COMMENTARY

How to Search for Specific Markers of Cancer Stem Cells

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Abstract

According to cancer stem cell hypothesis, cancer stem cells with unlimited self-renewal and multi-differentiation properties such as adult stem cells are the root cause of cancer initiation and progression, and targeted therapy to cancer stem cells is to become the most efficient therapy of cancer. However, specific markers should be discovered to define cancer stem cells accurately before targeted therapy. Therefore, we propose a model of specific markers of cancer stem cells and how to search these markers.

Key Words: Cancer stem cells - markers - search and identification

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Introduction

Cancer is a type of tissue with different differentiated stage malignant cells which is termed heterogeneity(Dick, 2008). The traditional model of heterogeneity is the stochastic model which defines each cancer cell with the potential of initiation and progression of cancer. Another contrary one is the intrinsic model which defines cancer stem cell with unlimited self-renewal and multi-differentiation property such as adult stem cell is the root cause of cancer initiation and progression(Dalerba et al., 2007a). The second model is supported by more and more experimental evidence from 1997(Bonnet and Dick, 1997). It shows good prospective in cancer early diagnosis and targeted therapy to cancer stem cells. Therefore, it is very important to understand signaling network, microenvironment, specific markers and other fields of cancer stem cells. In this paper, we mainly collect some literature about cancer stem cell markers and propose a model of specific markers of cancer stem cells.

Cancer Stem Cells with Markers

In 1997, Dick reported that CD34+CD38- cancer cells define stem cells present in leukemia patients. Since 2003, studies have shown that cancer stem cells with specific markers are present in solid tumors of the breast, brain, prostate, pancreas, colon, lung, liver, renal, ovary cancer and melanoma (Table 1). The cancer stem cell hypothesis is supported by more and more experimental evidence. Cancer stem cells with specific markers present in cancer are believed to be real by many cancer research scientists.

CD133 and other markers

At present, several markers such as CD24, CD34, CD38, CD44, CD90, CD105, CD117, CD133, CD166,

Table 1. Cancer stem cells with specific markers

Type of cancer	Specific markers	Reference
AML	CD34+CD38-Lin-	(Bonnet and Dick, 1997)
AML	CD34+CD38-CD71-HLA-DR-CD90-CD117-CD123+	(Jordan, 2002)
Breast	CD24-CD44+Lin-	(Al-Hajj et al., 2003; Bauerschmitz et al., 2008)
Breast	ALDH1+	(Ginestier et al., 2007)
Brain	CD133+	(Galli et al., 2004; Singh et al., 2003; Singh et al., 2004)
Prostate	a2_1hiCD133+	(Collins et al., 2005)
Lung	SP-C+CCA+	(Kim et al., 2005)
Lung	CD133+	(Eramo et al., 2008)
Melanoma	CD20+MCAM+	(Fang et al., 2005)
Melanoma	CD133+ABCG2+	(Monzani et al., 2007)
Melanoma	MDR1+	(Keshet et al., 2008)
Melanoma	ABCG5+	(Schatton et al., 2008)
Colon	CD133+	(LaBarge and Bissell, 2008; O'Brien et al., 2007; Ricci-Vitiani et al., 2007; Shmelkov et al., 2008)
Colon	Lgr5+	(Barker et al., 2007)
Colon	IL-4+	(Todaro et al., 2007; 2008)
Colorectal	CD44+ESAhiCD166+	(Dalerba et al., 2007b)
Intestinal	Lgr5+	(Barker et al., 2009)
Intestinal	CD133+	(Zhu et al., 2009)
Pancreatic	CD44+CD24+ESA+	(Li et al., 2007)
Pancreatic	CD133+	(Hermann et al., 2007)
HNSCC	CD44+	(Prince et al., 2007)
B-pre ALL	CD34+CD38+ CD19+; CD34+CD38-CD19+	(Kong et al., 2008)
Ovarian	CD44+CD117+	(Zhang et al., 2008)
Ovarian	CD133+	(Baba et al., 2009)
Liver	CD90+	(Yang et al., 2008)
Liver	CD133+	(Suetsugu et al., 2006)
Renal	CD105+	(Bussolati et al., 2008)

AML: acute myeloid leukaemia; ALDH: aldehyde dehydrogenase; SP-C: surfactant protein C; CCA: also known as CC10 or CCSP; MCAM: melanoma cell adhesion molecule; ABCG: ATP-binding cassette superfamily G member; MDR: multi-drug resistance protein; ESA: epithelial specific antigen; HNSCC: head and neck squamous cell carcinoma; ALL: acute lymphocytic leukaemia

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ABCG5, Lgr5, IL-4, MDR1, ALDH1 and ESA are specific markers of cancer stem cells or cancer initiating cells, but these markers are also expressed in normal stem cells and in several organs such as breast, brain, prostate, pancreas, colon, lung, liver, renal, ovary and skin. Given these considerations, these candidate markers are not enough specific markers of cancer stem cells or cancer initiating cells.

