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New emerging roles of CD133 in cancer stem cell: signaling pathway and miRNA regulation

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Author contribution statement

Behzad Mansoori has provided constructing an idea or hypothesis for research.

Behzad Baradaran and Behzad Mansoori have provided planning methodology to reach the conclusion.

Behzad Baradaran and Marjan Aghajani have provided organizing and supervising the course of the project or the article and taking the responsibility

Ali Mohammadi have designed the images.

Marjan Aghajani, and Zahra asadzadeh, have provided articles searching and manuscript writing.

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Behzad Mansoori has provided taking responsibility in logical interpretation and presentation of the results.

Behzad Baradaran has provided taking responsibility in this necessary function.

Taking responsibility in the construction of the whole or body of the manuscript have been provided Behzad Baradaran.

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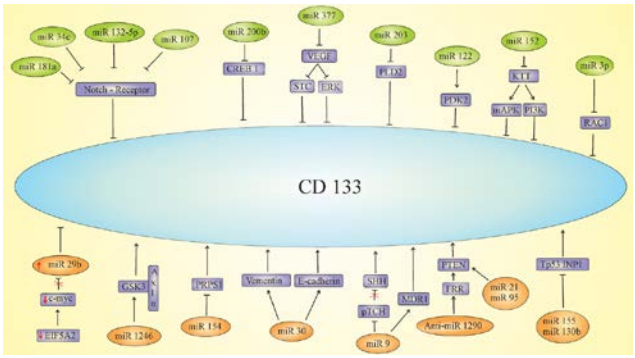
Abstract:

Cancer stem cells (CSC) are rare immortal cells within a tumor that are able to initiate tumor progression, development, and resistance. Advances studies show that, like normal stem cells, CSCs can be both self-renewed and given rise to many cell types, therefore form tumors. A number of cell surface markers, such as CD44, CD24, and CD133 are frequently used to identify CSCs. CD133, a transmembrane glycoprotein, either alone or in collaboration with other markers, has been mainly considered to identify CSCs from different solid tumors. However, the exactness of CD133 as a cancer stem cell biomarker has not been approved yet. The clinical importance of CD133 is as a CSC marker in many cancers. Also, it contributes to shorter survival, tumor progression, and tumor recurrence. The expression of CD133 is controlled by many extracellular or intracellular factors, such as tumor microenvironment, epigenetic factors, signaling pathways, and miRNAs. In this study, it was attempted to determine: 1) CD133 function; 2) the role of CD133 in cancer; 3) CD133 regulation; 4) the therapeutic role of CD133 in cancers.

Graphical Abstract

In this review, we concentrate on the role of CD133 in the development of cancers, CD133 associated signaling pathways, the role of miRNAs in regulating CD133, and ultimately the potential role of CD133 in detection, prognosis, and treatment of cancers.



Keywords: CD133, Cancer Stem Cell, WNT, Notch, TGF-β-SMAD, Jak/Stat, PI3K-Akt, Sonic hedgehog signaling, MAPK, miRNA

1. Introduction:

Human cancers display a strong intra-tumor heterogeneity. In fact, all the cells within a tumor are not the same. There are a variety of types of cells in a tumor. This heterogeneity of tumor is considerable both for tumor progression and therapeutic outcomes (Marusyk & Polyak, 2010). Various factors could effect this heterogeneity; however, the most important factor of heterogeneity in tumors arises from cancer stem cells (Heppner, 1984).

Cancer stem cells (CSCs) are rare immortal cells within tumors, which exhibit similar characteristics of stem cells, including; self-renewal and the capacity to differentiating. Furthermore, CSCs have been shown the ability of tumorigenicity (Visvader & Lindeman, 2012). CSCs have been characterized by several CSC markers. Recently, CD133 which is also known as prominin-1 has been used widely as a marker for identification of cancer stem cells from malignant tumors. CD133 expression was associated with recurrence, metastasis, resistance to traditional treatment, including; chemo- and radio-therapies, or poor prognosis in many cancers (S. Chen et al., 2013; Collins, Berry, Hyde, Stower, & Maitland, 2005).

The expression of CD133 is regulated by many extracellular or intracellular agents. Signaling pathways have a key role in the proper regulation of stem cell functions. JAK/STAT, Wnt/β-catenin, Notch, TGF-β, PI3K /AKT, Hedgehog and NF-kB pathways as important stemness signaling pathways that are involved in the maintenance of cancer stem cell properties (J.-W. Jang et al., 2017; Jeng et al., 2013; Kumar et al., 2016; Li,

Lee, Kim, Kim, & Cho, 2018; You, Ding, & Rountree, 2010). The expression of CD133, as a target gene of the cancer stem cell signaling pathways, is regulated by activation or suppression of the signaling pathways (C.-J. Chen, Yang, Huang, & Liu, 2017).

Also, the changes in the expression of microRNAs, a short non-coding RNA, have a key role in tumorigenesis (Calin & Croce, 2006; B Mansoori, Mohammadi, Shirjang, & Baradaran, 2015). Up and down-regulation of miRNAs have been observed in CD133+CSCs. Several miRNAs as both tumor suppressor and tumor promoter regulate CD133 expression in a variety of tissues and cells. Most miRNAs regulate CD133 expression indirectly. A particular miRNA which target CD133 expression has not been known yet (S.-X. Huang et al., 2017).

Since CD133+CSCs are the root of tumor initiation and drug resistance in many cancers, it is feasible to develop CSCs-directed therapeutic strategies by applying of CD133 as a target molecule and reduction of CD133+CSCs in order to cure cancer completely. The current studies display that CD133+CSCs may be a hopeful strategy in regenerative medicine (Swaminathan et al., 2013).

In this review, we concentrate on the role of CD133 in the development of cancers, CD133 associated signaling pathways, the role of miRNAs in regulating CD133, and ultimately the potential role of CD133 in detection, prognosis, and treatment of cancers.

2. What is a cancer stem cell?

Human cancers display a strong intra-tumor heterogeneity (Marusyk & Polyak, 2010). Although tumors originate from a single cell, the phenotypes of the cells within a tumor are not the same. There are various kinds of cells in a tumor; some are cancerous, while others are infiltrating normal cells which is sustain the tumorigenicity of the cancer cells (Fidler & Kripke, 1977). The nature of tumor heterogeneity can be a serious consequence both for tumor development and tumor treatment (Marusyk & Polyak, 2010). Various agents, such as microenvironment and epigenetic changes account for this heterogeneity (Marusyk & Polyak, 2010; Visvader & Lindeman, 2012), but the most substantial factor of heterogeneity in tumors arises from phenotypic flexibility and differentiation of cancer stem cells (Fidler & Kripke, 1977; Heppner, 1984).

Cancer stem cells were first identified in 1997 by Bonnet and Dick in acute myeloid leukemia (Bonnet & Dick, 1997). To explain the exact biology of cancer stem cells, it is better to care about the unique characteristics of normal stem cells (self-renewal and differentiation) (Lobo, Shimono, Qian, & Clarke, 2007). Although CSCs and the normal stem cells have similar properties, the origin of CSCs is not necessarily from the normal stem cells transformation (Visvader & Lindeman, 2012). This heterogeneity in cancer

cells has been driven to the various propagation models: the clonal evolution theory and cancer stem cell (Heppner, 1984).

The clonal evolution model (stochastic model) is a nonhierarchical model that cells in the predominant clonal have the similar ability to form a new tumor, and entry into the cell cycle is a stochastic event that happens with low probability (Nowell, 1976). However, the cancer stem cell model (CSC) is a hierarchical model, in which a small subset of cells has the tumorigenesis potential and cause heterogeneity through differentiation. This model has attracted lots of attention because it elucidates the resistance to both chemo- and radio-therapy and tumor relapse (Visvader & Lindeman, 2008).

3. CSC markers:

In recent studies, several molecular markers have been identified to describe various stem cell populations. Stem cells are, also determined by the presence or absence of specific marker (Shimono et al., 2009). The question is, however, all the normal stem cell markers that are also seen on cancer stem cells?

So far, a definite distinction between the markers of normal and cancer stem cells are not identified [9]. In fact, the similarity of cell surface markers explain how CSCs originate from normal stem cells through the acquisition of epigenetic and genetic alterations (Islam, Gopalan, Smith, & Lam, 2015). Therefore, the next question is, how do CSC markers distinguish from the normal stem cell markers?

Glycosylation may give the key (Brockhausen, 1999; Karsten & Goletz, 2013). Most markers of stem cell described until now are proteins. Just small number of stem cell markers have been shown are glycans bound to proteins or lipids (Fenderson & Andrews, 1992). It is likely that through the malignant transformation from a normal stem to a cancer stem cell, stem cell glycoprotein markers change their glycosylation. Consequently, cancer stem cells have cancer-specific glycans. Indeed, these cancer-specific glycans are CSC makers (Karsten & Goletz, 2013). Some CSCs markers, such as CD133, CD44, CD90, and some are internal markers (nestin, ALDH-1, and Sox-2) are located on the cell's surface (Table 1).

