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EDITORIAL

Thoughts about cancer stem cells in solid tumors

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Abstract

Cancer chemotherapy efficacy is frequently impaired by either intrinsic or acquired tumor resistance. A fundamental problem in cancer research is identifying the cell type that is capable of sustaining neoplastic growth and its origin from normal tissue cells. In recent years, the cancer stem cell (CSC) theory has changed the classical view of tumor growth and therefore the therapeutic perspective. Overcoming intrinsic and acquired resistance of cancer stem/progenitor cells to current clinical treatments represents a major challenge in treating and curing the most aggressive and metastatic cancers. On the other hand, the identification of CSCs *in vivo* and *in vitro* relies on specific surface markers that should allow the sorting cancer cells into phenotypically distinct subpopulations. In the present review, recent papers published on CSCs in solid tumors (breast, prostate, brain and melanoma) are discussed, highlighting critical points such as the choice of markers to sort CSCs and mouse models to demonstrate that CSCs are able to replicate the original tumor. A discussion of the possible role of aldehyde dehydrogenase and CXCR6 biomarkers as signaling molecules in CSCs and normal stem cells is also discussed. The author believes that efforts have to be made to investigate the functional and biological properties of putative CSCs in cancer. Developing diagnostic/prognostic tools to follow cancer development is also a challenge. In this connection it would be useful to develop a multidisciplinary approach combining mathematics, physics and biology which merges experimental approaches and theory. Biological models alone are probably unable to resolve the problem completely.

Key words: Cancer stem cells; Tumor; Asymmetric self renewal; Biomarkers

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INTRODUCTION

Cancer stem cells (CSCs) are a subpopulation of tumor cells that possess the stem cell properties of self renewal and differentiation, generating the heterogeneous lineages of cancer cells that comprise the tumor. Thus, CSCs can only be defined experimentally by their ability to replicate the generation of a continuously growing tumor. Contrary to normal stem cells which are notable for the vigilance with which their proliferation is controlled and the care with which their genomic integrity is maintained, CSCs are frequently distinguished by their lack of control of such processes. Identifying differences between normal stem cells and CSCs is important for understanding how cancers progress and for translating advances in CSC biology into therapies that help patients.

There are many issues related to the identification of CSCs that must be considered. The first is the use of

serial transplantation to validate a candidate CSC subpopulation, monitoring its capability to reproduce the heterogeneity of the primary tumor. Both xeno- and syngeneic transplantation may lose the intricate network of interactions with diverse support, such as those involving fibroblasts, endothelial cells, macrophages, mesenchymal stem cells, as well many of the cytokines and receptors involved in these interactions (for a more comprehensive discussion reed[1]). Another important problem is determining the best markers to identify CSCs. As discussed below this problem is still open. In light of recent findings reported for solid tumors like brain, prostate, breast and melanoma, I give my point of view on this issue. Moreover I discuss how to dissipate the shadows from the CSCs debate.

CSCs IN SOLID TUMORS: BREAST, PROSTATE, BRAIN AND MELANOMA

Tumor growth can be described either by the conventional model or by the CSC theory. According to the first model, cells are homogeneous and all are tumorigenic, while the CSC theory states that in the tumor there is a subpopulation sustaining tumor growth[1]. The first evidence of CSCs came from hematological tumors such as acute myeloid leukemia[2]. Later, CSCs were detected in breast, prostate, brain cancer and melanoma. In breast cancer the first evidence of a subpopulation with a specific cell-surface antigen profile (CD44+/CD24-) that can successfully establish itself as tumor xenograft was published in 2003[3]. More recently, aldehyde dehydrogenase (ALDH) was used as stem cell marker in 33 human breast cell lines[4]. ALDH is a detoxifying enzyme that oxidizes intracellular aldehydes and it is thought to play a role in the differentiation of stem cells *via* the metabolism of retinal to retinoic acid[5]. Interestingly, ALDH activity can be used to sort a subpopulation of cells that display stem cell properties from normal breast tissue and breast cancer[6]. ALDH activity, assessed by ALDEFLUOR assay, has been successfully used to isolate CSCs from multiple myeloma and acute leukemia as well as from brain tumors[7,8]. However in melanoma the ALDH phenotype was not associated with more aggressive subpopulations, arguing against ALDH as a "universal" marker[9].