Taken the marker CD133 for example, Yin reported that the CD133 surface antigen was originally discovered as the target of a monoclonal antibody, AC133, which was generated to bind the CD34+ population of hematopoietic stem cells and progenitors(Yin et al., 1997). After that discovery, interest has been directed towards the potential of CD133 as a cell surface marker of adult stem cells (see table 1 in reference(Mizrak et al., 2008)). Follow the discovery of CD133 positive subpopulation with stem cell properties, the use of CD133 as markers for cancer stem cells in tumor has been actively investigated. So for CD133 positive subpopulation with cancer stem-like properties are discovered in many types of tumor (see Table 2 of reference (Bidlingmaier et al., 2008))

Given these considerations, CD133 is a star marker in defining adult stem cells and cancer stem cells, but it is unlike to be an ideal marker of adult stem cells or cancer stem cells. Firstly, it is expressed in too many tissues and lack of tissue specificness to distinguish one tissue from another tissue. Secondly, it is both expressed in many cancer tissues and normal tissues and lack of cancer specificness to distinguish cancer from normal tissues. Thirdly, some study show that it is expressed in non-cancer stem cells and lack of stemness(Bidlingmaier et al., 2008). Therefore, it is improper to purify CD133 positive cancer cells as cancer stem cells and anti-CD133 targeted therapy will have many side effects. For example, the most important one is that harm will occur to normal stem cells of prostate, pancreas, intestinal, lung, liver, renal, ovary, skin and may make these normal stem cells mutate to cancer initiating cells.

A Model of Ideal Specific Markers

In our opinion, ideal specific markers of cancer stem cells should meet three criteria. First, stemness, which means that the specific markers are correlated with the ability of self-renewal and multi-differentiation, is to distinguish stem cells from non-stem cells (Glinsky, 2008); second, specificness of cancer, which means that the specific markers are only expressed in cancer tissues, is to distinguish cancer from normal tissues; third, specificness of tissue, which means that the specific markers are only expressed in one tissue like colon, is to distinguish colon from other tissues of body (Figure 1).

How to Search for Ideal Specific Markers

Does this kind of ideal specific marker exist in cancer stem cells? According to current limited literature, there is no research report discovering one ideal marker meeting all three criteria. Davidson said that each cell type in the human body, including normal stem cells and cancer stem cells, has a unique signaling network architecture that is maintained by cell-specific transcriptional regulatory states; this results in cell-specific expression of genes

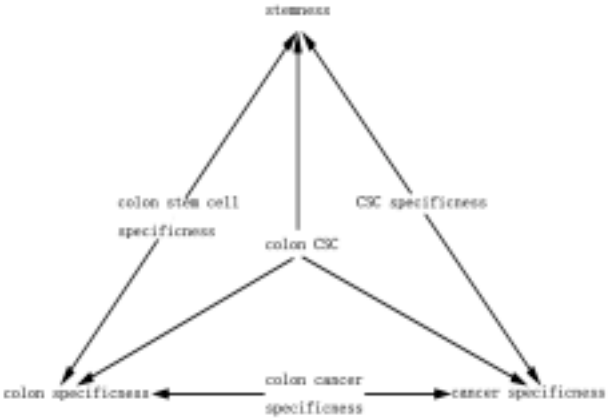

Figure 1. A Model of Ideal Specific Markers of Colon Cancer Stem Cells. Ideal specific markers of colon cancer stem cells should meet three criteria: stemness, cancer specificness and colon specificness. Stemness, which means that the specific markers are correlated with the ability of self-renewal and multi-differentiation, is to distinguish stem cells from non-stem cells; Cancer specificness, which means that the specific markers are only expressed in cancer tissues, is to distinguish cancer from normal tissues; Colon specificness, which means that the specific markers are only expressed in colon, is to distinguish colon from other tissues. If a marker meets both colon specificness and cancer specificness, it is an ideal specific marker of colon cancer; if a marker meets both colon specificness and stemness, it is an ideal specific marker of colon stem cell; if a marker meets both stemness and cancer specificness, it is an ideal specific marker of cancer stem cells.

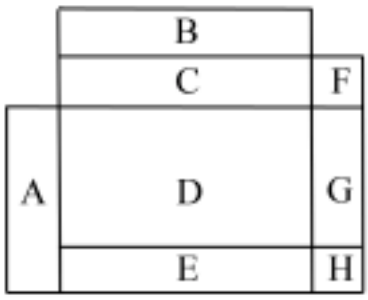

Figure 2. Genomes of Non-adult Stem Cells (non-ASCs), Adult Stem cells (ASCs), Non-cancerous Stem Cells (non-CSCs) and Cancer Stem Cells (CSCs). Genome of ASCs (C+D+F+G); Genome of non-CSCs (A+D+E) Genome of CSCs (D+E+G+H); Genome of non-ASCs (B+C+D) Genome A containing all mutated genes with no association with stemness only belongs to non-CSCs; Genome B containing normal genes with no association with stemness only belongs to non-ASCs; Genome C containing normal genes with no association with stemness belongs to ASCs and non-ASCs; Genome D containing normal genes with no association with stemness belongs to all cells; Genome E containing mutated genes with no association with stemness belongs to non-CSCs and CSCs; Genome F containing normal genes with association with stemness only belongs to ASCs; Genome G containing normal genes with association with stemness belongs to ASCs and CSCs; Genome H containing all mutated genes with association with stemness only belongs to CSCs. Therefore, only the genome H is ideal specific marker of cancer stem cells.