CSC markers are not general for any cancer type. Even none of these markers are particularly expressed by CSCs. Nevertheless, multiple markers have demonstrated suitable for the isolation of subsets enriched for CSCs (Medema, 2013). The combination of markers could provide a robust selection of the CSC phenotype (W. Li et al., 2017; Silva et al., 2011). For instance, the combination of high CD44 / CD24 and ALDH1 ratios can be a more suitable method for defining CSC in breast cancer. High CD44/CD24 expression is associated with cell proliferation and tumorigenesis. CD44+/24- is a proper prognostic indicator, one which would allow to the effective

treatment and outcomes to be predicted in patients with recurrent breast cancer (Horimoto et al., 2016; W. Li et al., 2017). Also, CD133 expression combined with aldehyde dehydrogenase-1 (ALDH1) provided a proper selection of ovarian CSCs. Also, CD133 and ALDH1 co-expression independently predicted survival in high-grade ovarian cancer (HGSOC) (Table 2) (Ruscito et al., 2017; Silva et al., 2011).

4. Molecular structure and function of CD133:

Studies have shown that CD133 as a CSC marker could regulate cell self-renewal and tumorigenesis in a variety of solid tumors. CD133 positive cells have higher tumorigenic and metastatic potential than cells which expressing CD44, or CD24 (H. J. Lee et al., 2011). Only CD133 positive cells were associated with metastasis to the lung (He et al., 2012; H. J. Lee et al., 2011). also, in pancreatic cancer CD133 is a significant cancer stem cells marker, and it can be a potential molecular target for treating intractable pancreatic cancer (H. J. Lee et al., 2011). CD133 as a cancer stem cell marker has been utilized widely in identification of stem cells from normal and cancerous tissues.

For the first time, Miraglia et al. 1997 following the applied of monoclonal antibody (production of AC133) described and isolated CD133 (Miraglia et al., 1997). CD133 antigen also known as prominin-1, is a glycoprotein, which is encoded by a single-copy gene on chromosome 4 (4p15.33) in human or chromosome 5 (5b3) in mice. Human CD133 is a five transmembrane glycoprotein of 865 amino acids, and its total molecular weight is 120 kDa, which localize to cellular protrusions. N-terminus of CD133 extends into the extracellular part and the C-terminus of this protein is present in the intracellular space. This protein consists of two large extracellular loops containing potential sites for N-linked glycosylation and two small cysteine-rich intracellular loops (Miraglia et al., 1997; Shmelkov, Clair, Lyden, & Rafii, 2005; Yin et al., 1997). The region between amino acids 845 and 857 in the CD133 C-terminal loop is necessary for the interaction of CD133 with Src to activates and phosphorylate FAK to promote cell migration (C. Liu et al., 2016). CD133 has eight potential glycosylation sites. AC133 and AC141 epitope, which are glycosylated epitope, form extracellular epitopes of CD133 (Campos et al., 2011). AC133 and AC141 epitopes have been widely utilized as markers for identifying CSCs in solid tumors (Kemper et al., 2010). Expression of AC133 in glioblastoma has demonstrated malignancy tumor features such as tumor differentiation and tumor growth (Campos et al., 2011). In colon cancer and melanoma cell lines, AC133 is correlated with the cell cycle DNA. AC133 might increase cells with high survivin expression and therefore promoted resistance to apoptotic factors (Jaksch, Múnera, Bajpai, Terskikh, & Oshima, 2008). This glycoprotein was called prominin because of its cellular locating in plasma membrane protrusions (Miraglia et al., 1997; Yin et al., 1997). Seven isoforms (s1, s2, s7, s9, s10, s11, and s12) in humans and three isoforms in the mouse (s3–s6 and s8) are identified for CD133 (Yu, Flint, Dvorin, & Bischoff, 2002).

In humans, this protein was initially known as an antigenic marker that is expressed on hematopoietic stem cells and progenitor cells as AC133 antigen (Yin et al., 1997). Early studies described that mouse prominin and the human AC133 antigen show similarity in cellular distribution and subcellular locality. Thus, it was proposed that AC133 antigen is named as “prominin (mouse)-like 1” (PROML1) (Corbeil et al., 2000). When the sequencing of the human genome was completed, However, it was cleared that human genome does not contain any open reading frame more closely related to mouse prominin than PROML1. therefore, human prominin has also defined the designation “CD133” (Corbeil et al., 2000).

lately, a second membrane protein is described to be structurally similar to prominin, but encoded by a different gene (Corbeil, Röper, Fargeas, Joester, & Huttner, 2001; Fargeas, Florek, Huttner, & Corbeil, 2003). So, this protein had been initially known as “prominin related protein” (prom-rp) (Corbeil et al., 2001; Fargeas et al., 2003).

Early researchers showed that CD133 is a key biomarker for identification and isolation of stem cells from normal and cancerous tissues. The inconsistent outcomes, however, are published. In the case of colon cancer cells, Shmelkov et al. in 2004 showed that both CD133+ and CD133–cells have potential to develop tumors. These results showed that CD133 expression is not limited to somatic and cancer stem cells (Shmelkov et al., 2008). Therefore, the question is that CD133 can be as a universal marker to identify stem cells from tissue types?

In bone marrow, heart and prostate, CD133 is restricted to the stem cells and can be used for identification of stem cells from these tissues. While in several other tissues, this antigen is expressed in different cells (Leong, Wang, Johnson, & Gao, 2008; Richardson et al., 2004). Therefore, it is not a marker particularly expressed in stem cells. However, in most cases CD133 alone or in combination with other markers is used for the isolation of normal stem cells from several tissues (De Wynter et al., 1998; Hess et al., 2006).

For the first time, CD133 was reported as a CSC marker by Singh et al. in 2004 for glioblastoma multiform (Singh et al., 2004). CD133 is currently applied for the isolation of cancer stem cells from malignant tumors. Moreover, high expression of CD133 is related to poor clinical outcomes in some cancers (S. Chen et al., 2013; Collins et al., 2005).

4.1. CD133 in cancers:

The expression of CD133 is associated with recurrence, metastasis, chemotherapy resistance, and poor prognosis in multiple cancers. For instance, the expression of CD133 is associated with tumor differentiation and tumor progression in colorectal carcinogenesis (Kazama et al., 2018). CD133 expression is a useful indicator of the post-

operative recurrence after resection in the patients with colon cancer (Nagata et al., 2018). Since studies reported that CD133-negative cells in colorectal cancers were more sensitive to chemotherapy, so targeting of CD133+cells may be a proper marker in the treatment of peritoneal metastasis of colon cancer (Nagata et al., 2018) . Ning et al., used anti-CD133 antibody loaded nanoparticles (CD133Ab-NPs-SN-38) to eliminate CD133+ cells and prevent colony formation in colon cancer (Ning et al., 2016).

Studies in glioblastoma showed that CD133, as a cancer stem cell marker, is overexpressed in glioblastoma cells and correlated with tumor recurrence, and shorter survival. Cytoplasmic expression of CD133 is also associated with chemotherapy resistance in gastric cancer. Therefore, it can be a useful prognostic marker in gastric cancer (Hashimoto, Aoyagi, Isobe, Kouhuji, & Shirouzu, 2014). Rudnick et al. showed that immunological targeting of CD133 in recurrent glioblastoma could be an effective treatment. They targeted CD133 by dendritic cell immunotherapies such as ICT-121 (Rudnick et al., 2017). In another study, lentiviral Vectors were applied to selective targeting and eliminating of CD133-positive cells in glioblastoma (Bayin & Placantonakis, 2018). Furthermore, since CD133+cells show resistance to the most of chemotherapy and radiation therapy, Kima et al. conjugated anti-CD133 monoclonal antibody with angiopep-2 (An2 peptide) to temozolomide (TMZ)-encapsulating liposome. since TMZ as a mainline treatment of glioblastoma, limited due to having poor penetration into glioblastoma site, They used liposomes as a drug delivery system to improve its therapeutic efficacy (J. S. Kim, Shin, & Kim, 2018).

Also, in hepatocellular carcinoma (HCC), CD133 positive cells show high potential for tumorigenicity and chemoresistance. Oxidative stress could up-regulate CD133 expression in HCC, and over-expression of CD133 increased the capacity of the defense mechanisms against reactive oxygen species (ROS), and led to increased drug resistance in liver cancer. Decrease of CD133 expression attenuated chemoresistance in HCC (Y. Song et al., 2017).

In thyroid cancers in adults, CD133 expression is associated with tumor size, lymph nodes metastasisand BRAF mutations, whereas in children, the expression of CD133 is not correlated with any clinical properties. Therefore, the presence of CD133 in the cells could suggest novel therapeutic alternatives for thyroid cancers in adults (Decaussin-Petrucci et al., 2015).

CD133 is used as a helpful biomarker to predict prognosis in multiple cancers. As an example, the higher CD133 expression in Cutaneous squamous cell carcinoma (cSCC) is associated with poorly prognosis (R. Xu, Cai, Luo, Tian, & Chen, 2016).

CD133 positive cells are the basis of tumor drug resistance, radio-resistance or distant metastasis in many cancers. Thus, it is feasible to develop CSCs-directed therapeutic

strategies by applying of CD133 as a target molecule and reduce CD133CSCs in order to cure cancer completely. For this purpose, various methods have been used, including monoclonal Ab, Dendritic cell immunotherapies, and radioimmunotherapy. Weng et al. in 2017 attempted to apply radioimmunotherapy (RIT) for targeting of CD133 positive colonic CSCs. They observed that RIT for CD133+CSCs inhibited tumor development in nude mice (Weng, Jin, Lan, & An, 2017).

