[Frontiers in Bioscience, Landmark, 18, 447-453, January 1, 2013]

$CD133^+$ cancer stem cells in lung cancer

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1. ABSTRACT

Lung cancer is the most preventable cancer worldwide but has a poor prognosis. Recent advances in the study of lung cancer stem cell (CSC) populations has led to a growing recognition of the central importance of cells with stem cell-like properties in lung tumorigenesis. High number of $CD133^+$ cells is associated with the maintenance, metastasis and drug-resistance of lung cancer. CD133 serves as a stemness biomarker for $CD133^+$ CSCs, which have been found in lung cancer tissues. This article reviews the major studies supporting the existence and importance of $CD133^+$ CSCs in the maintenance, metastasis and drug resistance of lung cancer. Continued research in the field of CD133+ CSCs biology is vital, as ongoing efforts promise to yield new prognostic and therapeutic targets.

2. INTRODUCTION

Lung cancer is the most preventable cancer, but is also the leading cause of cancer deaths worldwide (1). Its prognosis is poor; the 5-year survival is low due to late presentation, disease relapse and low rate of curative therapy (2). It is estimated that more people in the West die of lung cancer than prostate, breast, colon, and cervical cancer combined (3). Understanding lung cancer pathogenesis may improve future human therapies. Preliminary evidence has pointed to the existence of cancel stem cells (CSCs) in lung cancer (4). Ho and colleagues (5) isolated populations of cells that efflux Hoechst 33342 dye from six human lung cancer cell lines. These cell lines exhibit several properties typical of stem cells, including clonogenic proliferation, invasive phenotypes in culture, multi-drug resistance, and increased telomerase expression.

CD133 is a member of prominin family, and was first discovered from hematopoietic stem cells as their marker and found later in certain types of leukemic cells (6, 7). CD133 is also expressed in human central nervous system stem cells (8), human lymphatic/vascular endothelial precursor cells (9) and prostatic epithelial stem cells (10). It is an antigen of a 120 kDa five-transmembrane glycoprotein (11) whose function is still unknown. CD133 is found in the transit-amplifying zone of the colonic crypt, which is susceptible to malignant transformation (12). Recently, expression of CD133 has been reported in CSCs from a variety of solid tumors including brain (13), prostate (14), pancreas (15), melanoma (16, 17), colorectum (18, 19), liver and bile duct (20, 21), lung, ovary, etc. (12, 22, 23). Though several reports demonstrated that $CD133^-$ cells in human tumors also have tumorigenic activity when xenotransplanted to immunocompromised mice (24-26). CD133 is still generally considered as a cell marker for CSCs. This study reviews the role of $CD133^+$ CSCs in lung cancer to better understand the pathogenesis of lung cancer and to provide valuable therapeutic information for this disease.

3. $CD133^+$ CANCER STEM CELLS IN LUNG CANCER

Recent studies provide evidence supporting the existence of $CD133^+$ CSCs in lung cancer. Eramo and colleagues (27) demonstrate the existence of $CD133^+$ cells with stem cell properties in human lung cancers and in naphthalene-induced injury mouse models. In specimens of human non-small cell lung cancer (NSCLC) and SCLC, an enrichment of $CD133^+$ cells is found in these tumors compared with healthy lungs (27). The $CD133^+$ cells isolated from freshly resected human lung cancer specimens could be grown indefinitely in culture and generated tumor xenografts phenotypically identical to the original tumor in immunocompromised mice (27). Bertolini and colleagues (28) independently reported similar findings using $CD133^+$ cells isolated from 60 human lung cancer samples. Furthermore, Liu and colleagues demonstrate that CD133 could be one of the markers of lung cancer naive cells isolated from fresh samples of 40 patients (29).

In different sub-tumor types of lung cancer, the expression of CD133 is diverse. Moreira and colleagues in a study with specimens from 85 lung tumors, (30) report that isolated human tumor tissues positive for CD133 are seen in 58% of small cell carcinomas, 63% of large cell lung carcinomas, 19% of adenocarcinomas, and 0% of the squamous cell carcinomas. A positive signal for CD133 in small cell carcinomas is restricted to the lumen of rosette-like structures (30). CD133 has been proposed as a CSCs marker of SCLC based on the study of SCLC cell line H446 (31, 32), but it is not in NSCLC (32). Although CD133 is not the single marker of NSCLC, its role in NSCLC could not be ignored. In a human lung adenocarcinoma model of nude mice, the expression of CD133 mRNA in tumor and bone marrow is significantly higher than that in the liver, spleen, and skin (33). A population of $CD133^+$ cells isolated from NSCLC can give rise to spheres and act as tumor-initiating cells (34). CD133 combined with nestin was identified as a novel potential marker of lung cancer CSCs in a study of 121 patient samples (35). Double positive cells with $CD133^+$ $CD44^+$ in the adenocarcinoma cell line A549 express significant CSC properties with continuous proliferative capacity and differentiation potential (36).