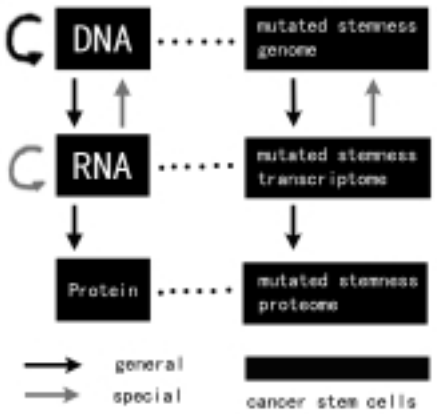

Figure 3. Central Dogma of Molecular Biology and Candidate Database of Ideal Markers for Cancer Stem Cells. According to central dogma of molecular biology, mutated stemness transcriptome is the set of all messenger RNA (mRNA) molecules, or "transcripts," produced by the mutated stemness genome; mutated stemness proteome is the entire complement of proteins translated by the mutated stemness transcriptome. The mutated stemness genome, transcriptome and proteome are candidate database of ideal markers for cancer stem cells, and each gene, transcript and protein in the database is likely to become an ideal marker for cancer stem cells.

(Davidson, 2006). The genomes of cancer cells and normal cells are similar except for a few mutations in cancer cells, so these mutated genes are only present in cancer cells and not in normal cells. However, not all mutated genes are associated with stemness, defined as the ability to self-renew and differentiate. Most mutated genes, which have no relationship with stem cells, are only present in non-cancerous stem cells and disappear after several cell cycles (referred to as maturation arrest)(Sell, 2005, 2006). Only a few mutated genes present in cancer cells correlate with stemness are ideal specific markers of cancer stem cells (Figure 2). These genes collection is termed mutated stemness genome here.

According to central dogma of molecular biology, the general transfers describe the normal flow of biological information: DNA replication: DNA can be copied to DNA, transcription: DNA information can be copied into RNA and translation: proteins can be synthesized using the information in mRNA as a template(Crick, 1970). Therefore, mutated stemness transcriptome is the set of all messenger RNA (mRNA) molecules, or "transcripts," produced by the mutated stemness genome; mutated stemness proteome is the entire complement of proteins translated by the mutated stemness transcriptome (Figure 3). The mutated stemness genome, transcriptome and proteome are candidate database of ideal markers for cancer stem cells, and each gene, transcript and protein in the database is likely to become an ideal marker for cancer stem cells.

Searching the Mutated Stemness Genome, Transcriptome and Proteome is an Enormous Project

It has been suggested that normal and cancer stem cells have potentially many common mechanisms for governing their populations (Reya et al., 2001). Such as adult stem cells, cancer stem cells have their own hierarchy: cancer stem cells (CSCs), cancer progenitor cells and cancer differentiated cells. Furthermore, Gao said “the CSC hypothesis covers the developing process of tumour-initiating cells (TICs), precancerous stem cells (pCSCs), migrating cancer stem cell (mCSCs), a cellular process that should parallel the histological process of hyperplasia (TICs) , precancerous lesions (pCSCs), malignant cancer (CSCs) and metastasis (mCSCs)” (Brabletz et al., 2005; Chen et al., 2007; Gao, 2008; Jung et al., 2006; Shen et al., 2008). TICs, pCSCs, CSCs and mCSCs have their own specific genes, transcripts and proteins, because each cell type in the human body has a unique signaling network architecture(Davidson, 2006). The mutated stemness genomes, transcriptomes and proteomes of pCSC, CSC and mCSC may be also different. The approach of genomics, transcriptomics and proteomics is greatly progressing, but it still has some bottlenecks(Ghosh and Poisson, 2009; Polychronakos, 2008). Therefore, how to search the mutated stemness genome, transcriptome and proteome is an enormous project. However, with the development of technology the approach of genomics, transcritptomics and proteomics will have great progression and ideal specific markers will be discovered more and more in the future.

Conclusions

Recently, many studies showed cancer stem cells or cancer initiating cells with specific markers are present in many types of cancer. These markers are not specific enough according to our ideal marker criteria. Therefore, we propose a model and a candidate database of ideal specific markers for cancer stem cells. We wish the model will be useful to search specific markers of cancer stem cells, although a lot of hard work still needs to be done.

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