·Cancer Stem Cell Column·

Research progression of CD133 as a marker of cancer stem cells

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[Abstract] More and more evidences support the cancer stem cell (CSC) hypothesis, which postulates that CSCs are responsible for tumor initiation, metastasis, recurrence and resistance to treatments. Therefore, they are the targets of antitumor therapy. Sorting CSCs using specific surface markers is the premise of investigating their biological behaviors. Recently, CD133 has been used extensively as a marker for the identification of stem cells from normal and cancerous tissues. Moreover, $CD133^-$ positive ($CD133^+$) tumor cells associate with the self-renewal, differentiation potentials, signal pathway, drug-resistance, recurrence, and prognosis of tumors. Therefore, $CD133^+$ cells could be potential targets of antitumor therapy in the future.

Key words: Stem cell, cancer stem cell, CD133

In the last decades of years, the incidence and mortality of tumors were increasing worldwide[1]. Although many progressions of antitumor therapies have been made, most tumor patients still cannot be cured, and are prone to recurrence and metastasis. In addition, the patients with malignant tumors always have short survival time and poor life quality. The identification of human cancer stem cells (CSCs) brought a hope for us[2]. Searching for specific surface markers to sort CSCs is the key to further investigate tumorigenesis, metastasis, recurrence and prognosis of tumors. Many studies suggested that CD133 was a specific surface marker for stem cells and CSCs. In this article, the important roles of CD133 in studies on stem cells and CSCs were reviewed.

CD133

Origins of CD133, AC133 and Prominin-1

Yin *et al.*[3] firstly separated and identified the human CD133 from $CD34^{bright}$ hemopoietic stem cells using the artificial AC133 monoclonal antibody. In the same year, Weigmann *et al.*[4] separated and identified Prominin-1 from mouse neuroepithelium stem cells. Due to the distinctly prominent structure on cell membrane surface, Prominin-1 was named according to the latin word 'prominere' which namely represents the meaning of 'prominent'. The CD133 was called as human Prominin-1 by some scholars. The molecular structure of human CD133 is similar to that of mouse Prominin-1, and about 60% of amino acid sequences are consistent between them. However, their tissue distributions are not identical[5,6]. Whether they have completely identical function is under investigation.

Structure

Human CD133 gene consisting of at least 37 exons is located in chromosome 4, and its length is about 152 kb[7,8]. The CD133 protein, a member of cell membrane protein superfamily, is a glycoprotein consisting of 865 amino acids, and its molecular weight is about 120 kDa[3]. The molecular structure of CD133 includes one extracellular NH_2- terminal, two big extracellular annuli, five membrane spaning domains, two small intracellular annuli containing rich cysteines and one intracellular -COOH structure (Figure 1).

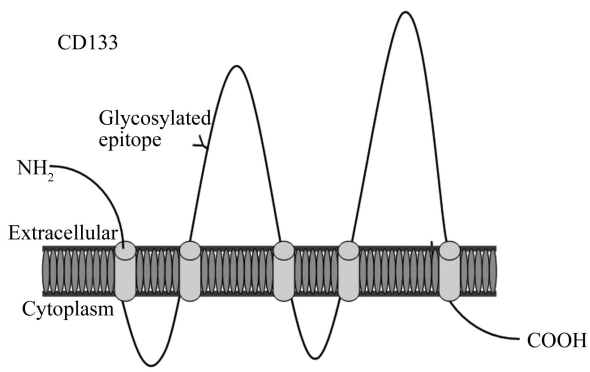

Figure 1 Structure of CD133

Transcriptional regulation

The human CD133 gene contains at least 9 different exons in

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the 5'-untranslated region (UTR), which lead to the generation of 7 kinds of 5'-UTR typing mRNA at least. Moreover, the mRNA expression shows a tissue-dependent pattern. The transcriptions of these subtypes of mRNA are regulated by 5 promoters (P1–P5). Through the luciferase reporter system, it was found that the activities of P1 and P2 promoters remarkably increased, and the activities of P3, P4 and P5 did not change obviously. In addition, the promoter activity could be inhibited by the methylation in vitro, suggesting that methylation might play a certain role in the regulation[8]. The recognition of tissue-specific promoter of CD133 provides an effective method for specifically sorting stem and precursor cells.

