

REVIEW



The role of CD133 in hepatocellular carcinoma

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ABSTRACT

Cancer stem cells (CSCs) represent a small subpopulation of cells found within tumors that exhibit properties of self-renewal, like normal stem cells. CSCs have been defined as a crucial factor involved in driving cancer relapse, chemoresistance and metastasis. Prominin-1 (CD133) is one of the most well-characterized markers of CSCs in various tumor types, including hepatocellular carcinoma (HCC). CD133+ cells have been demonstrated to be involved in metastasis, tumorigenesis, tumor recurrence, and resistance to treatment in HCC. CD133-related clinical prognosis prediction, and targeted therapy have highlighted the clinical significance of CD133 in HCC. However, there remains controversy over the role of CD133 in experimental and clinical research involving HCC. In this article, we summarize the fundamental cell biology of CD133 in HCC cells and discuss the important characteristics of CD133+ in HCC cells. Furthermore, the prognostic value of CD133, and therapeutic strategies for its targeting in HCC, is also reviewed.

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Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent types of liver cancers, and one of the leading causes of cancer-related deaths and is usually a consequence of chronic hepatitis infection and cirrhosis.¹ At present, the effective treatment for HCC remains liver transplantation and surgical resection. However, most patients with HCC are found to be at an advanced stage and therefore, inoperable. Even after surgical resection or transplantation, the long-term prognosis for HCC remains unsatisfactory due to its high recurrence and rate of metastasis. Cancer stem cells (CSCs) or tumor-initiating cells (TICs) are a subpopulation of cells within tumors that exhibit self-renewal properties similar to those of normal stem cells.² CSCs have been implicated in relapse, metastasis, and chemoresistance in different cancer types; thus, these cells represent promising targets for cancer therapy and prevention.³

CSCs have been identified in various solid tumor types, and this identification mainly involves the use of surface markers.⁴ In HCC, accumulating evidence has demonstrated the existence of CSCs and several CSC markers have been identified, including CD133, CD90, CD44, OV6, EpCAM, CD13, CD24, DLK1, α 2 δ 1, ALDH and K19.^{5,6} The identification of subpopulations of CSCs using specific markers will help to give new insights into further understanding HCC development, which may bring hope for the development of future treatments. To achieve this, we must further investigate markers of stemness and the cell properties associated with prognosis, metastasis, and resistance.

CD133/prominin 1 (PROM1) is one of the most frequently used cell surface markers used for the detection and isolation of CSCs from various solid tumors, including HCC.⁷ Moreover, over a decade ago, several studies found that CD133-positive

HCC cells have a potential for tumor initiation.^{8–10} Since then, CD133 has become the focus of research in liver cancer stem cells (LCSCs), and it has been demonstrated to be involved in metastasis, tumorigenesis, tumor recurrence, as well as treatment resistance in HCC. Furthermore, CD133 expression in HCC tissue has been found to be an independent prognostic factor for survival and tumor recurrence in HCC patients. However, currently, there remain some controversial points concerning the accuracy associated with using CD133 as a specific marker for LCSC detection and isolation.

The aim of this review, therefore, is to discuss the recent progress in CD133+ LCSC research with regard to identification, regulation and clinical relevance of CD133 in HCC.

Function of the CD133 molecule in liver cancer cells

CD133 is a single-chain transmembrane glycoprotein with five transmembrane domains separating two large glycosylated extracellular loops and two small intracellular loops, which localize into the protrusions of the cellular plasma membrane.^{11,12} To date, most studies have focused on the use of CD133 as a marker for CSCs, with little knowledge of its biological role in these cells. In addition to being widely used as a marker in LCSC identification and isolation, CD133 has been postulated to be involved in signal transduction. Recent evidence suggests that CD133 facilitates CSC-like properties by stabilizing EGFR-AKT signaling in HCC.¹³ It can also promote TM4SF5 expression, and this CD133-induced TM4SF5 expression and function, are important for liver cancer spherical cell growth.¹⁴ Knockdown of CD133 in CD133+ cells results in the downregulation of the stemness-related gene *c-Myc*.¹⁵ In addition to regulating stemness in LCSCs, CD133 can also confer

a malignancy potential by regulating the expressions of matrix metalloproteinase (MMP)-2 and a disintegrin, as well as the metalloproteinase (ADAM)9 in human HCC.¹⁶ CD133 has also been shown to be preferentially localized to plasma membrane protrusions and microvilli, suggesting that it may be involved in membrane organization.⁷ CD133-containing membrane particles, such as microvesicles (MV), have been reported to be released into various human body fluids.^{17,18} One study has found that CD133 released from the plasma membrane into the cytoplasm is involved in autophagy and promotes glucose uptake and also may function in HCC cell survival.¹⁹

