Editorial

Cancer stem cell heterogeneity in hereditary breast cancer

Max S Wicha

Comprehensive Cancer Center, Department of Internal Medicine, University of Michigan, 1500 East Medical Center Drive, Ann Arbor, MI 48109, USA

Corresponding author: Max S Wicha, mwicha@umich.edu

Published: 16 April 2008
Breast Cancer Research 2008, **10:**105 (doi:10.1186/bcr1990)
This article is online at http://breast-cancer-research.com/content/10/2/105
© 2008 BioMed Central Ltd

See related research article by Wright *et al*., http://breast-cancer-research.com/content/10/1/R10

Abstract

The cancer stem cell hypothesis proposes that tumors arise in stem or progenitor cells generating in tumors driven by a subcomponent that retains cancer stem cell properties. Recent evidence supports the hypothesis that the BRCA1 gene involved in hereditary breast cancer plays a role in breast stem cell function. Furthermore, studies using mouse BRCA1 knockout models provide evidence for the existence of heterogeneous cancer stem cell populations in tumors generated in these mice. Although these populations may arise from different stem/progenitor cells, they share the expression of a common set of stem cell regulatory genes and show similar characteristics in *in vitro* mammosphere assays and xenograft models. Furthermore, these 'cancer stem cells' display resistance to chemotherapeutic agents. These studies suggest that breast tumors may display intertumor stem cell heterogeneity. Despite this heterogeneity, cancer stem cells may share common characteristics that can be used for their identification and for therapeutic targeting.

In a recent publication, Wright and colleagues [1] used a mouse knockout model of BRCA1 to demonstrate cellular heterogeneity of cancer stem cells. They generated 16 cell lines from five independent BRCA1$^{\Delta exon\ 11}$/p53$^{+/-}$ mouse mammary tumors. They then examined the expression of cell-surface markers associated with cancer stem cells in these cell lines. Interestingly, cells derived from one tumor contained populations that were characterized as CD44$^+$/CD24$^-$ and that displayed stem cell properties, whereas cells derived from another tumor contained a cancer stem cell population that was characterized by CD133 expression. The CD44$^+$/CD24$^-$ phenotype previously has been described as identifying a cell population with stem cell properties in human breast tumors [2].

Sheridan and colleagues [3] recently reported that a number of basal mammary carcinoma cell lines contain a CD44$^+$/CD24$^-$ cell population, whereas luminal cell lines do not. In contrast to human cancer cells, normal mouse mammary stem cells have been reported to have a CD24$^+$ phenotype [4]. Although CD133 previously has not been reported to be expressed on breast cancer stem cells, this marker is expressed on a variety of other human cancer stem cells, including those of the brain, prostate, and pancreas. Interestingly, Wright and colleagues [1] found no overlap between the CD44$^+$/CD24$^-$ and the CD133$^+$ cell populations. This suggests that there may be heterogeneity within stem cell populations in BRCA1 tumors. As has previously been proposed for sporadic breast tumors, this heterogeneity may potentially result from different cells of origin [5].

The cancer stem cell hypothesis proposes that tumors arise in either normal stem or progenitor cells through the disregulation of self-renewal processes. This results in tumors that are driven by a cellular subcomponent that retains stem cell properties. Recently, our group reported that BRCA1 functions as a regulator of breast stem cell fate [6]. This suggests the possibility that the heterogeneity of stem cells reported by Wright and colleagues represents different cells of origin in tumors that contain CD44$^+$/CD24$^-$ stem cells and those that contain CD133$^+$ stem cells. Despite the fact that there was no overlap in expression of CD44$^+$/CD24$^-$ and CD133$^+$ cell populations in these cell lines, both cancer stem cell populations overexpressed the stem cell genes *Oct4*, *Notch1*, *ALDH1*, *Fgfr1*, and *Sox1*. This is consistent with our recent report that ALDH1 is a marker of both normal and malignant human mammary stem cells [7]. Furthermore, this suggests that a common set of 'stemness' genes may be shared between heterogeneous populations of cancer stem cells.

Wright and colleagues used both *in vitro* assays as well as xenograft models to demonstrate the stem cell properties of the CD44$^+$/CD24$^-$ and CD133$^+$ cell populations. Both of these populations form mammospheres *in vitro*, a characteristic shared by normal [8] and malignant [9] mammary stem cells. Interestingly, cells cultured as mammospheres or those with stem cell markers show resistance to chemotherapeutic agents such as cisplatin compared with the bulk of the cell population. The resistance of breast cancer stem cells to both radiation [10] and chemotherapy

[11] has also been reported by other investigators. In addition, the proportion of cells characterized as $CD44^+/CD24^{low}$ significantly increases following neoadjuvant chemotherapy in patients with breast cancer [11], demonstrating the clinical relevance of these concepts. Although transporters such as BCRP are overexpressed in some stem cells [12], Wright and colleagues [1] did not find an increase in expression of ABC transporters in either stem cell population. Thus, the mechanisms of drug resistance in these cells remains to be elucidated. Other potential mechanisms of chemoresistance of cancer stem cells include overexpression of chemotherapy metabolizing enzymes such as aldehyde dehydrogenase 1, changes in cell cycle kinetics, and overexpression of anti-apoptotic proteins [13].

