSCs expressed ESA^+ / $CD44^+$ and lacking the expression of CD2, CD3, CD10, CD 16, CD18, CD31, CD64 and CD140b (Lin^-) by flow cytometry (21). Moreover, recent studies has demonstrated that BC tumor cells give increase expression of CD44 and reduce expression of CD24 marker and are chemotherapy resistance (22).

Furthermore, scientists also have identified an additional marker and protein called ALDH, produced by CSCs and observed in tumors of patient biopsies, CD133 (prominin-1) (23), $CD49f^{hi}$ have been proposed as BCSC biomarkers. ALDH1, is present in normal mammary SCs and BCSC, an enzyme which is used for oxidation of the intracellular aldehydes (24). Lately, sulforaphane a compound derived from broccoli, can be crucial to prevent or treat breast cancer by targeting CSCs. Researchers has find out that sulforaphane targeted and killed CSCs can prevent growing of new tumors (25). In mammary gland, three lineages are generated by differentiated cells, which include alveolar epithelial cells; cells that produce milk, myoepithelial cells; contracted cells that covers alveoli and ducts and thirdly, ductal epithelial cells; cells lining the ducts. Till recently, due to lack of cell surface markers identification, isolation and characterization of breast CSs was limit in range (26).

NON-HODGKIN LYMPHOMA STEM CELLS (NHLSCS)

The CSCs has evidenced the presence of specific population of cell in cancers, moreover suggests that cancers are basically isolated from CSCs that are responsible for specific stem cells properties including self-renewal (11). Hence, the existence of CSCs has been proved in various cancers including acute myeloid leukemia. Thus, several surface markers, to isolate CSCS, has been discovered including colon, brain and breast (27).

Recently, it has been suggested that in non-Hodgkin lymphoma, lymphoma stem cells do not provide sufficient data to confirm presence of CSCs. So, the presence of lymphoma SCs remains unresolved (28). To detect the presence of CSCs, that have no identified surface marker for isolation of stem cell, side population analysis has been applied. The side population is majorly discovered as a stem cell population. Moreover, this analysis is particularly based on normal stem cells characteristic, which allows to protect themselves from cytotoxic agents (29).

Hodgkin lymphoma comprise of side population cells, they can give rise to larger cells similar to morphology of Reed-Sternberg cell, also reported that they are resistance to chemotherapy (30).

Both, non-Hodgkin and Hodgkin lymphoma presents identical gene organizations of clonal *IGH* in Reed-Sternberg cells. B-cell non-Hodgkin's lymphomas are obtained either from lymphoid cells or from mature B-lymphocytes, which develops chromosomal translocations through errors in the *IG* gene remodeling processes during normal B-cell differentiation (31, 32).

COLORECTAL CANCER STEM CELLS (CRCSCS)

Evidence demonstrates that the presence of CRCSCs in colorectal cancer (CRC) contribution to progression of tumor, chemotherapy resistance and failure in therapeutic approach (3, 33). Tumor cells carrying CD133 marker has high resistance to chemotherapy (34). Self-renewal and tumorigenic property of colorectal CSCs population in colon cancers has been evidenced in various studies employing the CD133 surface marker (3, 33). CD133 is the most common CSCs marker characterized (35). CD133 is a five transmembrane glycoprotein which was for the first time found in hematopoietic stem and progenitor cells (36). CD133 is found in various tumors, including brain cancer (37), colon (38, 39), liver (40), ovary (41), bone (42) and still in progress. CD133 (+) in cancers has ability to initiate tumor growth (3, 33). CD133 (+) cells can develop tumors with extended self-renewal and differentiation capabilities and without phenotypic alterations after serial transplantation. Tumorigenic potential of CD133 (+) has also been confirmed *in vitro study* (33). On the contrary, CD133 (-) has no ability to form tumors.