4.2. Regulation of CD133 expression:

The expression of CD133 is controlled by many extracellular and intracellular agents. Tumor microenvironment as a key extracellular factor plays an essential role in the regulation of CD133 expression. The significant micro-environmental factor in regulating CD133 expression is hypoxia. Several reports demonstrated that hypoxia could increase the expression of CD133 and promotes stem-like properties (Semenza, 2000; Soeda et al., 2009). Hypoxia could also induce the transcriptional activity of the hypoxia-inducible factors (HIF1/2) and regulates self-renewal of cancer stem cells by enhancement of the action of stem cell agents (Harris, 2002; Semenza, 2014). In glioma, hypoxia promotes the expansion of the CD133 stem cells through the activation of HIF-1a; consequently, improves the self-renewal of CD133 cells (Soeda et al., 2009). HIF-1α and CD133 can predict survival in patients with locally advanced rectal cancer (C. Cai et al., 2017). Also, in prostate cancer, a relation between the expression of CD133, HIF-1α, and VEGF has been reported. Hypoxia increases the expression of CD133, HIF-1α, and VEGF. Therefore, a treatment to change the expressions of CD133, HIF-1α, and VEGF can be a good approach to suppress prostate cancer (L. Liu, Liang, Guo, & Wang, 2017). Mainly, hypoxic microenvironment and mitochondria dysfunction (genetic and chemical) are indicators of cancer cell biology. CD133 level is regulated by bioenergetic stresses that act on mitochondrial functions in glioma cells. alterations in the cellular environment that cause changes of mitochondrial function are in charge of the enhanced expression of CD133 antigen in glioma cells, implying that CD133 is a bioenergetic stress marker in glioma (Griguer et al., 2008). So how can describe the difference between the stress induction and CSC maintenance? Campos et al. have reported that the AC133 epitope is a biological cancer marker and earlier than CD133 mRNA or protein demonstrate malignancy tumor properties. Studies have reported that hypoxia can improve AC133 level through transcription-dependent and transcription-independent in CD133 expression. So, modulation of AC133 levels exists independently of changes in CD133 mRNA transcription and CD133 protein translation (Campos et al., 2011). Cellular stress itself induces CSCs from non-CSCs through the expression of DNAJB8, a heat shock protein (HSP) 40 family member, by activation of heat shock factor 1 (HSF1) (Kusumoto et al., 2018).

p53 is another regulatory factor for CD133. The expression of CD133+ cancer stem cells is regulated by p53 at the transcriptional level through directly binding to the CD133 promoter and decreasing CD133 expression. p53 binds to CD133 promoter and then

recruitment of HDAC1 (Histone deacetylase 1). HDAC1 makes easy the epigenetic changes of CD133 promoter and also inhibits CD133 expression at the transcriptional level (Park et al., 2015).

Also, the expression of CD133+ cancer stem cells was down-regulated by Ikaros as a transcription factor. Ikaros could interact with CtBP, and CtBP-Ikaros complex worked as a transcription inhibitor complex and suppress CD133 expression through directly bind to the P1 promoter of CD133 (Lin Zhang et al., 2014).

Epigenetic factors are key factors, which are involved in regulating of CD133 expression. For instance, it is revealed that the expression of CD133 is negatively in ovarian and endometrial cancer cells, that is associated with the level of methylation of the CD133 P2 promoter (Min, So, Ouh, Hong, & Lee, 2012). Abnormal DNA methylation usually reported in many human cancers. Sp1 as a regulator of CD133 promoter activity interacts with Myc in controlling of CD133 expression in glioma cell. DNA methylation also limits the accessibility of Sp1 and Myc to the CD133 promoter and subsequently regulate CD133 expression (Gopisetty, Xu, Sampath, Colman, & Puduvalli, 2013). Also, CD133 hypomethylation is a prognostically adverse finding in gastrointestinal stromal tumors (Geddert et al., 2017). In another study, Yi et al. combined DNA methyltransferase inhibitor 5-aza-2'-deoxycytidine (DAC) and radiation for treatment of pancreatic cancer. They found that the combination treatment can meaningfully decrease the growth of tumor compared to irradiation or 5-aza-dC treatment alone (Yi, Kwon, Kang, & Yang, 2017).

4.3. CD133 signaling pathways:

Signaling pathways have different crucial roles in the proper regulation of stem cell functions and are strictly regulated in the normal stem cells. Not surprisingly, stemness signaling pathways in CSCs acts abnormally (Kroon et al., 2013; Merchant & Matsui, 2010).

JAK/STAT, Wnt/β-catenin, Notch, TGF-β, PI3K/AKT, Hedgehogand NF-kB pathway as significant stemness signaling pathways are implicated in the stimulation and maintenance of stemness features of CSCs (J.-W. Jang et al., 2017; Jeng et al., 2013; Kumar et al., 2016; Li et al., 2018; You et al., 2010). The expression of CD133cscmarker, as a target gene of these signaling pathways, is modulated by the activation or suppression of these signaling pathways (C.-J. Chen et al., 2017). Dysfunctions of these pathways contribute to the abnormalities of CD133+cells, such as the self-renewal, proliferative, differentiation, resistance to apoptosis, chemotherapy, increased invasiveness, metastasis and cancer recurrence (C.-J. Chen et al., 2017; Kroon et al., 2013; Merchant & Matsui, 2010).

These signaling pathways interact with each other's. The cross-talk between various pathways occur in many cancers. For instance, the cell signaling pathways that are unique for breast cancer stem cells have not yet been described. The PI3K, mTOR, STAT3, and PTEN signaling pathways, that arrange a complex signaling network, were found to be necessary for breast cancer cells survival and proliferation (Zhou et al., 2007).Also, in hepatocellular carcinoma (HCC), frizzled 2 (FZD2) pathway could trigger STAT3 pathway, without presentation of IL-6. FZD2-STAT3 signaling axis induced epithelial to mesenchymal transition (EMT) and so lead to metastasis behavior in HCC (Gujral et al., 2014).

Understanding the mechanism of actions of CSCs signaling pathways maybe is a hopeful strategy to improve the cancer treatment outcomes and leads to the elimination of CSCs.

4.3.1. Wnt pathway:

Wnts proteins are secreted by glycoproteins which is critical for regulation of cell proliferation, migration and differentiation in both normal and cancer stem cells (Anastas & Moon, 2013; Reya & Clevers, 2005). Hyper-activated WNT-beta-catenin signaling is related to many cancers, which regulates the self-renewal and migration of CSCs. It also promotes tumor growth and tumor recurrence (Mao et al., 2015). When Wnt binds to Frizzled receptor, the cytoplasmic domain of Lrp as a coreceptor becomes phosphorylated, separating GSK-3b and Axin and applying the Dvl and finally disintegrates the destruction structure. Activation of Wnt signaling could up regulate beta-catenin and increase its nuclear translocation (Figure 1a) (Nelson & Nusse, 2004). CD133 acts as a main factor in β-catenin signaling and inhibition of its degradation in the cytoplasm. Recently, it has been reported that CD133 could promote clonal proliferation and renal repair by controlling of Wnt signaling through the regulation of b-catenin levels (Brossa et al., 2018).

CREB binding protein (CBP), transcriptional co-factor, is enabled to directly interact with Beta-catenin to induce CD133+CSCs proliferation in liver cancer through the repression of PP2A-PTEN signaling. PP2A is an important regulator of canonical WNT signaling that acts as a tumor suppressor by targeting of oncogenic signaling, such as Raf, MEK, and AKT via de-phosphorylation of PTEN (Tang, Berlind, & Mavila, 2018).

Another study in liver cancers showed that the increased clonogenic potential of CSCs is correlated with changes in Wnt/β-catenin signaling, which is positively related to the CD133 expression. Aberrant activation of Wnt/β-catenin signaling and β-catenin mutations have been observed in most hepatocellular carcinoma (HCC). Beta-catenin after translocation to the nucleus, serve as an activator of T-cell factor (Tcf) transcription. Enhanced the activation of β-catenin/TCF transcriptional activity has been positively correlated with HCC tumorigenesis. Therefore, it can be expected that the β-catenin/TCF

signaling might be a good therapeutic target in liver cancers. Kim et al. applied CWP232228, which prevent the binding of β-catenin to TCF and consequently inhibited the self-renewal capacity of CSCs (J.-Y. Kim et al., 2016).

In colorectal cancer, TNIK (Traf2- and Nck-interacting kinase) as a component of the β-catenin has been known. TNIK regulates the downstream of Wnt signaling that is required for the tumor-initiating function of CD133 CSCs, and inhibiting of TNIK suppresses cell surface expression of CD133 through repressing of Wnt signaling (Uno et al., 2018).

Also, different studies showed that epithelial-type of CD133+ cells in lung cancer are more resistant to the chemotherapy through MDFIC-mediated Wnt/β-catenin signaling activation. Human I-mfa domain-containing protein (MDFIC) could raise the number of free β-catenin through increased the transcriptional activity of Wnt/β-catenin signaling. Therefore, knockdown and overexpression of MDFIC could modulate the ability of drug resistance in lung cancer cells (C.-J. Chen et al., 2017).

Collectively, these data showed that eradicating of CSCs may be a potential therapeutic target for a complete treatment of cancers. Jang et al. reported that the inhibition of Wnt/β-catenin signaling by shRNA-mediated Wnt1 silencing down-regulated the expression of stem cell markers and metastatic capacity (G.-B. Jang et al., 2015).