Therefore, in summary, although CD133 is widely used as a marker for LCSC, its role in LCSCs remains controversial, and more research is needed to elucidate its exact function. Only when this is achieved, can an effective means of clearing CD133+ cells be obtained.

Characteristics of CD133+ HCC cells

Since CD133+ cells are thought to represent a subpopulation that exhibits stem cell properties in several solid tumors, the identification of these cells in HCC has been investigated, based on the analysis of tumorigenesis, or other stemness functional characteristics.

Tumorigenesis, self-renewal and aggressiveness

In HCC, the role of CD133+ cells as a representative subset of LCSCs was first demonstrated by Suetsugu et al. in 2006. They isolated CD133+ cells from Huh7 cells and found these possessed a high proliferative and tumorigenic potential.⁸ The tumorigenic potential of CD133+ cells was further confirmed by Ma et al.⁹ In addition to their proliferative and tumorigenic properties, CD133+ cells were demonstrated to possess unique characteristics such as the ability to self-renew, and the ability to differentiate.⁹ These researchers also found that CD133+ HCC cells could promote tumor angiogenesis, growth, and self-renewal through neurotensin/interleukin-8/CXCL1 signaling.²⁰ CD133+ cells also demonstrated great invasiveness and lymphatic metastatic capacity in HCC.^{21,22}

Chemoresistance

CSCs have been identified as the reason for resistance to chemotherapeutic agents and radiotherapy. Several studies have found that the CD133+ populations of HCC cells are responsible for multiple drug resistance. A recent study has shown that CD133+ HCC cells had significant capacity for cisplatin-resistance when compared to CD133- HCC cells, and that overexpression of miR-124 caused sensitization of cisplatin-induced cytotoxicity against CD133+ HCC cells by targeting the SIRT1/ROS/JNK pathway.²³ CD133+ HCC cells can also confer chemoresistance to doxorubicin (DOX) and 5-fluorouracil (5-FU), through activation of the Akt/PKB pathway.²⁴ Furthermore, a recent study has found that CD133+ cells in HCC were resistant to vincristine and 5-FU through the NOTCH signaling pathway activation.²⁵ Sorafenib and regorafenib are multikinase inhibitors used for the treatment of advanced HCC; however, CD133+ HCC cells

frequently confer resistance to Sorafenib and Regorafenib.²⁶ Although CD133+ cells have been reported to be resistant to a variety of anti-tumor drugs, the mechanism of drug resistance remains to be further elucidated.

Radioresistance

CD133+ HCC cells have been suggested to contribute to radioresistance in several studies. Piao et al. demonstrated that the CD133+ cell subpopulation was significantly enriched after radiation exposure due to resistance in radiation-induced apoptosis. Furthermore, an in vivo study found that there was an increased tumor formation in irradiated CD133+ cells when compared to a CD133- cell group.²⁷ They also showed that CD133+ HCC cells were involved in radioresistance through the activation of the MAPK/ERK survival pathway. Lee et al. found that a knockdown of 14-3-3 ζ can inhibit radioresistance and enhance apoptosis induced by γ -irradiation in CD133+ liver CSCs.²⁸ Furthermore, CD133+ HCC cells also showed greater resistance to sublethal irradiation and had enhanced metastatic capability after irradiation.²⁹