Subtypes

CD133 is divided into two subtypes: CD133-1 and CD133-2. The CD133 reported firstly was named as CD133-1. Yu *et al.*[8] separated and identified AC133-2 (CD133-2). The difference between the two subtypes is that, in the process of mRNA splicing, the deletion of a small exon (exon 4) containing 27 nucleotides leads to the loss of 9 amino acids at the NH_2 terminal outside cell membrane. The CD133-2 mRNA is predominant in many kinds of fetal and adult tissues, while the CD133-1 mRNA is predominant in fetal brain and adult skeletal muscle, but cannot be detected in the fetal liver and kidney, adult pancreas, and so on. Therefore, it is suggested that CD133-1 and CD133-2 might play different roles in fetal development and organ maturation process.

Sorting of stem cells and cancer stem cells

Using specific cell surface molecule as marker, the separation and sorting of stem cells or CSCs are the basis for further investigations. Currently, the sorting technologies are divided into two categories: magnetic activated cell sorting (MACS) and fluorescence activated cell sorting (FACS). In MACS, the monoclonal antibody against CD antigen is used as primary antibody and incubated with single cell suspension. Then, the immunomagnetic bead-labeled secondary antibody is incubated with the above single cell suspension. Through a special magnetic field of magnetic beads, the stem cells or CSCs are adsorbed in a magnetic sorting column, and are finally eluted and collected[9]. In FACS, the sorting is performed mainly through the specific proteins (such as CD molecules, and so on) expressed on the surface of stem cells or precursor cells, or the up-regulated or down-regulated proteins in stem cells. The single cell suspension is labeled by the monoclonal antibody that labeled by one or more than two kinds of fluorescein (such as FITC, PE, and so on) with different excitation wavelength to sort stem cells or CSCs[10].

CD133 and stem cells

Since Yin *et al.*[3] firstly reported that CD133 molecule existed in $CD34^+$ human hemopoietic stem cells, CD133 became a distinct molecular marker in identification and separation of stem and precursor cells due to its characteristic of down-regulated expression in differentiated cells. de Wynter *et al.*[11] and Gordon *et al.*[12] found that $CD133^+/CD34^+$ cells had higher clonogenicity and transplantation success rate than $CD133^-/CD34^-$ cells. Gallacher *et al.*[13] reported that, in $CD34^-CD38^-$ cell population in human cord blood, $CD133^+$ cells were the unique subpopulation which could form $CD34^+$ cells. Moreover, compared with $CD133^-$ cells, $CD133^+$ cells had more than 400 folds of transplantation capability in NOD/SCID mice. Lang *et al.*[14] found the advantage of $CD133^+$ cells in human gene allotransplantation. Subsequently, Bitan *et al.*[15] reported 5 cases of transplantation using $CD133^+$ stem cells from non-matching donors, and the lethal acute and chronic graft versus host reaction (GVHD) were avoided.

Likewise, as the surface characteristic molecule of stem cells and precursor cells, $CD133^+$ has been extensively reported in other cells fields outside the hematological system, including endothelial precursor cells[16], fetal brain stem cells[17], embryonic epithelial cells[18], prostate epithelial stem cells[19], muscle cells[20], and so on.

CD133 and cancer stem cells

At the earliest, the cancer stem cell theory came from a hypothesis 150 years ago[21]. According to this theory, a small subpopulation of cells exist in tumor cells, and this subpopulation of cells have stem cell-like characteristics. For example, CSCs are characterized by self-renewal, infinite proliferation, differentiation potential and high oncogenicity[22]. Recent studies found that stem cells and CSCs had some same specific surface molecular markers such as CD133, nestin, ESA, and so on, which further validated the hypothesis that stem cells existed in tumors.