Moreover, some others markers for detection and evaluation of CSCs and their role in clinical significance of CRC has been observed. These markers include CD44 which is expressed in many cancers which include colorectal cancer (43-45), CD166 (43-47), CD29 (47, 48), CD24 (38, 48, 49), Lgr5 (39, 48) nuclear beta-catenin (50), EpCam (51), ALDH1 (51, 52), CDCP1 and CXCR4 (38) and CC188 (53). The use of the combination of these markers to identify CSCs in colorectal cancers will uncover more about the function of CSCs and will also play a significant role in clinical usage.

CHRONIC MYELOID LEUKEMIA (CML) STEM CELLS

Chronic Myeloid Leukemia is a systemic disturbance of hematopoietic stem cell. Tyrosine Kinase Inhibitors (TKI) therapy fails to heal patients of CML even though having capability to cause rapid remission, which has been demonstrated for leukemic stem cells presence in CML (54).

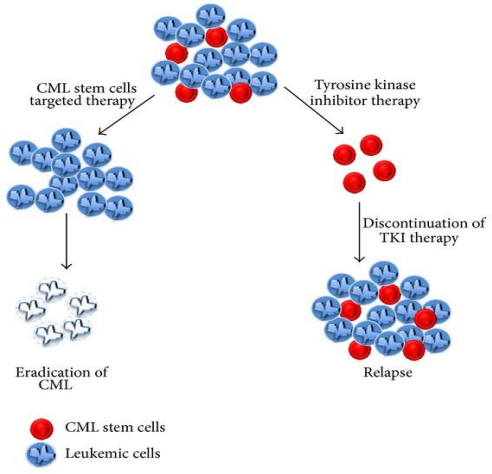

Fig. 2. Schematic representation of CML stem cells response to therapy. Figure adapted from (55).

The property of cells including self-renewal and raising heterogeneous CML SCs population of is somehow alike to normal hematopoietic SCs but only difference is of gene marker of BCR-ABL which is particular to CML. SCs of CML exist as inactive state. Recently, studies state that CML SCs are not completely dependent on BCR-ABL gene, for their survival purpose and are not fully addicted to this oncoprotein (56).

The presence of leukemic SCs was conformed and was unresponsive to imatinib, which support the disease and acts as a reservoir of leukemia cells (43, 56). It has been noticed that TKI has ability to target progenitors better as compare to imatinib as they have high affinity to BCR-ABL gene. Drugs similar to imatinib, are not successful to fully cure the illness, patient have tendency to generate resistance against chemo and radiotherapy and disease reoccurs once the drug is discontinue (54, 57).

Several subsets of $CD34^+$ cells were isolated from CML patients, BCR-ABL mRNA presence was assessed in each of the subsets of $CD34^+$ cells. BCR-ABL mRNA was determined in $CD34^+$ $CD38^-$ and $CD34^+$ $CD38^+$ cells (58). CML SCs are reported as a tiny subpopulations of cells that express Lin−, CD34+, CD38− and CD90+ (59). Moreover, it is also suggested that CML SCS forms a small subpopulation of the Lin−, CD34+, CD38− and CD90+ (60). Hence, some substitute targeted potential therapies are required for the suppression of CML stem cells, which function either alone or in combination with TKI.

OVARIAN CANCER STEM CELLS (OCSCS)

The CSCs are a small groups of tumor cells which has capability to self-renew and give rise to other SCs, also these cells goes through bulk cell proliferation and differentiation to producing mature cancer cell leading to formation of secondary/tertiary tumors (21, 61)**.**

The reason behind 90% of cancers originates from ovary surface epithelium is that stem cells reside this area. In early stage of ovarian cancer (OC), the number of epithelial ovarian CSCs was used to predict progression of the disease (62)

First CSCs were isolated in leukemia cells that express CD34 marker (1). Afterwards, various different types of CSCs were discovered, in ovarian CSCs, colon (46) and prostate cancers (5) and were evidence in many ovarian cancer patient (63). Various CSCs share identical biomarkers, as in ovarian CSCs. So the development of therapies that target directly the biomarkers of CSCs can meliorate clinical result and patient's survival (64).

