MINI REVIEW

Emerging Roles of Krüppel-Like Factor 4 in Cancer and Cancer Stem Cells

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Abstract

Cancer stem cells (CSCs) are rare subpopulations within tumors which are recognized as culprits in cancer recurrence, drug resistance and metastasis. However, the molecular mechanisms of how CSCs are regulated remain elusive. Krüppel-like factors (KLFs) are evolutionarily conserved zinc finger-containing transcription factors with diverse functions in cell differentiation, proliferation, embryogenesis and pluripotency. Recent progress has highlighted the significance of KLFs, especially KLF4, in cancer and CSCs. Therefore, for better therapeutics of cancer disease, it is crucial to develop a deeper understanding of the mechanisms of how KLF4 regulate CSC functions. Herein we summarized the current understanding of the transcriptional regulation of KLF4 in CSCs, and discussed the functional implications of targeting CSCs for potential cancer therapeutics.

Keywords: Kruppel-like factor 4 - cancer - cancer stem cells - cancer therapy

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Introduction

Nowadays, cancer is one of the major causes of mortality all across the world (Siegel et al., 2014). Approximately one-third of cancer patients die within five years after diagnosis. Currently, such therapies as surgical resection, radiotherapy, chemotherapy, and hormonal therapy, are designed to target all cancer cells. However, the benefits of these therapies are limited due to the existence of therapy-resistant cancer cells, which are able to regenerate the entire cancer cell populations after treatments (Dean et al., 2005). In the past few years, it has been recognized that these cells are cancer stem cells (CSCs), which are defined by their capacity of self-renewal and differentiating into subpopulations that possess different phenotypes (Dalerba et al., 2007). Until now, CSCs have been found to stand on top of a hierarchically organized apex similar to non-neoplastic tissues, and exhibit a unique feature of clonal growth and tumor formation (Visvader and Lindeman, 2008). Although CSCs are not necessarily cancerous stem cells, they have something in common with normal stem cells: plasticity (Tang, 2012). Moreover, both experimental and clinical studies indicate that CSCs can survive most cancer therapeutics. Therefore, complete cure for cancer cannot be achieved without complete ablation of CSCs (Li et al., 2013).

Kruppel-like factors (KLFs) are a family of DNA-binding transcriptional regulators expressed in a wide variety of tissues in human beings. They have diverse and essential functions in multiple cellular processes, including proliferation, inflammation, differentiation, migration, pluripotency and maintenance of homeostasis. Recent studies have also showed that the expression and activity of KLFs were altered in certain types of cancer. In addition, individual KLFs can be oncogenes or tumor suppressors depending on tumor, tissue type, or cancer stage. Moreover, KLF4 has been reported as one of the four factors used to reprogram adult fibroblasts into induced pluripotent stem cells (iPSCs) (Yamanaka, 2007), and reprogramming of cancer cells with pluripotency factors has been proposed as a potential cancer therapy. Therefore, it is not surprising to find out that KLF4 may play an important role in maintaining CSC populations. This review mainly focuses on the current understanding of KLF4 and its role in regulating CSC functions, and discusses the implications of targeting CSCs for cancer treatment.

Cancer Stem Cells

Cancer has been viewed as the result of tumor cell disorders and its unlimited cell growth and invasion. There is substantial evidence to support that cancer might be the consequence of genetic mutations, and abnormal interactions between microenvironment and corresponding types of cells (Reya et al., 2001). Disorders in the microenvironment are thought to be the driving force of tumor development and breakdown of tissue homeostasis (Ho and Fusenig, 2011). Therefore, cancer can be viewed as a "disorganized" tissue, with CSCs at the top of the hierarchy of heterogeneous tumor cells. This

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concept, which was first demonstrated in human acute leukemia, has drawn attention from basic and clinical researchers (Lapidot et al., 1994).

CSCs have been termed as a small subset of cancer cells that constitute a reservoir of self-sustaining cells, which have the capacity of self-renewal and generating heterogeneous lineages of cancer cells that comprise the tumor (Clarke et al., 2006). Unlike normal stem cells, self-renewal is typically downregulated in CSCs (Kreso and Dick, 2014). Until now, CSCs are recognized to represent a distinct cell population that has the capacity of self-renewal and clonal long-term repopulation (Clarke et al., 2006; Nguyen et al., 2012). However, it is still impossible to distinguish CSCs from non-CSCs in certain cancer types because most cells have CSC features. In addition, some cancer cells have been reported to exhibit plasticity by transitioning between a stem and non-stem cell state. Similar to CSCs, transitory cells also have the capability of clonal tumor initiation, however, prospective isolation is still difficult. In most cases, they are referred to as tumor-initiating cells (TICs). The existence of CSC population remains a controversial topic due to questions about the robustness of CSC markers (Magee et al., 2012), however, three independent studies successfully identified and tracked CSCs in brain, skin and intestinal tumors of mice (Chen et al., 2012; Driessens et al., 2012; Schepers et al., 2012). These findings might provide further evidence to support that CSCs are the driving force of tumor development (Gilbertson and Graham, 2012). The CSCs have been identified in several solid tumors based on expression of certain CSC surface markers. Until now, CSCs have been defined by such cell surface markers as CD24, CD29, CD34, CD44, CD90, CD133, aldehyde dehydrogenase-1 (ALDH-1) and epithelial-specific antigen (ESA) (Keymoosi, et al., 2014; Sabet, et al., 2014) (Table 1).