4. $CD133^+$ CANCER STEM CELLS IN MAINTENANCE OF LUNG CANCER

In the maintenance of lung cancer, $CD133^+$ CSCs play a significant role and different signal pathways are involved. Cells with high CD133 readily reconstitute the range of CD133 expression seen in the original xenograft tumor of SCLC, whereas cells with low CD133 could not (37). Compared with $CD133^-$ NSCLC cells, $CD133^+$ NSCLC cells have greater tumorigenicity, greater radioresistance, and higher expression of octamer-binding transcription factor 4 (Oct-4), Nanog homeobox, and sex-determining region Y, box 2 (Sox2) and high p-STAT3 levels (38). The tumorigenicity in the CD133 (high) subpopulation depends on continued expression of the basic helix-loop-helix transcription factor achaete-scute complex homolog 1 (37). One of regulatory mechanisms of CD133 expression in cancer cells involves mTOR and hypoxia-inducible factor-1 alpha (39). This finding suggests the involvement of the mTOR signal and oxygen-sensitive intracellular pathways in the maintenance of stemness in CSCs (39). Zhou and colleagues found that N-acetylglucosaminyltransferase V (Mgat5) is expressed at a relatively high level in $CD133^+$ lung adenocarcinoma cells, and knockdown of Mgat5 in $CD133^+$ cells inhibits cancer cell growth both *in vitro* and *in vivo* (40). In addition, CD133 can be induced by hypoxia in human lung cancer cells by up-regulation of octamer binding transcription factor 3/4 Oct-4 and SRY-box containing gene 2 (SOX2) (41).

Oct-4 expression plays a crucial role in maintaining the self-renewing, cancer stem-like, and chemoradioresistant properties of lung cancer-derived $CD133^+$ cells (42). By targeting the Oct-4 gene, miR-145 can inhibit $CD133^+$ lung adenocarcinoma stem cell proliferation (43). A study carried out by Zhang and colleagues showed that both the Oct-4 protein level and $CD133^+$ cells ratio were remarkably decreased in the pre-miR-145 mimics group, whereas they were significantly increased in the anti-miR-145 inhibitor group. MiR-145 can inhibit the proliferation of lung cancer stem cells in lung adenocarcinoma A549 cell line via a decrease in Oct-4 expression. Thus, miR-145 is a potential protective miRNA against lung cancer (43) (Figure 1). Yin and colleagues independently reported that an increase of miR-145 could reduce the proliferation and invasion as well as the ratio of $CD133^+$ initiating cells and the tumorsphere growth capacity of the human A549 cell line (44). MiR-145 can impair the proliferation of human lung adenocarcinoma-initiating cells by targeting Oct-4 and can lead to inhibition of lung cancer development (44). More recently, Chiou and colleagues report that lung adenocarcinoma-associated CSCs with CD133 marker exhibits low miR145 and high Oct-4/Sox-2/Fascin1 expression, CSC-like properties, and

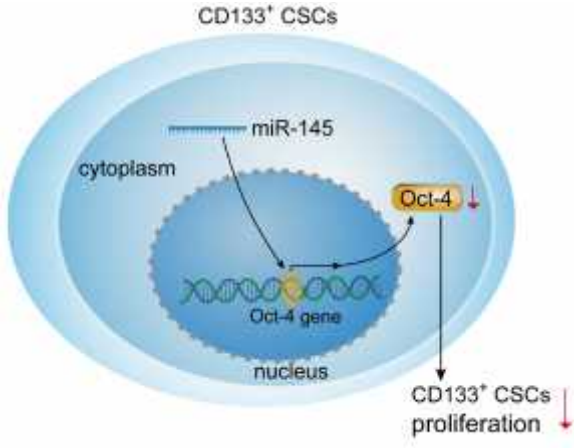

Figure 1. MicroRNA-145 and Oct-4 in regulating the proliferation of $CD133^+$ lung cancer stem cells. Oct-4 expression plays a crucial role in maintaining the self-renewing, cancer stem-like, and chemoradioresistant properties of lung cancer-derived $CD133^+$ cells. MicroRNA (miR)-145 can inhibit the proliferation of $CD133^+$ lung cancer stem cells via down-regulating Oct-4 expression. Thus, miR-145 is a potential protective miRNA of lung cancer.