4.3.2. NOTCH signaling:

The Notch signaling pathway as a strictly conserved cell signaling system plays a key function in the controlling of cell proliferation, differentiation and survival. Notch signaling is initiated when ligand binds to Notch receptor, where goes through a two-step proteolytic cleavage by γ-secretase and ADAM family proteases. Subsequently, the Notch Intracellular Domain (NICD) is released and translocated into the nucleus (Ranganathan, Weaver, & Capobianco, 2011). Dysfunction of Notch signaling is involved in many diseases and abnormally activated in many cancers. Thus, targeting the Notch pathway through notch inhibitors, especially gamma-secretase inhibitors has exhibited notable potential to cure cancer (Figure 1b)(Kumar et al., 2016; Ranganathan et al., 2011).

Notch1 signaling pathway induces CD133 expression in melanoma and leads to the cell migration and angiogenesis. Notch1 at the transcriptional level up-regulates CD133 expression that activates MAPK (mitogen-activated protein kinase), and regulates MMP-2/9 (matrix metalloproteinase 2/9) and VEGF (vascular endothelial growth factor) expression in CD133+ cells. Consequently, the inhibition of Notch1 and MAPK pathways is able to down-regulatCD133 expression and limit angiogenesis and metastasis in melanoma (Kumar et al., 2016).

Several studies revealed that the inhibition of Notch1 signaling can be a promising treatment for many cancers. For example, in lung cancer, blockade the Notch pathway using the γ-secretase inhibitor DAPT can inhibit the growth of CD133+CSCs and increase the effect of chemotherapy with cisplatin (CDDP). Indeed, blockade of Notch signaling enhanced the effect of chemotherapy with cisplatin. DAPT/CDDP co-therapy induced cell cycle arrest and effectively eliminated CD133+ cells (J. Liu et al., 2014). Also, some studies in Glioblastoma indicated that Notch pathway inhibition decreases CD133+ cells and restricts tumor growth. Inhibition of Notch signaling reduced proliferation, suppress growth of tumor through decreased AKT and STAT3 phosphorylation. Synergistically targeting of NOTCH, AKT, and STAT3 pathways could be a faithful treatment for Glioblastoma (Fan et al., 2010). In hepatocellular carcinoma, have been showed that Lidamycin (LDM) down-regulated CD133 expression. Lidamycin down-regulated Notch signaling and decreased the expression of NICD protein. This data suggested that down regulation of Notch signaling pathway may be a potential underlying molecular mechanism between LDM and CD133 (!!! INVALID CITATION !!!).

4.3.3. Sonic hedgehog signaling:

Sonic hedgehog (Shh) is a key factor in the hedgehog protein family. In this pathway, SMO is normally inhibited by PTCH. Binding of SHH to PTCH activates SMO and the signal transduction is occurred by the activation of GLI family (Villavicencio, Walterhouse, & Iannaccone, 2000). The Shh signaling pathway has a key role in controlling of cell growth and differentiation. The improper activation of this pathway occurs in many malignancies (Figure 1c) (Scales & de Sauvage, 2009). For example, in liver cancer, Shh signaling pathway is abnormally activated in CD133+CSCs, and plays a key role in the maintenance of CSC properties. so, inhibited the Shh signaling pathway may be a potential therapeutic strategy for hepatocarcinogenesis (Jeng et al., 2013).

In glioma, CD133+ CSCs are more resistant to chemotherapy. In fact, cooperation of Shh and Notch pathways increases the resistance of CD133+ CSC to Temozolomide Therapy. After treatment with TMZ, the activity of Notch and Shh pathway in CD133+ glioma cells were notably enhanced, and caused Notch1 and GLI1 upregulation. There is a possibility that inhibition of Shh and Notch pathways could increase the sensitivity of CD133+ Glioma Stem Cells to Temozolomide treatment (Ulasov, Nandi, Dey, Sonabend, & Lesniak, 2011).

4.3.4. TGF-β/SMAD signaling:

Transforming growth factor (TGF-beta) is a secreted polypeptide, which is produced by tumor cells. TGF-beta signaling pathway has been involved in the development and maintenance of stem cells plays important roles in cancers, and dysregulation of TGFβ can result in tumor development. TGF has a dual role in human cancer from tumor

suppression to tumor progression. At the early stage of the tumor, TGFβ has protective effects and acts as a tumor suppressor, but as tumors are developed, TGFβ signaling switches to increase cancer development, invasion, and metastasis (Figure 1d) (Nagaraj & Datta, 2010).

TGFβ is identified to be correlated with CD133 expression. Intrahepatic cholangiocarcinoma (ICC), CD133+ cells exhibited both higher levels of TGF-β1 and p-Smad2 (X. Cai et al., 2018). TGFβ is capable to up-regulat CD133 expression through demethylation of promoter-1. CD133 expression is regulated by DNA methylation. DNMT1 and DNMT3β expressions were regulated by TGFβ stimulation. TGFβ stimulation effectively inhibited DNA methyltransferases 1/3beta activity and subsequently leads to significant demethylation in CD133 promoter-1. DNMT3α and DNMT3β expressions were noticably higher in CD133− cells compared with CD133+ cells. These results supported why CD133 expression in CD133− cells was silenced by CpG hypermethylation in promoter. The underlying mechanisms involved in the regulation of CD133 expression through TGFβ is dependent on the Smads pathway. The blocked Smads pathway could attenuate TGFβ-induced CD133 expression; consequently, inhibiting of TGFβ may be effect on the overall cancer progression to malignancy (You et al., 2010).

On the other hand, CD133+ CSCs play a vital fuction in the tumorigenesis by an acquired resistance to TGF-β–mediated apoptosis in the early stage of liver cancers (Ding et al., 2009). TGF-β induces apoptosis in hepatocytes (Gressner, Lahme, Mannherz, & Polzar, 1997), and activated MAPK signaling appears to confer a relative resistance of TGF-β–induced apoptosis in CD133+ cells. Increased MAPK signaling results in an over activated Erk1/2 specifically in CD133+ CSCs. Therefore, improper MAPK/Erk pathway may have a role in the initiation and development of CD133+CSCs in liver cancer through an acquired resistance of TGF-β–mediated apoptosis (Ding et al., 2009).

4.3.5. BMP–BMPR signaling:

Bone morphogenetic proteins (BMPs) are a subgroup of the TGF-b superfamily members. The activated BMP receptor I (BMPRI) phosphorylates SMAD1/5/8. After phosphorylation, the phosphorylated Smads complexes with Smad4 translocate into the nucleus to regulate the transcription of target genes. BMPs signaling play vital functions in the development of human diseases. Misregulation of the BMP signaling is involved in several cancers (R. N. Wang et al., 2014). BMP signaling has a key role in the regulation of CD133+CSCs. High-dose exogenous of BMP4 induces CD133+CSC differentiation and inhibits the self-renewal and tumorigenic potential of HCC, while low-dose exogenous of BMP4 upregulates the expression of CD133 (Lixing Zhang et al., 2012).

Also, in glioblastoma, BMP signaling is expressed in CD133+CSCs, and inhibits the initiation of tumor (Piccirillo et al., 2006).

4.3.6. RTK signaling:

Receptor Tyrosine Kinases (RTKs) are cell surface receptors that have an extracellular ligand-binding motif and intracellular region containing the kinase domain, which includes tyrosine kinase activity and phosphorylate tyrosine residues (Ségaliny, Tellez-Gabriel, Heymann, & Heymann, 2015).

RTKs have an vital role in the development of cancers (Zwick, Bange, & Ullrich, 2001). Aberrant activity of various types of RTKs, such as epidermal growth factor receptors (EGFRs), vascular endothelial growth factor receptors (VEGFRs), and insulin-like growth factor receptors (IGFRs) are detected in various cancers (Ségaliny et al., 2015). Ligand binding leads to autophosphorylation of RTKs that leads to the regulation of different downstream signaling pathways, such as MAPK, PI3K/Akt, Src, andJAK / STAT. These pathways play important functions in the regulation of cancer stemness properties and tumor progression (Ségaliny et al., 2015).

4.3.6.1. JAK/STAT signaling:

Evidence showed that JAK/STAT signaling pathway is activated aberrantly in CSCs and regulates tumorigenesis by increasing of tumor cell proliferation, angiogenesis, and immunosuppression (Schroeder et al., 2014; Zhou et al., 2007). STAT3 signaling pathway plays a key role in CD133+CSCs (Figure 2a). It is reported that STAT3 regulates the proliferation, invasiveness and apoptosis of cancer cells by up-regulating of CD133 expression at early stage of colon cancer. Inactivation of STAT3 by siRNA down-regulates CD133 and suppresses colon cancer progression (Li et al., 2018).

In medulloblastoma (MB), STAT3 pathway is activated in CD133+ MB stem cells (MBSCs) and promotes tumorigenesis through regulation of c-MYC. STAT3 and c-MYC are over activated in CD133+ cells in medulloblastoma. The inhibition of STAT3 signaling in MBSCs is responsible for limitation of CD133+cells proliferation (Garg et al., 2017).