It is universally acknowledged that CSCs are generated from the transformation of normal stem cells (Figure 1). Similar to normal stem cells, CSCs are defined by multiple functional properties: 1) CSCs can go through unlimited cell divisions; 2); CSCs are on the top of tumor hierarchy and can generate all cell types in a tumor; 3) some CSCs are able to shuttle between quiescent, slow-cycling and active states; 4) some CSCs can exhibit resistance to conventional cancer therapies (Baccelli and Trumpp, 2012). Recent studies have indicated that these functional properties of CSCs might be sustained by tumor microenvironment, termed as "niche" (Cabarcas et al., 2011). The niche is the environment in which CSCs reside, and it is responsible for maintaining the self-renewal capacity and undifferentiated state of CSCs (Oskarsson, 2013). Elucidation of mechanisms of signal transduction between tumor and CSCs within the niche has been complicated by the fact that CSCs represent such a rare subpopulation of tumor cell populations and are thus difficult to identify *in vivo* (Ho and Fusenig, 2011). KLF4, as an essential regulator for maintaining stemness of somatic stem cells and embryonic stem cells (ESCs), has been suggested to play a vital role in the maintenance of CSCs (Tetreault et al., 2013).

Role of KLF4 in Tumorigenesis

Since the first identification of KLF1 in 1993 (Miller and Bieker,1993), a diverse family of its homologous genes has been discovered, known as KLFs. In general, the KLF family members can be divided into three groups on the basis of functional and structural relationships. KLF family of gene regulatory proteins are transcription factors implicated in the regulation of such essential cellular processes as differentiation, proliferation, migration, apoptosis and pluripotency (McConnell and Yang, 2010). Alterations of their functions are involved in the pathology of diverse diseases, including metabolic disorders, cardiovascular disease and cancer. Due to the ever-increasing interest in the human cancer field, research

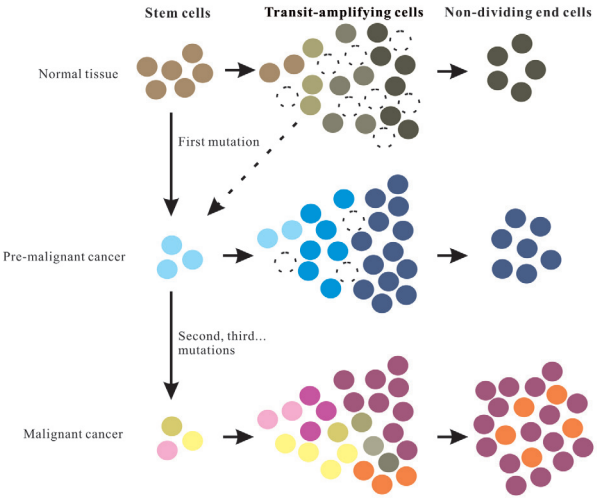

Figure 1. The schematic illustration of CSC evolution. Highly coordinated hierarchy of normal tissue cells is shown at the top, where cell turnover is characteristic of tissue maintenance. Stem cells give birth to transit-amplifying cells. Dashed circles represent cells that are differentiating. These cells finally give rise to mature cells that are non-dividing end cells. During the evolution of neoplastic populations, mutations or epigenetic changes (shown by color changes) will result in clonal expansion (middle of the figure). In the end, a mature malignant clone may be generated. These malignant cells have acquired a profile of aberrations (presented by multiple colors) and have lost many properties of normal differentiation characteristic of the transit-amplifying cells (indicated at the bottom of the figure). In this figure, CSCs are demonstrated as from normal tissue stem cells. However, multiple other scenarios can be envisaged in which CSCs arise from pre-malignant cells with 'later' phenotypes (indicated by dashed arrow)

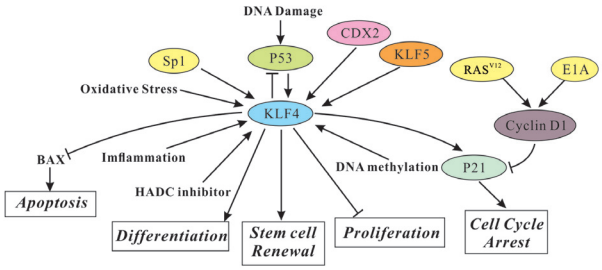

Figure 2. KLF4 Signaling Pathways. Expression of KLF4 is upregulated by many stimuli, including inflammation, DNA damage, oxidative stress, DNA methylation and HDAC inhibitors. Sp1, p53 and CDX2 positively regulate KLF4 promoter, whereas KLF5 suppresses it

on the regulation of KLFs in cancer diseases has become a rapidly emerging area.