In ovarian CSCs, CD44 is chiefly expressed, $CD44^+/CD24^-$ expression correlates with invasion and chemotherapy resistance (65, 66). CD24 expression affects metastasis and represents a pathetic prognostics in OC (67). Various different antibodies has been introduced against isoforms of CD44 (68). Relative high expression of surface marker CD117 was remarked in OC (63). Tumor cells carrying CD133 marker has high resistance to chemotherapy (34). Its expression mostly goes higher in advanced stages of OC than in benign stage or normal ovaries (64). The epithelial cell adhesion molecule (EpCAM) is a protein membrane that is expressed majorly in various different types of tumor, including ovary, neck, breast, pancreas, head, colon and lungs. EpCAM serves as therapeutic agent to ovarian cancer (69). Aldehyde dehydrogenase (ALDH) isoenzyme ALDH1A1 was discovered as marker of CSCs, as it is chemoresistance in the ovarian CSC (70). Various ALDH isoenzymes including ALDH1A3, ALDH3A2 and ALDH7A1 has very higher expression rate in ovarian cancers in comparison to normal healthy ovarian tissues (71). Hence, ALDH is a remarkable marker to analyze ovarian cancer stem cells (OCSCs) which are responsible for Ovarian cancer progression.

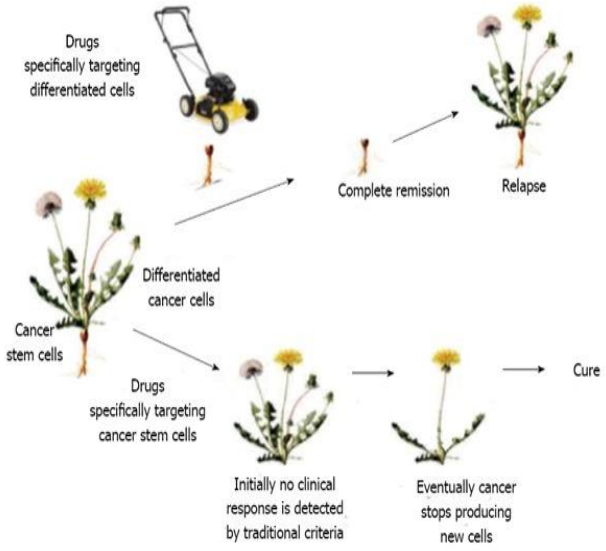

Fig. 3. Mode of action of drug delivery for specific cancer stem cells therapies. Figure adapted from (72).

CONCLUSION

Cancer Stem Cells (CSCs) from the day of their discoveries, have been known a big hurdle in cancer cure but with the huge research on their molecular biology, these are known as the hope to develop cancer treatment strategies. CSCs in every localized tumor behave in almost a similar way but the major issue is their stemness characteristics. Several questions are remained unanswered till now like why a tumor organ develops cancer stem cells for them? Or it's the stem cells of specific organ who transformed themselves toward cancer cells and then cancer development or there is another unknown mechanism? If the cancer stem cells are developed after the development of cancer in an organ then there are several hopes to find the solutions sooner but if the organ specific stem cells transformed themselves toward cancer cells and then these cells developed the localized cancer, then the story is a little bit more difficult to explore. Understanding the current studies, it can be concluded that we are unable to find out cure until we cannot understand the mechanism of CSCs origin and then their role in cancer development and progression.

CONFLICT OF INTEREST

The authors declare no-conflict of interest with any person or organization.