Also, in HCC, STAT3 is a transcriptional regulator of CD133+CSCs. CD133 is regulated by IL-6 mediated activation of STAT3 in HCC. Binding of IL-6 to its receptor could activateSTAT3. The activated STAT3 translocates to the nucleus and binds to the CD133 promoter and subsequent increases CD133 expression. Therefore, IL-6/STAT3 signaling pathway regulates CD133 expression in HCC (Ghoshal, Fuchs, & Tanabe, 2016). However, under hypoxic conditions, RNA interference silencing of STAT3 is responsible for CD133 downregulation, even in the excessive presence of IL-6. STAT3 signaling

interacts with NF-kB and up-regulates the transcription of HIF-1 and subsequently increases the level of CD133 in liver. These factors work with each other to enhance the expression of CD133 under hypoxic liver situation (Won et al., 2015).

4.3.6.2. PI3K-Akt signaling:

In response to ligand binding to RTK, PIP2 (phosphatidylinositol (3,4)-bis-phosphate) is phosphorylated to become PIP3 (phosphatidylinositol (3,4,5)-tris-phosphate). Then, PKB as a proto-oncogene binds to PIP3 and becomes activated by several kinases. The activated PKB is involved in the activation or repression of downstream mediators (Hemmings & Restuccia, 2012; Toker, 2012). PI3Ks play a significant role in cellular functions, including cell growth and differentiation. The activation of PI3K phosphorylates and activates AKT, which is downstream signaling molecule of PI3K (Figure 2b) (Cantley, 2002).

CD133 activates the PI3K/AKT signaling pathway in tumor cells in several cancers. In gastric cancer, CD133 increase the activation of PI3K/AKT pathway through interaction with PI3K-p85, which is a key molecular target of PI3K. It also has a role in the activation of the PI3K/AKT signaling pathway (S. Song et al., 2018).

Moreover, CD133 has a significant role in the TGF-β1-induced activation of the PI3K/ERK signaling pathway in gastric cancer cells. ERK signaling is also involved in the invasion and metastasis of cancer cells. CD133 as upstream of the ERK signaling pathway stimulate ERK signaling pathway in various cancer cells. The overexpression and silencing of CD133 directly could increase and decrease the expression of ERK pathway. Therefore, blocking of CD133 and the ERK pathway might be a hopeful therapeutic strategy in gastric cancer (!!! INVALID CITATION !!!).

Other studies in glioblastoma cells showed that CD133 and DNA-PK (DNA-dependent protein kinase) may increase MDR protein 1 (MDR1) via PI3K-Akt signal pathway. PI3K-Akt pathway, which increased in CD133+ GCSCs, interacts with the MDR1 promoter and induces MDR1 expression via NF-κB. CD133 leads to the phosphorylation and activation of Akt, which are responsible for nuclear translocation of NF-κB and consequently induction of MDR1. It is possible that the inhibition of DNA-PK deactivates Akt, NF-κB, and MDR1 and sensitizes cells to chemotherapy. (Xi et al., 2016).

4.3.6.3. MAPK signaling:

The mitogen-activated protein kinase (MAPK) pathway regulates many cellular processes, such as proliferation, differentiation, apoptosis, stress response and misfunction of the MAPK signaling are implicated in the development of cancer. The

MAPK/ERK pathway represents the best-characterized MAPK signaling pathway. In the MAPK/ERK pathway, the activated Ras phosphorylate and activate the RAF and MEK (MEK1 and MEK2). Subsequently, MEK activates a mitogen-activated protein kinase (MAPK) (J. Chen, Fujii, Zhang, Roberts, & Fu, 2001; Schaeffer & Weber, 1999). (Figure 2b)

Akt and MAPK pathways are concerned with the tumorigenesis of CD133+CSCs. In colorectal cancer (CRC), higher expression of CD133 is also associated with mutations in K-Ras and B-Raf, and mutant K-Ras inhibition or downstream mitogen-activated protein kinase (MEK) inhibition down-regulated CD133 expression (Kemper et al., 2012; YKl Wang et al., 2010).

CXCL3 expression is basically up-regulated in the HCC tumor tissues, positively associated with the expression of CD133 in HCC. CXCL3 could induce Erk1/2 phosphorylation in HCC cells and up-regulate CD133 expression. Erk1/2 activation also is able to inhibit the expression of Ikaros as a downstream gene. Ikaros down-regulated CD133 expression via the MAPK pathway and may indirectly decrease CXCL3 expression in HCC cells (Lin Zhang et al., 2016).

4.3.6.4. EGFR signaling:

The epidermal growth factor receptor (EGFR) is one of the receptor tyrosine kinases (RTKs), that plays an essential role in the controlling of cell Processes (Figure 2b). CD133 induces drug resistance and invasion by stabilizing of EGFR-AKT signaling in hepatocellular carcinoma. The EGFR expression is also positively associated with the expression of CD133 in HCC. EGFR is located into the cell membrane by CD133, and finally, CD133 stabilizes EGFR and promotes AKT signaling. Lack of CD133 could destabilize EGFR by promoting of EGFR internalization. Consequently, it leads to the suppression of EGFR-AKT signaling, and EGFR-deficient CD133+ HCC cells presented sensitivity to chemotherapy (J.-W. Jang et al., 2017).

4.3.6.5. IGFR signaling:

Insulin-like growth factor 1 receptor (IGF-1R), a receptor tyrosine kinase, is involved in differentiation, survival, and transformation of the cells. The expression of IGF2 was positively correlated with CD133 in primary esophageal squamous cell carcinoma (ESCC). Knockdown of IGF2 or inhibited PI3K/AKT could reduce the abilities of CD133+cells to drug resistance. On the other hand, miR-377 as a regulator of PI3K/AKT signaling is able to regulate the effects of IGF2 on CD133 expression. IGF2 up-regulated CD133 expression through down-regulation of miR-377 expression in a PI3K/AKT-dependent manner (W. W. Xu et al., 2018).

Bodzin et al. demonstrated that drug resistance and CD133 expression were increased after gefitinib treatment. The treated cells with gefitinib showed an increase in the phosphorylation of IGF-1R and Akt. They suggested that enhanced IGF-1R nuclear translocation after treatment with gefitinib might lead to IGF1-R activation and correlated with the upregulation of CD133 expression and drug resistance (Bodzin, Wei, Hurtt, Gu, & Doria, 2012).

4.3.6.6. VEGFR signaling:

Vascular endothelial growth factor (VEGF) is a critical factor in the induction of invasion and metastasis through activating of VEGFR2, as a receptor tyrosine kinase. CD133+ CSCs in hepatocellular carcinoma are promoted by VEGF/VEGFR2 pathway, and induces the stemness property, angiogenesis, and tumorigenesis. The function of CSCs on the induction of tumorigenesis is one of the reasons why activation of VEGF signaling is associated with the poor survival or outcome of HCC (K. Liu, Hao, Ouyang, Zheng, & Chen, 2017).

4.3.6.7. Src signaling:

Src kinase family is a classical non-receptor tyrosine kinase (Parsons & Parsons, 2004). Among of the kinase's substrates of Src, FAK (Focal Adhesion Kinase) as an important substrate of Src mediates tumor progressions and metastasis (Sulzmaier, Jean, & Schlaepfer, 2014). Activated FAK causes autophosphorylation of the binding site of Src family kinases (Sulzmaier et al., 2014). The Src-FAK complex has an important role in adhesion regulation and invasive of cancer cells (Figure 2c) (Guarino, 2010; H. I. Kim et al., 2015). Activation of Src signaling leads to dysregulation of cell-cell junction and induces tumor progression and invasion through phosphorylation of β-catenin. Consequently, it causes to the suppression of E-cadherin, and promotes EMT (Nagaharu et al., 2011). CD133, as a substrate for Src-family, is phosphorylated by Src and Fyn tyrosine kinases in medulloblastoma (Boivin et al., 2009).

Activation of FAK by the interaction between CD133 and Src induces cell invasion. Activation of Src could promote the phosphorylation of FAK and lead to increase the induced cell migration by CD133. The inhibition of Src activity by PP2, a Src family tyrosine kinase inhibitor, could prevent the activation of FAK phosphorylation and cell migration (C. Liu et al., 2016).

CD133/Src plays a role in the maintenance of CSCs through EMT modulation in head and neck cancer (Y.-S. Chen et al., 2011). Thus, targeting of CD133/Src signaling might be a possible therapeutic method for elimination of head and neck cancer initiating cells (Y.-S. Chen et al., 2011).

4.3.7. Others signaling:

4.3.7.1. CD90 signaling:

CD90, also called as Thy-1, is a glycoprotein that is known as a marker for cancer stem cell (CSC) in several cancers (Avalos et al., 2009). In some cancers, CD90 has been known to control tumor initiation ability and leads to the higher cell proliferation and tumor progression (Figure 3a) (Kong et al., 2013).

CD90 as a marker for cancer stem cell could up regulate the expression of CD133 in liver cancer. Inhibition of CD90 by either shRNA or antibody also could down-regulateCD133 expression. CD90 binds to integrin through the RING-finger-like domain (RLD) residues. Mutation of this binding site decreases the expression of CD133. Furthermore, CD90 up-regulates CD133 expression through the signal axis of mTOR and AMP-activated protein kinase (AMPK) in liver cancers. Therefore, targeting of CD90-integrin-AMPK-CD133 signal axis could be beneficial in liver cancer (W.-C. Chen et al., 2015). On the other hand, CD90 also enables to activate the opposite phosphorylation of mTOR and AMPK for ovarian cancer development. So, CD90 is a potential tumor suppressor in ovarian cancer (W.-C. Chen et al., 2016).