chemoradioresistance by using miRNA/mRNA-microarray and quantitative RT-PCR (45). They found that in $CD133^+$ lung adenocarcinoma-associated CSCs, the expression of miR145 is negatively correlated with the levels of Oct-4/Sox-2/Fascin1 in lung adenocarcinoma patient specimens, and an Oct-4 (high) Sox-2 (high) Fascin1 (high) miR-145 (low) phenotype predicts poor prognosis. They also found that the repressive effect of miR145 on tumor metastasis is mediated by inhibiting the epithelial-mesenchymal transition (EMT) and metastatic ability, partially by regulating Oct-4/Sox-2/Fascin1, Tcf-4, and Wnt-5a. An *in vivo* study shows that polyurethane-short branch-polyethylenimine-mediated miR-145 delivery to xenograft tumors reduces tumor growth and metastasis, sensitizes tumors to chemoradiotherapies, and prolongs the survival times of tumor-bearing mice. These results demonstrate that miR-145 acts as a switch regulating $CD133^+$ lung CSCs and EMT properties, and provides insights into the clinical prospect of miR145-based therapies for malignant lung cancers (45).

In addition, in $CD133^+$ lung adenocarcinoma cells, Galectin-3 (Gal-3) is expressed at a relatively higher level and could induce $CD8^+$ T cell apoptosis *in vitro* (46). A study with 102 specimens of lung cancer showed that CD133 might induce apoptosis of tumor-infiltrating lymphocytes in NSCLC and tumor evading host immune surveillance (47). Furthermore, CD133 might be an independent risk factor of NSCLC participants (47). The potential prognostic value of CD133 expression in stage I lung adenocarcinomas was investigated in 177 patients. Results show that the level of CD133 expression is an independent prognostic marker and its expression combined with proliferating activity and/or vessel invasion could have excellent prognostic value to predict postoperative recurrence in patients with stage I lung adenocarcinomas (48). However, for patients with resected early-stage NSCLC, CD133 did not show significant association with the prognosis (49).

As for the postoperative relapse, NSCLC patients with the dual expression of CD133 and ATP-binding cassette superfamily G member 2 (ABCG2) have a high risk of early relapse after operation of lung resection (50). Thus, $CD133^+/ABCG2^+$ is an independent predictor of postoperative recurrence for patients with stage I NSCLC. Furthermore, $CD133^+/ABCG2^+$ NSCLC tumors have a significantly higher microvessel density and higher expression levels of angiogenic factors than the other subgroups (50).

5. $CD133^+$ CANCER STEM CELLS IN THE METASTASIS OF LUNG CANCER

CD133 has been associated with lung cancer metastasis, especially lymphoid metastasis, in several studies. Zhang and colleagues (51) immunohistochemically detected CD133 in the specimens from 77 patients with NSCLC, with a positive expression rate of CD133 and a positive correlation between CD133 expression and lymphoid metastasis, as well as a negative correlation between CD133 expression and the survival time of the patients. These findings suggest that CD133 expression is associated with lymphoid metastasis and prognosis of NSCLC, and its overexpression often suggests unfavorable prognosis of NSCLC (51). More recently, Hsieh and colleagues independently reported a similar finding that CD133 is increased in H1299-R (H1299-R2–H1299-R5) NSCLC cell line, which shows an increase in the number of metastatic lung nodules (52).

Among sub-tumor types of NSCLC, CD133 has been reported in the metastasis of squamous carcinomas. Lin and colleagues (53) found that the level of CD133 expression was significantly higher in the lymph node metastasis group than those in the non-metastasis group. CD133 is expressed in pulmonary squamous carcinomas, and there is a relationship between degree of expression and lymph node metastasis (53).

In the metastasis of lung cancer related to CD133, the insulin-like growth factor (IGF) system could regulate this process. In a study with an indirect co-culture model, IGF binding proteins-2 and -4 enhanced the migration of human $CD34^-/CD133^+$ hematopoietic stem and progenitor cells (HSPCs). IGF binding proteins-2 and -4, which are expressed in lung epithelial cancer cells, enhance the migration of $CD34^-/CD133^+$ HSPCs independent of IGF-I. (54).

6. $CD133^+$ CANCER STEM CELLS IN THERAPY OF LUNG CANCER

CD133 has a prognostic impact in NSCLC patients treated with induction chemoradiotherapy. A clinical study with 50 patients with a median follow-up period of 72 months shows that the 5-year overall survival

rate of the NSCLC patients with $CD133^+$ specimens is significantly worse than that of the patients with both CD133-negative expressions (55). The prognostic impact of CD133 is associated with a therapeutic effect on lung cancer, especially the effect of chemotherapy. In an *in vitro* study, differentiated progenitors, which lose expression of CD133 can acquire drug sensitivity in the treatment of lung tumor cells with doxorubicin, cisplatin, or etoposide (56).