REFERENCES

1. Bonnet D, Dick JE. Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell. Nature medicine. 1997;3(7):730-7.
2. Singh SK, Hawkins C, Clarke ID, Squire JA, Bayani J, Hide T, et al. Identification of human brain tumour initiating cells. nature. 2004;432(7015):396-401.
3. O'Brien CA, Pollett A, Gallinger S, Dick JE. A human colon cancer cell capable of initiating tumour growth in immunodeficient mice. Nature. 2007;445(7123):106-10.
4. Li W, Ma N, Ong LL, Nesselmann C, Klopsch C, Ladilov Y, et al. Bcl-2 engineered MSCs inhibited apoptosis and improved heart function. Stem cells. 2007;25(8):2118-27.
5. Collins AT, Berry PA, Hyde C, Stower MJ, Maitland NJ. Prospective identification of tumorigenic prostate cancer stem cells. Cancer research. 2005;65(23):10946-51.
6. Seo D-C, Sung J-M, Cho H-J, Yi H, Seo K-H, Choi I-S, et al. Gene expression profiling of cancer stem cell in human lung adenocarcinoma A549 cells. Molecular cancer. 2007;6(1):75.
7. Prince M, Sivanandan R, Kaczorowski A, Wolf G, Kaplan M, Dalerba P, et al. Identification of a subpopulation of cells with cancer stem cell properties in head and neck squamous cell carcinoma. Proceedings of the National Academy of Sciences. 2007;104(3):973-8.
8. Kim CF, Dirks PB. Cancer and stem cell biology: how tightly intertwined? Cell stem cell. 2008;3(2):147-50.

9. Ahmed N, Abubaker K, Findlay J, Quinn M. Cancerous ovarian stem cells: obscure targets for therapy but relevant to chemoresistance. Journal of cellular biochemistry. 2013;114(1):21-34.
10. Valent P, Bonnet D, De Maria R, Lapidot T, Copland M, Melo JV, et al. Cancer stem cell definitions and terminology: the devil is in the details. Nature Reviews Cancer. 2012;12(11):767-75.
11. Reya T, Morrison SJ, Clarke MF, Weissman IL. Stem cells, cancer, and cancer stem cells. nature. 2001;414(6859):105-11.
12. Kelly PN, Dakic A, Adams JM, Nutt SL, Strasser A. Tumor growth need not be driven by rare cancer stem cells. Science. 2007;317(5836):337-.
13. Takebe N, Ivy SP. Controversies in cancer stem cells: targeting embryonic signaling pathways. Clinical Cancer Research. 2010;16(12):3106-12.
14. Jaiswal S, Traver D, Miyamoto T, Akashi K, Lagasse E, Weissman IL. Expression of BCR/ABL and BCL-2 in myeloid progenitors leads to myeloid leukemias. Proceedings of the National Academy of Sciences. 2003;100(17):10002-7.
15. Phillips TM, McBride WH, Pajonk F. The response of CD24−/low/CD44+ breast cancer–initiating cells to radiation. Journal of the National Cancer Institute. 2006;98(24):1777-85.
16. Balic M, Lin H, Young L, Hawes D, Giuliano A, McNamara G, et al. Most early disseminated cancer cells detected in bone marrow of breast cancer patients have a putative breast cancer stem cell phenotype. Clinical cancer research. 2006;12(19):5615-21.
17. 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 Research. 2006;8(5):1-13.
18. Fanali C, Lucchetti D, Farina M, Corbi M, Cufino V, Cittadini A, et al. Cancer stem cells in colorectal cancer from pathogenesis to therapy: controversies and perspectives. World journal of gastroenterology: WJG. 2014;20(4):923.
19. Venkitaraman AR. Cancer susceptibility and the functions of BRCA1 and BRCA2. Cell. 2002;108(2):171-82.
20. 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(3):259-73.
21. Al-Hajj M, Clarke MF. Self-renewal and solid tumor stem cells. Oncogene. 2004;23(43):7274-82.
22. Li X, Lewis MT, Huang J, Gutierrez C, Osborne CK, Wu M-F, et al. Intrinsic resistance of tumorigenic breast cancer cells to chemotherapy. Journal of the National Cancer Institute. 2008;100(9):672-9.
23. Wright MH, Calcagno AM, Salcido CD, Carlson MD, Ambudkar SV, Varticovski L. Brca1 breast tumors contain distinct CD44+/CD24-and CD133+ cells with cancer stem cell characteristics. Breast Cancer Research. 2008;10(1):R10.
24. Ginestier C, Hur MH, Charafe-Jauffret E, Monville F, Dutcher J, Brown M, et al. ALDH1 is a marker of normal and malignant human mammary stem cells and a predictor of poor clinical outcome. Cell stem cell. 2007;1(5):555-67.
25. Li Y, Zhang T, Korkaya H, Liu S, Lee H-F, Newman B, et al. Sulforaphane, a dietary component of broccoli/broccoli sprouts, inhibits breast cancer stem cells. Clinical Cancer Research. 2010;16(9):2580-90.
26. Kakarala M, Wicha MS. Implications of the cancer stem-cell hypothesis for breast cancer prevention and therapy. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2008;26(17):2813.