4.3.7.2. NF-KB signaling pathways:

NF-kB protein as a nuclear transcription factor needs to migrate to the nucleus and combine with DNA. NF-kB is inactivated in the cytoplasm via binding to IkB proteins. To activate NF-kB, the NF-kB protein must be separated from its inhibitors (Figure 3b) (Kanarek & Ben-Neriah, 2012). Studies showed that CSC properties in CD133+cells are increased through the activation of NF-κB signaling. Inhibition of Bmi-1, a polycomb ring finger oncogene, inhibits the sphere formations properties of CD133+cells in liver cancer by repression of NF-κB signaling (D.-Q. Ma et al., 2018). In pancreatic cancer, CD133 induces EMT and increases invasiveness through NF-κB activation. Activation of NF-κB upregulated EMT-associated gene expression that was similar to that observed with CD133 overexpression (Nomura et al., 2015).

In the canonical NF-kB signal transduction cascade, activation of signaling happens by binding of ligands, such as IL-1b to their own receptors (Al-Lamki et al., 2016; Nomura et al., 2017). NFkB in CD133+pancreatic cells is regulated by IL-1 signaling. IL-1 signaling may be an important mediator of EMT induction in pancreatic cancer stem cells. Furthermore, the overexpression of CD133 promotes secretion of IL-1β in pancreatic cancer. Thus, invasiveness in CD133+ pancreatic cells maybe suppresses through inhibition of IL-1 signaling and attenuation of NF-κB activity (Nomura et al., 2017).

4.3.7.4. Death receptor signaling:

The tumor necrosis factor (TNF) superfamily are released from the cell membrane by extracellular proteolytic cleavage and functions as a cytokine. Interaction of TNF with TNFR promotes the NF-κB pathway. Binding of TNF-α to the receptor induces TNFR-1 trimerization, which launches a cascade of apoptosis. In the next step TRAF-2 is recruited to the complex, that prevents apoptosis (Rath & Aggarwal, 1999). The binding of TRAF-2 to the complex, activates the expression of cFos/cJun gene via the activation of MAPK signaling (Natoli et al., 1997). cFos/cJun as transcription factors promote transcription of antiapoptotic genes (Beg & Baltimore, 1996).

CD133+cells are upregulated in renal clear cell carcinomas (ccRCC) in responding to TNFR2 signaling. The commitment of TNFR2 by TNF up-regulated CD133+cells expression and responsiveness to cell cycle-dependent cytotoxicity. Therefore, there is a possibility that TNFR2 agonist improves the effect of chemotherapy for ccRCC (Al-Lamki et al., 2016).

Also, the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) can enhance apoptosis in many cancers. Hypersensitivity of CD133+cells to TRAIL is correlated with the c-Myc-mediated up-regulation of Death receptor 5 (DR5) and down-regulation of c-FLIPL in the cells (Yan Wang et al., 2004). The suppression of CD133 expression due to the reduction of c-Myc, leads to a decrease in the expression of DR5 and an increase in the expression of c-FLIPL. It also is responsible for the weakness of TRAIL-induced cytotoxicity and apoptosis of CD133+cells (Figure 3c) (S.-H. Lee, Hyun, Kim, Kang, & Kim, 2016).

4.4. The roles of miRNAs in CD133 regulation in cancer:

MicroRNAs (miRNAs) are short non-coding RNA that control a widespread range of biological processes. In cancer cells, miRNAs have been shown to be hardly dysregulated (Calin & Croce, 2006; B Mansoori et al., 2015; Behzad Mansoori, Shotorbani, & Baradaran, 2014). The role of miRNAs in regulating of stem cells was firstly identified by Rosalind Lee et al. 1993 through analyzing of two microRNAs, lin-4 and let-7 (R. C. Lee, Feinbaum, & Ambros, 1993; Mohammadi et al., 2016).

miRNAs are involved in the progression of human cancers by various mechanisms, including; amplification or deletion of miRNA genes, irregular transcriptional control of miRNAs, and dysregulated epigenetic changes (Calin & Croce, 2006; Behzad Mansoori, Mohammadi, Shirjang, & Baradaran, 2017; Pan, Wang, & Wang, 2010). Also, miRNAs regulate the stage-specific expression of signaling pathways, which are critical to the correct management of the processes (Figure 4) (Ajani, Song, Hochster, & Steinberg, 2015; Asadzadeh et al., 2018).

Up and down-regulation of miRNAs have also been observed in CD133+CSCs. Several miRNAs regulate CD133 expression as both tumor promoter and tumor suppressor in a variety range of cells and tissues by regulation of signaling pathways. Some miRNAs have been implicated in the regulation of CD133 expression via targrting Notch signaling pathway. For instance, upregulation of miR-181a as a tumor suppressor inhibits the proliferation, invasion, and induced cell apoptosis of glioma cells. miR-181a down-regulated the expression of CD133+CSC in glioma by targeting Notch2. Indeed, there is an imbalanced expression of miR-181a and Notch2 in the GSCs (S.-X. Huang et al., 2017). Also, miR-107 as a tumor suppressor gene in glioma, inhibits CD133+CSC proliferation by targeting of the Notch2 receptor and MMP-12 (matrix metalloproteinase-12) mRNA expression. However, miR-107 does not have effects on MMP-2 and MMP-9 expressions (Y. Liu et al., 2017). miR-139-5p inhibits the CD44+ and CD133+ expression and suppresses drug resistant by inhibition of Notch1 in colorectal carcinoma cells (CRC). Notch1, as a target of miR-139-5p in CRC cells, has an important role in miR-139-5p- induced drug re-sensitization. miR-139-5p expression is negatively correlated with Notch1 expression. The overexpression of miR-139-5p could reduce the CD44+ and CD133+ population in CRC by down-regulation of Notch1, and decreased the drug-resistant (K. Xu et al., 2016). miR-34c overexpression in CD133+ prostate cancer stem cell can diminish self-renewal capacities of CD133+cells. Notch1 as a target of miR-34C, is crucial to maintaining the properties of CSC. miR-34C down-regulates self-renewal properties of CD133+cells in prostate cancer by targeting of Notch1 (Y. Chen et al., 2016).

In gliomas, miR-200b, a member of the miRNA-200 family, is a potential tumor suppressor gene that inhibits the growth of tumor by targeting CD133 or CREB1 (CAMP responsive element binding protein 1) (C. Zhao et al., 2017; W.-j. ZHAO, YANG, & HE, 2014).

miR-377 has a significant role in the initiation, invasion and angiogenesis of esophageal squamous cell carcinoma (ESCC) cells by inhibiting of CD133 and VEGF (B. Li et al., 2017). VEGF plays a predominant role in angiogenesis by binding to VEGF receptors (Gavalas et al., 2013). VEGFR1 or VEGFR2 blockade in esophageal cancer (EC) could inhibit VEGF-induced Src and Erk signaling; consequently, restriction of cancer progression. (W. W. Xu et al., 2015). The underlying molecular mechanisms of how miR-377 down-regulating CD133 and VEGF in ESCC are not clear.

miR-203 as a stemness inhibitor down-regulates the capacity of CD133+ glioblastoma stem cells properties. The precise mechanism of miR-203 that effects on CD133+CSCs in glioblastoma is unknown yet.(Deng, Zhu, Luo, & Zhao, 2016). However, some studies demonstrated that phospholipase D2 (PLD2) protein may be oncogene in glioblastoma and is a direct target of mir-203. miR-203 could directly downregulate PLD2 protein (Z.

Chen et al., 2014). It is suggested that mir-203 could inhibit self-renewal, proliferation and increased apoptosis in the CD133+ glioblastoma stem cell by restriction of PLD2 (Deng et al., 2016).

The over expression of miR-122 is associated with the inhibition of CSC phenotypes and spheroid formation by regulation of glycolytic metabolism in CD133+CSCs in HCC. CD133 +CSCs are very glycolytic and their stemness properties are decreased when glycosylation process is inhibited. MiR-122 inhibits glycolysis by directly targeting of PDK4. PDK4, a mitochondrial OXPHOS suppressor, causes the unusual use of pyruvate and extensive generation of lactate through PDH inactivation. Extracellular lactate causes cell migration and invasion. The CD133+ cells display the low level of miR-122, which enhanced the expression of PDK4. Thus, miR-122 as a tumor suppressor inhibits CSC properties by targeting of PDK4 in CD133+ HCC cells (K. Song et al., 2015).

miR-152 inhibited proliferation and colony formation of CD133+ cells in liver cancer through downregulating of KIT (Ghazanchaei, Mansoori, Mohammadi, Biglari, & Baradaran, 2018; H. Huang, Hu, Li, Lu, & Li, 2015). KIT, a tyrosine kinase receptor (RTK), is a well-established proto-oncogene that is contributed in the invasion, metastasis, chemosensitivity, cancer stem cell properties and several malignant human diseases (Siemens, Jackstadt, Kaller, & Hermeking, 2013; Yasuda et al., 2006). The ligand for KIT is SCF (Stem cell factor). Binding of SCF to KIT leads to receptor dimerization, which activates the intrinsic tyrosine kinase activity of KIT. A number of important downstream signaling cascades are activated by the SCF/KIT pathway, including; MAPK, PI3K and JAK/STAT (Rönnstrand, 2004).