Another interesting pathway that has been extensively studied is the Notch receptor signaling pathway (for a recent review see[10]). An important issue is the toxicity of potential treatments against these proteins. Even if the Notch pathway appears promising, it is also active in normal tissues, thus inhibition of Notch may have severe side effects. Therefore, as suggested by Harrison and colleagues, it seems important to study the complexity of the Notch pathway to target CSCs more successfully[10].

On the other hand, in a recent study, 275 patients with primary breast cancers of different subtypes and histological stages were analyzed for CD44+CD24- putative stem cell marker as well as for other markers (vimentin, osteonectin, connexin 43, ADLH, CK18, GATA3, MUC1). This study revealed a high degree of diversity in the expression of several of the selected markers in different tumor subtypes and histological stages[11]. I would like to point out that the latter findings could be explained by the fact that none of these markers are really specific for CSCs. In glioblastoma multiforme there is evidence for the existence of a more aggressive subpopulation of cancer cells and several markers have been identified[12-14]. Similarly, several candidate populations of prostate stem/progenitor cells have been reported including those expressing high levels of CD44, integrin $\alpha 2\beta 1$, or CD133[15]. Interestingly, two recent independent studies in the mouse prostate have identified two different populations of stem cells (SCs). One, marked by CD117 (c-Kit), seems to be localized in the basal layer[16] and the other, called castration-resistant Nkx3.1-expressing cells, in the luminal layer[17]. Identification and characterization of normal prostate SCs is clearly relevant to understanding the origin of human prostate cancer, as suggested by recent reviews[14,18]. In fact, it is difficult to ascertain the potential overlap and the lineage relationships of the various candidate stem cells that have been identified[19]. This is due, in part, to the distinct methodologies and assays employed[19]. In melanoma seven papers were published from 2005-2008 showing that a CSCs subpopulation exists[20-25]. However, in 2008 one paper argued against the existence of CSCs, based on the following observations: a relatively large fraction of melanoma cells (up to about 25%) was shown to initiate tumors in severely immunocompromised NOD/SCID IL2Rγ^{null} mice; the fraction of tumor-inducing cells depends upon assay conditions; several putative CSC markers appear to be reversibly expressed[26]. This paper, therefore, suggests that the detection of CSCs depends on how severely immunocompromised the mice are. The authors analyzed the expression of more than 50 surface markers on melanoma cells derived from several patients (A2B5, cKIT, CD44, CD49B, CD49D, CD49F, CD133, CD166) but focused on CD133 and CD166[26]. Using these markers they did not find any enrichment of tumor-initiating cells, but always found a high frequency of tumorigenic cells. However, in a recent paper it was shown that CD133 is highly expressed in melanoma cells and it is not a good marker for sorting CSCs[21]. Moreover, in 2010 Boiko and colleagues using the same immunocompromised mice could not confirm Quintana data[26]. Boiko *et al*[27] used CD271, a nerve growth factor receptor, as marker to identify CSCs.

DO CSCs EXHIST?