27. Warner JK, Wang JC, Hope KJ, Jin L, Dick JE. Concepts of human leukemic development. Oncogene. 2004;23(43):7164-77.
28. Martinez-Climent JA, Fontan L, Gascoyne RD, Siebert R, Prosper F. Lymphoma stem cells: enough evidence to support their existence? haematologica. 2010;95(2):293-302.
29. Goodell MA, Brose K, Paradis G, Conner AS, Mulligan RC. Isolation and functional properties of murine hematopoietic stem cells that are replicating in vivo. The Journal of experimental medicine. 1996;183(4):1797-806.
30. Nakashima M, Ishii Y, Watanabe M, Togano T, Umezawa K, Higashihara M, et al. The side population, as a precursor of Hodgkin and Reed-Sternberg cells and a target for nuclear factor-κB inhibitors in Hodgkin's lymphoma. Cancer science. 2010;101(11):2490-6.
31. Bräuninger A, Hansmann M-L, Strickler JG, Dummer R, Burg G, Rajewsky K, et al. Identification of common germinal-center B-cell precursors in two patients with both Hodgkin's disease and non-Hodgkin's lymphoma. New England Journal of Medicine. 1999;340(16):1239-47.
32. Schmitz R, Renne C, Rosenquist R, Tinguely M, Distler V, Menestrina F, et al. Insights into the multistep transformation process of lymphomas: IgH-associated translocations and tumor suppressor gene mutations in clonally related composite Hodgkin's and non-Hodgkin's lymphomas. Leukemia. 2005;19(8):1452-8.
33. 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(7123):111-5.
34. Ferrandina G, Bonanno G, Pierelli L, Perillo A, Procoli A, Mariotti A, et al. Expression of CD133-1 and CD133-2 in ovarian cancer. International Journal of Gynecologic Cancer. 2008;18(3):506-14.
35. Ren F, Sheng W-Q, Du X. CD133: a cancer stem cells marker, is used in colorectal cancers. World Journal of Gastroenterology: WJG. 2013;19(17):2603.
36. Yin AH, Miraglia S, Zanjani ED, Almeida-Porada G, Ogawa M, Leary AG, et al. AC133, a novel marker for human hematopoietic stem and progenitor cells. Blood, The Journal of the American Society of Hematology. 1997;90(12):5002-12.
37. Wu N, Xiao L, Zhao X, Zhao J, Wang J, Wang F, et al. miR-125b regulates the proliferation of glioblastoma stem cells by targeting E2F2. FEBS letters. 2012;586(21):3831-9.
38. Schneider M, Huber J, Hadaschik B, Siegers GM, Fiebig H-H, Schüler J. Characterization of colon cancer cells: a functional approach characterizing CD133 as a potential stem cell marker. BMC cancer. 2012;12(1):96.
39. Yang Z-L, Zheng Q, Yan J, Pan Y, Wang Z-G. Upregulated CD133 expression in tumorigenesis of colon cancer cells. World journal of gastroenterology: WJG. 2011;17(7):932.
40. Ma S. Biology and clinical implications of CD133+ liver cancer stem cells. Experimental cell research. 2013;319(2):126-32.
41. Long H, Xie R, Xiang T, Zhao Z, Lin S, Liang Z, et al. Autocrine CCL5 signaling promotes invasion and migration of CD133+ ovarian cancer stem-like cells via NF-κB-mediated MMP-9 upregulation. Stem cells. 2012;30(10):2309-19.
42. Tirino V, Desiderio V, d'Aquino R, De Francesco F, Pirozzi G, Galderisi U, et al. Detection and characterization of CD133+ cancer stem cells in human solid tumours. PloS one. 2008;3(10):e3469.
43. Chen K-l, Pan F, Jiang H, Chen J-f, Pei L, Xie F-w, et al. Highly enriched CD133+ CD44+ stem-like cells with CD133+ CD44 high metastatic subset in HCT116 colon cancer cells. Clinical & experimental metastasis. 2011;28(8):751-63.