CD133 HCC cells is also epigenetically regulated by miR-142-3p (Chai et al., 2014). mir-142-3p inhibited the migration and invasion of hepatocellular carcinoma (HCC) cells through down-regulation of RAC1 (a GTPase that regulates a diverse array of cellular events) (Wu et al., 2011). miR-142-3p also directly targets CD133 to regulate stem cell-like features of CD133 in HCC. Expression of CD133 is inversely correlated with miR-142-3p. So, the lower expression of miR-142-3p in HCC cells is correlated with tumor growth, invasion, migration and chemotherapy resistant (Chai et al., 2014).

The overexpression of eukaryotic initiation factor 5A2 (EIF5A2) promotes up-regulation of CD133 expression in HCC. HCC cells with high level of EIF5A2 have ability to enhance tumor development. Down-regulation of miR-29b as a tumor suppressor is responsible for EIF5A2-maintained HCC cell stemness (Bai et al., 2018). Although the mechanism of EIF5A2 in the regulation of miRNA-29b have not been well-known, it is reported that c-Myc, Hedgehog and NF-κB can suppress miR-29 expression at transcriptional levels (Mott et al., 2010). In HCC cells, c-Myc, which is promoted by

EIF5A2, binds to the miR-29b promoter to inhibit the miR-29b expression and consequently up-regulates the CD133 levels (Bai et al., 2018).

miR-1246 as a tumor promoter induces self-renewal, drug resistance, tumorigenicity and metastasis by activation of the Wnt/β-catenin pathway in CD133 liver cancer stem cells. Wnt/β-catenin is activated in CD133 liver cancer stem cells. Also, miR-1246 can promote CD133 liver CSCs by down regulation of AXIN2 and GSK3β (glycogen synthase kinase 3β). Further, the overexpression of Oct4 along with miR-1246 results in activation of Wnt signaling in CD133+ liver CSCs by suppressing of AXIN2 and GSK3β (Chai et al., 2016).

It is reported that the level of miR-154 is higher in glioblastoma multiforme (GBM), and act as a promoter in CD133+ GBM cells. The Ribose-phosphate diphosphokinase (PRPS1) is a direct target of miR-154 in CD133+ GBM, and acts as an inhibitor for the proliferation and migration of CD133+ GBM cells. PRPS1 is significantly higher in CD133+cells and is negatively regulated by miR-154. It is suggested that knockdown of miR-154 or overexpression of PRPS1 could inhibit the proliferation and migration of CD133+ GBM (Yang, Yan, Wang, Ma, & Li, 2016).

miR-30 family (miR-30a, -30b, and -30c) as a tumor promoter, increases migratory and invasive capacities of CD133+ pancreatic cancer stem-like cells (Tsukasa et al., 2016). While, miR-30 family acts as tumor suppressors in non-small-cell lung cancer, breast cancer and gastric cancer (Cheng et al., 2012; Kumarswamy et al., 2012; Z. Liu et al., 2014; Tsukasa et al., 2016). Therefore, miR-30 family plays different roles as oncogenes or tumor suppressor genes depending on the cancer type. Studies displayed that the miR-30 family members have ability to suppress EMT by targeting of vimentin (!!! INVALID CITATION !!! [42-44]). Tsukasa et al. showed that vimentin expression was actually increased by the overexpression of miR-30 family in CD133+cells in pancreatic cancer and results in the inducing of EMT (Tsukasa et al., 2016). Several factors, especially TGF-β and TNF-α, Wnt, Notch, and Hedgehog pathways, induce EMT. Cells that undergo EMT lose their epithelial markers and take on a mesenchymal phenotype. These cells can increase invasion and chemoresistance (Krantz, Shields, Dangi-Garimella, Bentrem, & Munshi, 2010).

miR-9 in CD133+ glioblastoma cells is upregulated and leads to chemoresistance to temozolomide. miR-9 activates the SHH signaling through downregulation of PTCH1 (SHH receptor) at the level of post-transcription. Also, PTCH1 knockdown results in reduced cell death. In contrast, knockdown of Gli1 and MDR1 enhanced TMZ-induced cell death. miR-9 has crucial role in the upregulation of the MDR1 (ABCB1) gene in the CD133+ glioblastoma cells)Munoz, Rodriguez-Cruz, & Rameshwar, 2015(. In prolonged chemotherapy, MDR protein 1 and CD133 are increased in the recurrent

cancers. Other studies showed that the overexpression of CD133+CSCs may lead to the resistance to apoptosis of CD133+ cancer stem cells by increasing the level of ABCB1 with ABC transporter activity (Angelastro & Lamé, 2010). Also, studies reported that CD133 and DNA-PK increase MDR1 via the PI3K or Akt signal pathway in multidrug-resistant glioblastoma cells (Ghasabi et al., 2018; Xi et al., 2016).

Antagomir-1290 inhibited the proliferation, and invasion of CD133+ cells in non-small cell lung cancer by targeting of Fyn-related Src family tyrosine kinase (FRK) (Sun et al., 2015). FRK as a direct target of antagomir-1290 has a suppressor effect on cancer cells through phosphorylation and activation PTEN as a suppressor gene. PTEN is negatively correlated with PI3K-AKT in non-small cell lung cancer (J. Xu, Li, Wang, Chen, & Fang, 2014). Antagomir-1290 could increase FRK expression, which promotes the expression of PTEN in CD133+cells. PTEN show antitumor effects by the PI3K-AKTsignal inhibition in CD133+cells (Sun et al., 2015). The similar study showed that miR-21 and miR-95 expression were significantly higher in the ALDH1+CD133+cells than in ALDH1-CD133- cells in lung cancer and result in radioresistance in NSCLC. Inhibition of miR-21 and miR-95 can suppress tumor development through increasing PTEN, SNX1, and SGPP1 expression and reduction of Akt phosphorylation in the ALDH1+CD133+cells in lung cancer (J. Zhang et al., 2015).

The overexpression of miR-155 increases tumor sphere formation capacities in CD90+ and CD133+ CSCs in liver cancer. TP53INP1 (Tumor Protein 53-Induced Nuclear Protein 1) is a direct target of miR-155. TP53INP1 as a tumor suppressor gene induces cell cycle arrest and apoptosis. miR-155 increases the proportion of CD90+ and CD133+ CSCs through down-regulation of the TP53INP1 in liver cancer (F. Liu, Kong, Lv, & Gao, 2015). Also, miR-130b promotes proliferation and self-renewal in CD133+ Liver cancer cell through downregulating and silencing of TP53INP1 as a downstream target of miR-130b. Silencing of TP53INP1 promoted spheroid formation, tumorigenicity, and self-renewal (S. Ma et al., 2010).

However, most of these miRNAs display indirect regulation of CD133 expression. A specific miRNA which targets CD133 expression, has not been known yet.

5. Conclusion:

Despite significant advances in cancer treatment, the treatment of cancer is still a challenge. Cancer may occasionally come back after cancer initial treatment. CSCs have important impacts on chemotherapy resistance and recurrence in various cancers. Currently, most anti-cancer therapeutics may not be effective against CSCs. Because of CSCs primary role, most studies will move toward developing strategies for selective targeting of these chemo-resistant CSCs. There are several therapeutic strategies to deal with them. For example, ATP-binding cassette (ABC) transporters which are associated

with multidrug resistance in CSCs, inhibition of CSCs signaling pathways such as Notch, Wnt, and Hedgehog, metabolic strategies for their eradication, and targeting against CSCs Surface Markers. There is evidence that directly targeting CD133 as a CSC marker might be a promising therapeutic strategy in regenerative medicine. Using antibodies against CD133 is one of the CSC therapy strategies. Using an anti-CD133 targeted toxin in ovarian cancer seems to be eliminating CD133 CSCs and reduces growth and progression of cancer.

Nanomedicine is a successful method against CD133-expressing cells. The CD133-targeted nanoparticles were able to internalization into CD133 cells and eradication of the CSCs. Alibolandi et al. used a PEGylated nanoparticle conjugated with a CD133-targeted RNA aptamer (Apt-PEG-AcCMC-SN38). Targeting of colorectal CSCs with Anti-CD133-conjugated SN-38 nanoparticles could eliminate CD133 cells. Researchers also developed a magnet-bead based miRNA delivery System. This system makes sure magnetic guidance to the site of interest and enables efficient miRNA delivery with no significant cytotoxic effects. Since carrying capability is significant in the demonstration the efficacy of any nanomedicine, the improvement of efficient nanocarriers such as improved cellular intake and enhanced the capacities of penetrating in the deepest interiors of CSCs are necessary for increase of their anti-CD133 potential in future.

Different types of immune cells are known to affect the CSCs in the tumor microenvironment. Cancer immunotherapy is expected to become the best cancer treatment option. Studies demonstrate that AC133 mAb -conjugated RIT successfully inhibits colon cancer progression, while cancer cell doubling time and median survival time were increased by targeting CD133 CSCs in nude mice. Also, immunological targeting of CD133 in recurrent glioblastoma by dendritic cell immunotherapies, such as ICT-121, could be a major treatment for these patients. The results from a continuing phase I clinical trial show the success of ICT-121 administration to recurrent glioblastoma cases. CSCs express high amounts of programmed death ligand 1 (PD-L1) which is an immune checkpoint. Researches are demonstrating the clinical use of anti-PD-1/PDL-1 mAb promoted colorectal CSC self-renewal by increasing the expression of CD133. In future clinical trials, studies of CD133cells capacity to respond to immune checkpoint may be a main determining agent.