Although CD133 is not the only NSCLC cell marker which has been identified, it could be the drug-resistance related CSC marker in NSCLC. Its role in the therapeutic effect on NSCLC is significant. CD133 expression was retrospectively examined in a total of 88 cases of previously untreated NSCLC by immunohistochemistry, showing a significant association between the expression of resistance-related proteins glutathione S-transferase, thymidylate synthase, catalase, O(6)-methylguanine-DNA methyltransferase, p170 and CD133 (57). Since CD133 expression is linked to a resistant phenotype, detection of $CD133^+$ cells may be useful to predict the efficacy of cytotoxic therapy (57).

In an *in vitro* study with cisplatin treatment, highly tumorigenic lung cancer $CD133^+ABCG2^+$ and $CD133^+CXCR4^+$ cells are spared by cisplatin treatment of lung tumor xenografts established from primary tumors (58). A tendency toward shorter progression-free survival is also observed in $CD133^+$ NSCLC patients treated with regimens of cisplatin combined with platinum (58). In an *in vitro* study with H1299-R (H1299-R2--H1299-R5) NSCLC cell line, CD133 is increased in expression, and there is increased drug resistance to cisplatin (52).

In addition, Vroling and colleagues (59) found that $CD133^+$ circulating hematopoietic progenitor cells (HPCs) predict for response to sorafenib plus erlotinib in NSCLC patients. This result suggests that the presence of pre-treatment $CD133^+$/HPCs is a promising candidate biomarker to further explore for use in selecting NSCLC patients who might benefit from sorafenib plus erlotinib treatment. An *in vitro* study about the cucurbitacin treatment on NSCLC shows that cucurbitacin I inhibits the stemness gene signature of $CD133^+$ NSCLC cells isolated from NSCLC patients and facilitates the differentiation of $CD133^+$ NSCLC cells into $CD133^-$ NSCLC cells (38). Xenotransplantation experiments revealed that cucurbitacin I plus radiotherapy or chemotherapeutic drugs significantly suppressed tumorigenesis and improved survival in NSCLC-$CD133^+$-transplanted, immunocompromised mice (38). Therefore, cucurbitacin I inhibits tumorigenic ability and enhances radiochemosensitivity in NSCLC-derived $CD133^+$ cells (38). A more recent study found that in response to both 5-FU and MTX in NSCLC cells, the number of $CD133^+$ cells is significantly increased in NSCLC cell lines A549, H460, and H23 (60), which indicates that the expression of drug-resistance related CSC marker CD133 in NSCLC cell lines could be considerably enhanced by 5-FU and MTX. As a drug-resistance related CSCs marker, there is no doubt that CD133 is involved in the drug resistance of NSCLC. However, it is still unconfirmed whether the increased expression of CD133 is the property of drug-resistance of CSCs in NSCLC, or is the corresponding response to chemotherapeutic drugs.

7. CONCLUSIONS

The relationship between CSCs and cancer formation is becoming increasingly attractive with respect to lung cancers. The link between CD133 and CSCs is now firmly established. While the function still is not clearly defined, CD133 is an important stemness biomarker in CSCs. Since $CD133^+$ CSCs are closely related with the metastasis of lung cancer, especially lymphoid metastasis, and resistance of several chemotherapeutic drugs, CD133 can have an important prognostic impact in patients with lung cancer, NSCLC in particular. Targeting and monitoring $CD133^+$ CSCs may lead to significant advances in prediction of outcome and lung cancer therapy.

8. ACKNOWLEDGMENTS

This project is supported by the National Nature Science Foundation of China (NSFC) (No: 30973822; Project name: The research of dual-regulation effect of Shuanghuang Shengbai Granule on both hematopoietic stem cells (HSCs) and lung cancer stem cells(CSCs)' proliferation and differentiation.

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Abbreviations: CSC: cancer stem cell; NSCLC, non-small cell lung cancer; Oct-4: octamer-binding transcription factor 4; Sox2: sex-determining region Y, box 2; SOX2: SRY-box containing gene 2; EMT: epithelial-mesenchymal transition; Gal-3: Galectin-3; ABCG2: ATP-binding cassette superfamily G member 2; HSPCs: hematopoietic stem and progenitor cells; IGF: insulin-like growth factor

Key Words: Cancer Stem Cell, Non-Small Cell Lung Cancer, Hematopoietic Stem, Progenitor Cells, Review

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