Specifically, KLF4 has been reported to be implicated in diverse cellular processes, including self-renewal, proliferation, differentiation, apoptosis and cell cycle arrest. KLF4 is highly expressed in the post-mitotic cells in both gut and skin (Zheng et al., 2009). Downregulation of KLF4 in gastric cancer, colon adenomas, intestinal adenomas, prostate cancer, esophageal cancer, and lung cancer may contribute to malignant transformation and cellular hyperproliferation, which is consistent with its role in growth inhibition and cell cycle arrest (Choi et al., 2006). Recently, it has also been reported that KLF4 is expressed in ESCs, and forced expression of a combination of four transcription factors, including Oct4, c-myc, Sox2, and KLF4, can reprogram fibroblasts into iPSCs that are similar to ESCs, suggesting that KLF4 is critical for the maintenance of stem cells (Wernig et al., 2007). In addition, forced expression of KLF4 can inhibit ES cells from differentiating into erythroid progenitors, and can increase their ability to generate secondary embryoid bodies, indicating a role of KLF4 in maintaining the self-renewal capacity (Zheng et al., 2009). Also, it has been demonstrated that KLF4 plays a crucial role in cellular invasion and migration during embryogenesis (Garvey et al., 2010). Overexpression of KLF4 potently inhibits the migration and invasion of colon cancer cells, which facilitates the suppression of tumorigenesis by KLF4 (Dang et al., 2003). Moreover, laminin-5 and urokinase-type plasminogen activator receptor (uPAR), which play pivotal roles in cell growth, invasion and migration, have also been indicated to be regulated or associated with KLF4 (Wang et al., 2004). Furthermore, it has been shown that KLF8, whose function and structure are closely similar to KLF4 (Eaton et al., 2008), promotes both mesenchymal and stem cell population in kidney (Wang et al., 2007). KLF8 can also induce the invasiveness and motility in normal epithelial cells through regulation of E-cadherin (Wang and Zhao, 2007). Taken together, these studies indicate that KLF4 may play significant roles in regulating stem cell motility and self-renewal. These two processes are now believed to give rise to tumorigenesis. Therefore, we make a further insight into whether KLF4 plays a role in invasion and metastasis of CSCs and cancer cells.

Role of KLF4 in CSCs

Until now, most studies implicating KLFs in regulation of CSCs pertain to KLF4. The ability of cancer cells to invade and migrate is required in breast cancer (Yu et al., 2011). KLF4 can maintain telomerase activity in both normal stem cells and CSCs, indicating a role of KLF4 in long-term proliferative potential of stem cells (Wong et al., 2010). Moreover, KLF4 can enhance the binding of β-catenin, which transactivates telomerase reverse transcriptase (TERT), which indicates a potential link between stem cells and tumorigenesis (Wu et al., 2013). Also, epithelial-mesenchymal transition (EMT) is thought to be reminiscent of CSCs as previously described, showing features similar to many cancer systems (Yang and Weinberg, 2008). However, interesting findings in prostate and bladder cancer have demonstrated that the metastatic phenotype and self-renewal capacity in those cancers require an epithelial-like program instead of a mesenchymal-like feature (Hao et al., 2014).These inconsistencies reveal the limitations of current CSC models, and may be due to difference in tumor origins and specificity of cancer cell types. TGF-β is a well elucidated transcription factor that controls EMT process during tumorigenesis (Miettinen et al., 1994), and it can induce KLF4 synthesis in vascular smooth muscle cells (King et al., 2003). It has also been shown that with the crosstalk between KLF4 and TGF-β signaling, KLF4 can promote EMT in breast CSCs (Yu et al., 2011). KLF4 can also inhibit B cell-specific Moloney murine leukemia virus integration site 1 (BMI1), an intestinal stem cell marker that enhance colon tumor formation and cancer cell proliferation, while β-catenin promotes BMI1 expression (Yu et al., 2012). In colon CSC-enriched spheroid cells, KLF4 is essential for maintaining CSC-like cells (Leng et al., 2013). It has been shown that KLF4 was highly expressed only in CSC-enriched spheroid cells of DLD-1 colon cells, and it acted as an oncogene for colon cancer development. Inhibition of KLF4 expression reduced the expression of colon CSC marker genes (Leng et al., 2013).