44. Haraguchi N, Ohkuma M, Sakashita H, Matsuzaki S, Tanaka F, Mimori K, et al. CD133+ CD44+ population efficiently enriches colon cancer initiating cells. Annals of surgical oncology. 2008;15(10):2927-33.
45. Du L, Wang H, He L, Zhang J, Ni B, Wang X, et al. CD44 is of functional importance for colorectal cancer stem cells. Clinical cancer research. 2008;14(21):6751-60.
46. Dalerba P, Dylla SJ, Park I-K, Liu R, Wang X, Cho RW, et al. Phenotypic characterization of human colorectal cancer stem cells. Proceedings of the National Academy of Sciences. 2007;104(24):10158-63.
47. Fang D, Kim Y, Lee C, Aggarwal S, McKinnon K, Mesmer D, et al. Expansion of CD133+ colon cancer cultures retaining stem cell properties to enable cancer stem cell target discovery. British journal of cancer. 2010;102(8):1265-75.
48. Vermeulen L, Todaro M, de Sousa Mello F, Sprick MR, Kemper K, Alea MP, et al. Single-cell cloning of colon cancer stem cells reveals a multi-lineage differentiation capacity. Proceedings of the National Academy of Sciences. 2008;105(36):13427-32.
49. Choi D, Lee HW, Hur KY, Kim JJ, Park G-S, Jang S-H, et al. Cancer stem cell markers CD133 and CD24 correlate with invasiveness and differentiation in colorectal adenocarcinoma. World journal of gastroenterology: WJG. 2009;15(18):2258.
50. Horst D, Kriegl L, Engel J, Jung A, Kirchner T. CD133 and nuclear β-catenin: the marker combination to detect high risk cases of low stage colorectal cancer. European Journal of Cancer. 2009;45(11):2034-40.
51. Langan RC, Mullinax JE, Ray S, Raiji MT, Schaub N, Xin H-W, et al. A pilot study assessing the potential role of non-CD133 colorectal cancer stem cells as biomarkers. Journal of cancer. 2012;3:231.
52. Huang EH, Hynes MJ, Zhang T, Ginestier C, Dontu G, Appelman H, et al. Aldehyde dehydrogenase 1 is a marker for normal and malignant human colonic stem cells (SC) and tracks SC overpopulation during colon tumorigenesis. Cancer research. 2009;69(8):3382-9.
53. Xu M, Yuan Y, Xia Y, Achilefu S. Monoclonal antibody CC188 binds a carbohydrate epitope expressed on the surface of both colorectal cancer stem cells and their differentiated progeny. Clinical Cancer Research. 2008;14(22):7461-9.
54. O'hare T, Zabriskie MS, Eiring AM, Deininger MW. Pushing the limits of targeted therapy in chronic myeloid leukaemia. Nature reviews Cancer. 2012;12(8):513-26.
55. Hamad A, Sahli Z, El Sabban M, Mouteirik M, Nasr R. Emerging therapeutic strategies for targeting chronic myeloid leukemia stem cells. Stem cells international. 2013;2013.
56. Nicholson E, Holyoake T. The chronic myeloid leukemia stem cell. Clinical Lymphoma and Myeloma. 2009;9:S376-S81.
57. Copland M, Hamilton A, Elrick LJ, Baird JW, Allan EK, Jordanides N, et al. Dasatinib (BMS-354825) targets an earlier progenitor population than imatinib in primary CML but does not eliminate the quiescent fraction. Blood. 2006;107(11):4532-9.
58. Maguer-Satta V, Petzer AL, Eaves AC, Eaves CJ. BCR-ABL expression in different subpopulations of functionally characterized Ph+ CD34+ cells from patients with chronic myeloid leukemia. 1996.
59. Wisniewski D, Affer M, Willshire J, Clarkson B. Further phenotypic characterization of the primitive lineage− CD34+ CD38− CD90+ CD45RA− hematopoietic stem cell/progenitor cell sub-population isolated from cord blood, mobilized peripheral blood and patients with chronic myelogenous leukemia. Blood cancer journal. 2011;1(9):e36-e.