Singh *et al.*[23,24] firstly reported that CD133 could be used as a characteristic surface of brain CSCs. They screened out $CD133^+$ cells from brain tumor using CD133 antibody, and found that these cells had very strong capabilities of proliferation, self-renewal and differentiation. Moreover, these cells could differentiate into the tumor which had the same phenotype as the brain tumor.

Olempska *et al.*[25] found that the expressions of CD133 and ABCG2 were up-regulated in 2 of 5 pancreatic carcinoma cell lines, suggesting that CD133 might be a specific surface molecule of pancreatic CSCs. Hermann *et al.*[26] also confirmed the existence of $CD133^+$ CSCs in pancreatic cancer tissues. In addition, the CSCs sorted from human colon and liver carcinomas using CD133 marker showed the potentials of self-renewal, differentiation, clone formation and proliferation in vitro. After inoculation into immune deficiency mice, these cells had the capability of re-forming original type of tumor[27-30].

Therefore, more and more experimental evidences support that CD133 might be a specific surface molecule of CSCs, especially solid tumor stem cells, suggesting that CD133 is likely to become an effective target of antitumor therapy. To date, various types of tumors, in which CD133 was reported as a specific marker of CSCs, are listed in Table 1.

Table 1 Studies that have used CD133 to isolate populations with cancer stem cell properties

Tumor	Cell source	Antibody	Characterization	Authors	References
Brain tumor	Primary tumors	CD133-1	In vitro	Singh et al.	23,24
Pancreatic cancer	Primary tumors	CD133-1	In vitro and in vivo	Olempska et al. and Hermann et al.	25,26
Colon cancer	Primary tumors	CD133-1	In vitro and in vivo	O'Brien et al. and Ricci-Vitiani et al.	27,28
Hepatocellular carcinoma	Cell lines	CD133-1	In vitro and in vivo	Yin et al. and Suetsugu et al.	29,30
Prostate cancer	Primary tumors	CD133-1	In vitro	Collins et al.	31
Renal carcinoma	Primary tumors	CD133-1	In vitro and in vivo	Bruno et al.	32
Laryngeal carcinoma	Cell lines	CD133-1	In vitro	Zhou et al.	33
Melanoma	Primary tumors and cell lines	CD133-1	In vitro and in vivo	Monzani et al.	34
Lung cancer	Primary tumors	CD133-1	In vitro and in vivo	Eramo et al.	35
Ovarian cancer	Primary tumors	CD133-1/2	In vitro and in vivo	Ferrandina et al.	36

CD133 as a potential new therapy target

CD133, drug-resistance of tumors and regulation of related signal pathways

One tough problem in tumor therapy is that tumor cells, with stem cell-like characteristics, show various degrees of insensitivity to current chemotherapy or radiotherapy. In the process of treating tumors, a few tumor cells can escape from the effect of antitumor drugs, and may form secondary tumors which have stronger tolerance to existing treatments. $CD133^+$ CSCs, with stem cell-like characteristics, are insensitive to chemotherapy and radiotherapy. Currently, the functions of CD133 have not been fully investigated. Whether the existence of CD133 or the upregulation of CD133 expression is invovled in the mechanism of tumor drug-resistance is under investigation in worldwide.