A number of therapeutic approaches are being developed to therapeutically target breast cancer stem cells. Wright and colleagues demonstrate that the HSP90 inhibitor 17-DMAG sensitizes these cells to chemotherapy. These *in vitro* experiments have potential clinical implications since HSP90 inhibitors are currently in clinical trials. Furthermore, these studies indicate the feasibility of using *in vitro* mammosphere assays for the screening of compounds that are able to target cancer stem cells.

In summary, recent studies suggest that both hereditary and sporadic breast tumors may originate through the disregulation of self-renewal pathways in normal mammary stem and/or progenitor cells. The resulting tumors may be driven by heterogeneous populations of cancer stem cells. This heterogeneity may reflect different cells of origin and/or different mutation profiles in these cells. These heterogeneous cancer stem cell populations, in turn, may determine the overall molecular phenotype of tumors as assessed by molecular profiling. The development of suitable *in vitro* and mouse models should accelerate research aimed at identifying these diverse cancer stem cell populations. This should facilitate the identification of suitable targets for the development of strategies aimed at cancer prevention and therapy.

Competing interests

The author declares that they have no competing interests.

References

1. 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 Res* 2008, **10:**R10.
2. 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:**3983-3988.
3. Sheridan C, Kishimoto H, Fuchs RK, Mehrotra S, Bhat-Nakshatri P, Turner CH, Goulet R Jr., Badve S, Nakshatri H: **$CD44^+/CD24^-$ breast cancer cells exhibit enhanced invasive properties: an early step necessary for metastasis.** *Breast Cancer Res* 2006, **8:**R59.
4. Shackleton M, Vaillant F, Simpson KJ, Stingl J, Smyth GK, Asselin-Labat ML, Wu L, Lindeman GJ, Visvader JE: **Generation of a functional mammary gland from a single stem cell.** *Nature* 2006, **439:**84-88.
5. Dontu G, El-Ashry D, Wicha MS: **Breast cancer, stem/progenitor cells and the estrogen receptor.** *Trends Endocrinol Metab* 2004, **15:**193-197.
6. Liu S, Ginestier C, Charafe-Jauffret E, Foco H, Kleer CG, Merajver SD, Dontu G, Wicha MS: **BRCA1 regulates human mammary stem/progenitor cell fate.** *Proc Natl Acad Sci U S A* 2008, **105:**1680-1685.
7. Ginestier C, Hur M, Charafe-Jauffret E, Monville F, Dutcher J, Brown M, Jacquemier J, Viens P, Kleer CG, Liu S, Schott A, Hayes D, Birnbaum D, Wicha MS, Dontu G: **ALDH1 is a marker of normal and malignant breast stem cells and a predictor of poor clinical outcome.** *Cell Stem Cell* 2007, **1:**555-567.
8. Dontu G, Abdallah WM, Foley JM, Jackson KW, Clarke MF, Kawamura MJ, Wicha MS: ***In vitro* propagation and transcriptional profiling of human mammary stem/progenitor cells.** *Genes Dev* 2003, **17:**1253-1270.
9. Ponti D, Costa A, Zaffaroni N, Pratesi G, Petrangolini G, Coradini D, Pilotti S, Pierotti MA, Daidone MG: **Isolation and *in vitro* propagation of tumorigenic breast cancer cells with stem/progenitor cell properties.** *Cancer Res* 2005, **65:**5506-5511.
10. Phillips TM, McBride WH, Pajonk F: **The response of $CD24^{(-/low)}/CD44^+$ breast cancer-initiating cells to radiation.** *J Natl Cancer Inst* 2006, **98:**1777-1785.
11. Yu F, Yao H, Zhu P, Zhang X, Pan Q, Gong C, Huang Y, Hu X, Su F, Lieberman J, Song E: **let-7 regulates self renewal and tumorigenicity of breast cancer cells.** *Cell* 2007, **131:**1109-1123.
12. Kim M, Turnquist H, Jackson J, Sgagias M, Yan Y, Gong M, Dean M, Sharp JG, Cowan K: **The multidrug resistance transporter ABCG2 (breast cancer resistance protein 1) effluxes Hoechst 33342 and is overexpressed in hematopoietic stem cells.** *Clin Cancer Res* 2002, **8:**22-28.
13. Korkaya H, Wicha MS: **Selective targeting of cancer stem cells: a new concept in cancer therapeutics.** *BioDrugs* 2007, **21:**299-310.