In my view it is quite clear that those involved in the CSC field must keep in mind that the only way to show that sorted putative CSCs are actually CSCs, is to replicate the heterogeneity of the tumor in syngeneic or immunodeficient mice. While it is possible that more severely immunocompromised mice are better than NOD/SCID mice, both are models, where the intricate interactions with the environment, such as mesenchymal cells, endo-

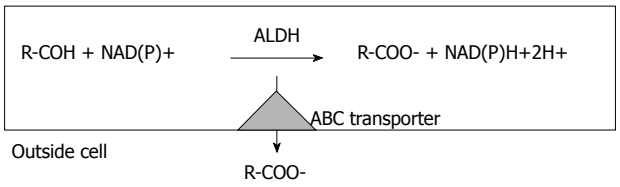

Figure 1 A generalized ALDH reaction in a living cell.

thelial cells, and fibroblasts, are lost[1]. Moreover, another important issue is the choice markers for sorting CSCs. The most common strategy is to use markers that are expressed in normal stem cells. However, most of the time the functional role of these markers in stem cells is unknown and their role in stem cell biology is unclear. There are two exceptions reported in the literature. One is ALDH, which seems to play a specific functional role in stem cells[6-8] and the other is CXCR6[28]. ALDH actually determines cell survival through the ability to detoxify many potentially cytotoxic molecules and contributing to drug resistance (Figure 1) Several stem cell types, including some CSCs, reside in and have metabolic pathways attuned to a hypoxic environment and the increase in ALDH activity may reflect the demands of surviving in such niches[29]. A recent review summarizes the physiological role of ALDH[30].

The chemokine receptor CXCR6, known as Bonzo, STRL33 or TYMSTR is selectively expressed on the surface of CD4+ T cells, CD8+ T cells[31], NKT cells[32], natural killer cells[33] and plasma cells[34]. Moreover, CXCR6/CXCL16 is overexpressed in many cancer cells such as breast cancer[35]. CXCR6 is therefore expressed in stem cells when they grow asymmetrically and is down regulated when they switch to grow symmetrically[28]. Moreover, CXCR6 was recently shown to be expressed in a subpopulation of melanoma cells with higher self renewal capability[28]. The latest discoveries concerning melanocyte stem cells, such as their localization in the hair follicle, is discussed in a recent review[36].

An interesting recent paper shows that overexpressing Oct4 cells in human melanoma acquire a stem cell phenotype, increasing the expression of CSC markers[37]. This paper raises a number of new questions that will probably be studied in the next few years. In my opinion, one of the most important questions is whether this effect is caused by all the cells or by a subpopulation, such as CSCs.

PERSPECTIVES

I believe that much effort will be required to investigate the functional and biological properties of putative CSCs in cancer. Moreover it would be useful to confirm the expression of proposed markers in human biopsy samples. The development of diagnostic/prognostic tools to follow cancer development is also a challenge. It would be useful to develop a multidisciplinary approach combining mathematics, physics and biology, merging experimental approaches and theory. In fact, biological models alone are not probably able to resolve the problem completely.

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London, United Kingdom

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CiRA Symposium: Advances in Nuclear Reprogramming and Stem Cell Research
Kyoto, Japan

February 26 - March 2, 2012
Gordon Research Conference: Reprogramming Cell Fate
Galveston, TX, United States

March 9, 2012
Cell Culture Technology: Recent Advances, Future Prospects
London, United Kingdom

March 11-16, 2012
Keystone Symposia: The Life of a Stem Cell: From Birth to Death
Olympic Valley (Lake Tahoe), CA, United States

March 25-30, 2012
Keystone Symposia: Advances in Islet Biology
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March 28-29, 2012
Single Cell Analysis Europe
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April 1 - 6, 2012
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Breckenridge, CO, United States

April 25-28, 2012
3rd International Congress on Responsible Stem Cell Research
Aula Nuova del Sinodo
Vatican City, Vatican City

April 27-29, 2012
2nd Institute of Advanced Dental Sciences & Research International Conference 2012: Fundamentals of Conducting and Reporting Research--Biological, Pharmaceutical, Medical & Dental Sciences
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Co-organized by the Society for Biological Engineering (SBE) and the ISSCR
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April 30, 2012
Stem Cells to Tissues
Boston, MA, United States

April 30, 2012
Regenerative Biology: From Stem Cells to Tissues
The Joseph B Martin Conference Center, Harvard Medical School
Boston, MA, United States

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Acknowledgments

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Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

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