60. Goldman JM. Chronic myeloid leukemia stem cells: now on the run. Journal of Clinical Oncology. 2009;27(2):313-4.
61. Gupta PB, Chaffer CL, Weinberg RA. Cancer stem cells: mirage or reality? Nature medicine. 2009;15(9):1010-2.
62. Steffensen KD, Alvero AB, Yang Y, Waldstrøm M, Hui P, Holmberg JC, et al. Prevalence of epithelial ovarian cancer stem cells correlates with recurrence in early-stage ovarian cancer. Journal of oncology. 2011;2011.
63. Bapat SA, Mali AM, Koppikar CB, Kurrey NK. Stem and progenitor-like cells contribute to the aggressive behavior of human epithelial ovarian cancer. Cancer research. 2005;65(8):3025-9.
64. Burgos-Ojeda D, Rueda BR, Buckanovich RJ. Ovarian cancer stem cell markers: prognostic and therapeutic implications. Cancer letters. 2012;322(1):1-7.
65. Zhang L, Teng C, An T. Progress in treating diabetes mellitus with adult stem cells. Sheng wu gong cheng xue bao= Chinese journal of biotechnology. 2008;24(2):177-82.
66. Meng E, Long B, Sullivan P, McClellan S, Finan MA, Reed E, et al. CD44+/CD24− ovarian cancer cells demonstrate cancer stem cell properties and correlate to survival. Clinical & experimental metastasis. 2012;29(8):939-48.
67. Surowiak P, Materna V, Kaplenko I, Spaczyński M, Dietel M, Kristiansen G, et al. Unfavorable prognostic value of CD24 expression in sections from primary and relapsed ovarian cancer tissue. International Journal of Gynecologic Cancer. 2006;16(2).
68. Heider K-H, Kuthan H, Stehle G, Munzert G. CD44v6: a target for antibody-based cancer therapy. Cancer Immunology, Immunotherapy. 2004;53(7):567-79.
69. Imrich S, Hachmeister M, Gires O. EpCAM and its potential role in tumor-initiating cells. Cell adhesion & migration. 2012;6(1):30-8.
70. Landen CN, Goodman B, Katre AA, Steg AD, Nick AM, Stone RL, et al. Targeting aldehyde dehydrogenase cancer stem cells in ovarian cancer. Molecular cancer therapeutics. 2010;9(12):3186-99.
71. Saw Y-T, Yang J, Ng S-K, Liu S, Singh S, Singh M, et al. Characterization of aldehyde dehydrogenase isozymes in ovarian cancer tissues and sphere cultures. BMC cancer. 2012;12(1):329.
72. Di J, Duiveman-de Boer T, Figdor CG, Torensma R. Aiming to immune elimination of ovarian cancer stem cells. World journal of stem cells. 2013;5(4):149.