Hambardzumyan *et al.* [37] reported that the stem cell-like characteristics of $CD133^+$ cell-formed brain tumor might be associated with Notch signal pathway. The block of Notch signal pathway through the inhibition of γ- secretase could inhibit Hes1 expression and promote the apoptosis of brain tumor cells[38]. At the same time, when the Notch-inhibited tumor cell line with high differentiation was re-inoculated into NOD/SCID mice, it could not form a new tumor. Moreover, the block of Notch pathway led to the loss of about 5 folds of $CD133^+$ cells, and weakened their capability of excreting Hoechst dye. In pleomorphic brain glioma with high malignancy, the self-renewal of $CD133^+$ cells may be associated with HEDGEHOG-GLI (HH-GLI) pathway, and express stem cell-specific genes, such as OLIG2, BMI1, BCAN, OCT.4, NANOG, PTEN, ABCG2, PDGFR-A, SOX2 and NRD1[39]. The block of HH-GLI pathway by SMO siRNA suppresses the proliferation and tumorigenic ability of $CD133^+$ cells, and prolongs the survival time of mice with brain tumor. In comparative drug test, temozolomide, an anti-neuroglioma drug, showed inhibitory effect on cell proliferation, but had no effect on the self-renewal of glioma cells; on the other hand, cyclopamine, a HH-GLI pathway inhibitor, effectively decreased the quantity of tumor cell clones, suggesting that using these two drugs in combination would be more effective for removing CSCs[40].

Liu *et al.* [39] investigated the cells collected from glioma patients, and found that the expression levels of nervous precursor cell markers, such as CD90, CD44, CXCR4, and nestin, were higher in $CD133^+$ cells than in $CD133^-$ cells. Moreover, in $CD133^+$ cells, the anti-apoptosis genes such as Bcl-2, Bcl-xL, FLIP, c-IAP2, XIAP, and NAIP were highly expressed, while the expression of promoting apoptosis gene Bax was down-regulated. In addition, it was reported that the expression of ATP pump related ABCG5 was up-regulated[40]. Frank *et al.* [41] found that the $CD133^+$/$ABCG5^+$ melanoma was insensitive to adriamycin. Moreover, the CD133 and ABCG5 were highly expressed in melanoma cells collected from patients, suggesting that they might be key molecules for tumor drug-resistance and become effective therapeutic targets.

CD133 and stem cell therapy

CD133 has become a useful specific marker for sorting hemopoietic stem cells. Moreover, accumulating data showed that $CD133^+$ cells may play a more important role in treating stem cell-associated diseases. Bhatia *et al.* [42] reported that, compared with $CD34^+$ cells, $CD133^+CD34^-$ cells could generate the same regeneration potency after transplantation, and could differentiate into $CD133^+CD34^+$ cells. In addition, Lang *et al.* [14] demonstrated in the early clinical trial that, compared with $CD34^+$ cells, $CD133^+$ cells could slightly improve the state of transplantation. Torrente *et al.* [43] found that $CD133^+$ cells in circulation could be used in treating muscular dystrophy. Stamm *et al.* [44] reported that the transplantation of $CD133^+$ bone marrow could improve the function of infarcted myocardium, and the related machanism might be involved in the aggregation of $CD133^+$ endothelial precursor cells in blood vessels.

CD133 and tumor targeted therapy

With the constant deepening of experimental studies toward microcosmic fields and the continous progression of research methods, more evidences confirmed the existence of CSCs in tumor cells, and CD133 is very likely to become a specific surface marker of numerous CSCs. Because CSCs or CSC-formed secondary tumors are insensitive to chemotherapy or radiotherapy, CD133-targeted therapy will become the new research direction for antitumor therapy. The new therapy research focuses include classical signal pathway specifically targeting certain stem cells[45,46], specific block of cell cycle[47], application of interfering RNA in transcriptional machanism[48], specific degradation targeting mitochondrion[49], and related immunotherapy[50].

Conclusions

In summary, CD133 will play a very important role in the studies on stem cell-related diseases and CSCs. The specific sorting of stem cells using CD133 as a common cell surface marker of many kinds of tumor will be helpful to investigate biological characteristics, signal transduction pathway, chemotherapy- or radiotherapy-resistant mechanism of CSCs. At the same time, CD133 will probably become a target for tumor targeted therapy, and bring a great breakthrough for tumor therapy. However, some individual reports[51] showed that CD133- colon carcinoma cells also had CSC-like characteristics. Therefore, whether CD133 is a common specific marker of CSCs or there are other specific markers needs to be confirmed by further investigation.

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