In addition, KLF4 is upregulated in CSC-like cell lines in breast cancer. Downregulation of KLF4 decreases tumor formation *in vivo*, while overexpression of KLF4 increases CSC population (Yu et al., 2011). Therefore, it seems that KLF4 can suppress the EMT process and inhibit metastasis in breast cancer cells (Yori et al., 2010, 2011), however, it can also induce CSC-like properties to promote metastasis and invasion. In lung cancer cell lines, inhibition of KLF4 by Numb-like protein (NUMBL) maintains progenitor-like cells (Vaira et al., 2013). Further, KLF4 can also be upregulated by zinc finger E-box-binding homeobox 1 (ZEB1) via downregulation of stemness-inhibiting microRNAs (miRs) and control the CSC-like properties of colorectal and pancreatic cancer cells (Wellner et al., 2009). Moreover, miR-7, a brain-specific miRNA, can suppress the expression of KLF4 and reduce brain metastases of breast CSC-like cells (Okuda et al., 2013).

Interestingly, KLF4 can reprogram somatic cells into CSC-like cells in combination with SOX2, OCT4 and MYC (Nishi et al., 2013). Recent progress has demonstrated that P53 mutations can enhance the efficiency of reprogramming, and upregulation of KLF4 in mutant somatic cells, or P53-knockout cells, produces aggressive cancers in mice (Sarig et al., 2010). Reprogramming of cancer cells by pluripotency factors has been proposed as potential cancer therapies due to their capability to restore terminal differentiation of cancer cells *in vitro*, increase the responsiveness of cancer cells to chemotherapy *in vitro*, and reduce the tumorigenicity *in vivo* (Zhang et al., 2013).

Although some of KLFs have also been implicated in CSCs, their roles are still unclear. KLF5 has been shown to be a positive regulator of proliferation and mediating cancer progression (Chen et al., 2006). Recently, the role of KLF5 on ovarian CSC viability has been explored

(Dong et al., 2013). The increased expression of KLF5 was associated with high survivin expression. Moreover, silencing of KLF5 by siRNA inhibited the expression of survivin, which also sensitized the CSC populations to apoptosis induced by chemotherapies (Dong et al., 2013). KLF8 has also been shown to be implicated in CSCs. As KLF8 is a well-known EMT-inducer, upon its overexpression a large portion of the MCF-10A cells obtained stem cell properties (Wang et al., 2013). KLF8 has been shown to promote tumorigenic stem cell induction by targeting miR-146a (Wang et al., 2013). KLF9 has also been identified as a unique differentiation-induced transcription factor in glioblastoma-derived neurospheres (Ying et al., 2011). KLF9 induced neurosphere cell differentiation, and inhibited neurosphere-derived xenografts growth and neurosphere formation *in vivo*. KLF9 regulated glioblastoma neurosphere cells by binding Notch1 promoter and inhibiting its downstream signaling, which indicated that it has tumor-suppressing functions in glioblastoma CSCs (Ying et al., 2011).

Conclusions and Future Directions

CSCs are a subpopulation of tumor cells that play critical roles in cancer propagation, therapeutic resistance, metastasis, and tumor recurrence. They have been identified to be responsible for such malignant properties of cancer as phenotypic heterogeneity, chemoresistance and dormancy. Therefore, efforts should be done to elucidate the molecular mechanisms of regulating CSCs. KLFs have long been shown as an important regulator in tumors, and the study of their functions in human cancers has been a rapidly emerging field. Although much has been explored about the functions of KLFs in cancer, the special effect of each KLFs in mediating CSC functions still remains to be uncovered. In this review, we have summarized the current understanding of the transcriptional regulation and functional implication of KLF4 in cancer development and CSC regulation. A better understanding of regulatory mechanism of KLF4 in cancer and CSCs might provide potential therapeutic strategies in cancer therapy. However, there is still a long way to go before we can fully understand its regulatory functions. For using KLF4 and other KLFs as viable targets for CSCs, we need figure out that which KLFs can contribute to tumorigenesis and malignant progression. Regulating a single KLF with redundant functions in CSCs is unlikely to be an effective therapy. In addition, recent progress has also highlighted the importance of tumor microenvironment for the initiation and maintenance of CSCs, which has been defined as another area where targeting KLFs might be effective. With further elucidation of the transcriptional regulation and functional implication of KLF4 and other KLFs in CSCs, we hope to achieve utility of these transcriptional regulators as targets for therapeutic and diagnostic interventions.

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