Over the decades, CD133 as a suitable prognostic marker for various cancers have come forward. The main purpose of screening early-stage cancer includes methods that ensure minimally invasive procedure and come with high sensitivity and specificity. The rising number of studies have shown that CD133 is an appropriate prognostic marker that correlates with low survival in many cancers. In ovarian cancer, overexpression of CD133 trends toward associate with poor overall survival. CD133 may be a useful prognostic marker in patients with ovarian cancer. CD133 tumor status can be as a worse

prognosis of patients with endometrioid endometrial carcinoma (EEC). CD133 could be considered as a complementary approach in the management of primary treatment for patients with EEC as it provides a more accurate evaluation of prognosis and adjuvant therapy.

Some of the considerable researches based on the combination of various CSC markers along with CD133 appears to be prospective with regard to more sensitivity and specificity. In head and neck squamous cell carcinoma (HNSCC), Nanog and Oct-4 along with CD133 have prognostic value in patients. CD133 and SOX2 might be correlated with poor prognosis in advanced cancer. Studies have reported that CD133 and SOX2 may be hopeful targeted therapy for advanced human cancer.

The concept of CSC-targeted therapy proved by the promising results obtained in CSC-related clinical trials. So, CD133-targeted therapy facilitates eradication of cancer cells that are resistant to conventional therapies and responsible for cancer treatment failure. This future approach may offer a more durable patient response.

Conflict of interest

All the authors declare no conflict of interest.

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Figures

Figure 1. Overview of signaling pathways that are involved in cancer stem cell maintenance, development, proliferation and differentiation. Wnt signaling pathway, Notch signaling pathway, Hedgehog signaling pathway, and TGF-β signaling pathway have been involved in the development and proliferation of CD133+CSCs. These signaling pathways as key regulatory mechanisms may control self-renewal and differentiation of CD133+CSCs and thereby may be hopeful therapeutic interventions.

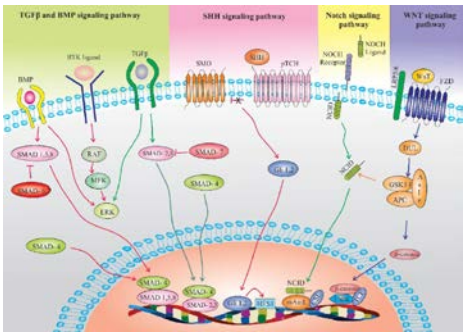


Figure 2. Overview of signaling pathways that are involved in cancer stem cell maintenance, development, proliferation, and differentiation. JAK/STAT signaling pathway, RTK signaling pathway, and Src signaling pathway have been involved in the development and proliferation of CD133+CSCs. These signaling pathways as key regulatory mechanisms may control self-renewal and differentiation of CD133+CSCs and thereby may be hopeful therapeutic interventions.

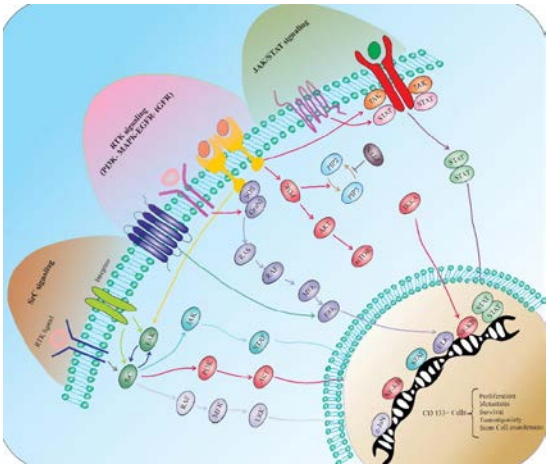


Figure 3. Overview of signaling pathways that are involved in cancer stem cell maintenance, development, proliferation, and differentiation. CD90 signaling pathway, NF-KB signaling pathway, and death receptor signaling pathway have been involved in the development and proliferation of CD133+CSCs. These signaling pathways as key regulatory mechanisms may control self-renewal and differentiation of CD133+CSCs and thereby may be hopeful therapeutic interventions.

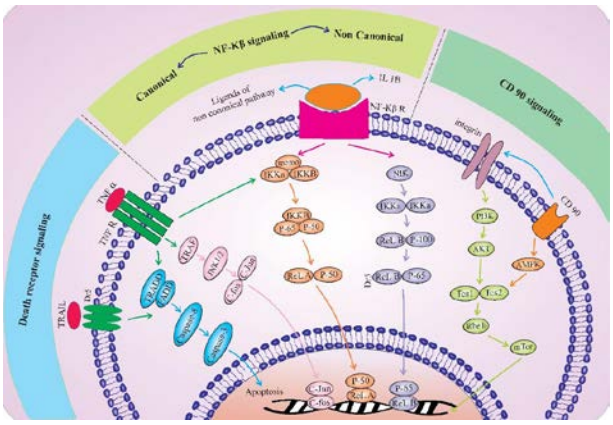
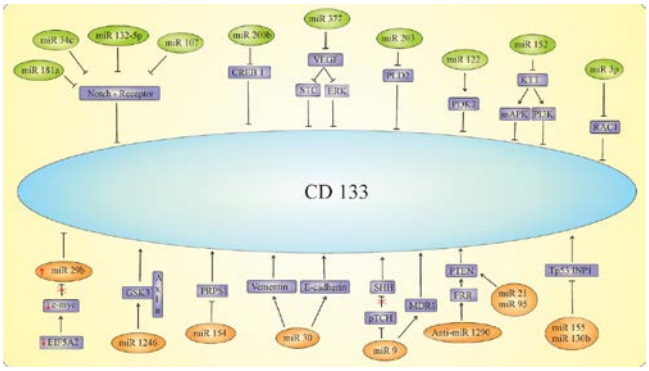


Figure 4. miRNAs as both tumor suppressor (green) and tumor promoter (Orange) accurately and concertedly regulate CD133 expression through targeting multiple molecules and regulating the stage-specific expression of signaling pathways.



Tables

Table 1

Csc marker			Functions	Expressed on	
				Nsc / Pro cell	Tumor type
Surface markers	**Membrain proteins**	CD133 (AC133)	Marker for hematopoietic stem cells – pentaspan transmembrain glycolpro – organization of plasma membrain	Adsc – Hsc – ESC - PSC	Lung,colon,breast,brain, osteosarcoma,glioma
		CD44	Hyaluronic acid receptor -	Adsc –Hsc	Brest,prostat,ovariant,

			cell adhesion	- Psc – HProg	gastric,head and neck
		CD90	Signal transduction – cell adhesion -	ESC – PSC – Adsc – Msc – ProgC	Lung,Breast,glioma,Liver
		CD29 (Integrin □	cell adhesion	ESC – PSC – Adsc - Msc	Colon,Breast
		CXCR ½	Receptor for chemokine	Adsc - Msc	Pancratic,Breast
		ABCB-5	ABC transporter	Adsc	Melanoma
		CD326 (EpCAM) (ESA)	Cell adhesion – signal transduction	ESC – PSC	Colon,Breast,gastric, pancratic
Internal markers	**Cytoplasmic proteins**	nestin	Intermediate filament pro (class VI)	Nsc - HProg	Melanoma,glioma

		ALDH-1	Resistance to alkylating agents	Adsc	Breast,prostat,Melanoma , Colon, head and neck
	Nuclear proteins	Oct ¾	Transcription factors	ESC – PSC	Ovariant,
		Sox-2	Transcription factors	ESC – PSC	lung squamous cell carcinoma

Abbreviations: ***Nsc*** normal stem, ***Pro cell*** progenitor cells, ***CSC*** cancer stem cell, ***AdSC*** adult stem cell, ***Msc*** Mesenchymal stem cells, ***ESC*** embryonic stem cell, ***HProgC*** hematopoietic progenitor cell, ***HSC*** hematopoietic stem cell, ***ProgC*** progenitor cell, ***PSC*** pluripotent stem cell.

Table 2

Tumor type (Reference)	**CSC surface markers**
Lung	$CD133^{+}$, $ABCG2^{high}$, $CXCR4^{+}$, $ALDH^{+}$
colon	$CD133^{+}$, $CD44^{+}$, $CD24^{+}$, $CD166^{+}$, $EpCAM^{+}$

Breast	$CD44^{+}$ $CD24^{-/low}$ Lineage $ESA^{+,-}$ $ALDH^{high}$, $CD44^{+}$ $CD90^{+}$
prostate	$CD133^{+}$, $CD44^{+}$, $CD166^{|+}$, $ALDH^{+}$
Ovarian	CD133 , CD44 , CD117 , CD24 , Nanog , oct ¾ ,
Melanoma	CD133 , CD20 , CD271 , ABCB5 , ALDH
Glioma(Brain)	CD133 , CD15 , $CD49_f$, CD90 , $BCRP_1$, A_2B_5 , $SSEA_1$
Gastric	CD44 , EpCAM
Osteosarcoma	CD133
Head and Neck	CD44 , C-Met , ALDH
Lukemia (AML)	$CD34^{+}$/$CD38^{-}$, CD133 , CD123

Liver	CD133 , $CD49_f$, CD90 , CD44 , CD24
Pancratic	CD133 , CD44 , CD24 , $CXCR_4$, c-Met , ALDH , $ABCG_2$, EpCAM , Nestin