Metabolic reprogramming and plasticity

Due to the high rate of proliferation and a lack of vasculature, the nutrient and oxygen supply to solid tumors is generally lower than that seen in normal tissues. Therefore, cancer cells must adjust their metabolic phenotypes to adapt to these more unfavorable microenvironmental conditions. One important common feature of this altered metabolism is an increase in glucose uptake.³⁰ It has been reported that in comparison to CD133- cells, CD133+ HCC cells preferentially survived when glucose was restricted by the IL-6/STAT3 pathway mediated glucose uptake.³¹ Similarly, a different study found that overexpression of CD133 enhanced glucose uptake and autophagy in low glucose media, and may help cells to survive in the harsh tumor microenvironments.¹⁹ Autophagy is important as it allows tumor cells to survive under conditions of nutrient stress, by recycling the by-products of autophagic degradation. Autophagy can also influence CSCs phenotype through autophagy mediated regulation of metabolism.³² Significantly, CD133+ HCC cells showed higher survival rates during times of oxygen and nutrient deprivation which was found to be dependent upon higher rates of autophagy.³³

The identification of LCSCs using a combination of CD133 and other surface markers

Although CD133+ cells are regarded as mainstream LCSC markers because of their strong tumor initiating capability, there remains some controversy whether CD133 represents a single marker for CSCs. Salnikov et al. found that CD133+ and CD133- HCC cells have no significant difference in migratory properties, and that the expression of CD33 had no correlation with prognosis in HCC patients.³⁴ It has been observed that there are differential expression patterns of CD133 in several HCC cell lines, which ranged from 48% to 60% in PLC8024s to 49% to 65% in Huh7s. Therefore, as a single marker, CD133 may not be sufficient to determine

CSCs in HCC.³⁵ A recent study has provided evidence that LCSCs at the single-cell level are phenotypically, functionally, and transcriptionally heterogeneous.³⁶ Thus, identification of other markers, expressed along with CD133, is needed to better characterize the CSC population in HCC. Other cell surface markers that are expressed along with CD133 have been found to be capable of identifying CSCs in HCC. Ma et al. found that CD133+ ALDH+ cells confer significantly more tumorigenic capacity than their CD133-ALDH+ or CD133-ALDH- counterparts, which may help to characterize the liver CSCs more specifically.³⁵ Wu et al. identified a subset of CD13+ CD133+ cells as liver CSCs through the detection of sphere formation, stemness analysis and tumor formation in xenograft models.³⁷ A different study by Wang et al. isolated the CD13+ CD133+ cells from both HCC cell lines and HCC primary cells and further identified them as liver CSCs.³⁸ When compared to CD133+ CD44- cells, these CD133+ CD44+ cells had greater tumorigenic and chemoresistance capabilities, and also exhibited preferential expression of stem cell-related genes.³⁹ CD133+ CD44+ cells have also been reported to be associated with metastasis in liver cancer^{40,41} and CD133+/CD44+ in HCC cells have been found to have stem cell properties.⁴² A study by Chen et al. revealed that CD133+ EpCAM+ cells represent precisely CSCs in Huh7 cells.⁴³ As compared to CD133+ EpCAM-, CD133-EpCAM+, CD133-EpCAM- cells, they found that CD133+ EpCAM+ cells have higher differentiation, colony-formation, drug-resistant, spheroid formation and tumorigenic capacity.⁴³ A number of subsequent studies found that EpCAM+/CD133+ cells from the Huh7 cell line further verified their stem cell properties.⁴⁴⁻⁴⁶ However, this subgroup has not been found in other HCC cells. A recent clinical study found that patients with CD24+ CD133+ cells present in their tumors, had a worse clinical outcome than those with CD24+ CD133-, CD24- CD133+, or CD24- CD133-, present. Furthermore, CD24+ CD133+ cells showed significantly greater tumorigenicity and chemotherapy resistance to sorafenib than CD24- CD133- cells.⁴⁷

Regulation of CD133+ LCSCs self-renewal

Signaling pathways

Among all the stem cell-related signaling pathways (Figure 1), the Wnt/ β -catenin pathway has been found to be one of the most important in CSCs, including CD133+ LCSCs. Wnt/ β -catenin signaling has been found to be hyperactivated in CD133+ LCSCs and plays a crucial role in the maintenance of stemness in CD133+ LCSCs.^{48,49} Accumulating evidence has revealed that aberrant NF- κ B signaling is present in many types of CSCs.⁵⁰ In CD133+ LCSCs, increased activation of the NF- κ B signaling pathway was seen, and blockade of NF- κ B activation significantly inhibited the self-renewal of CD133+ LCSCs.^{51,52} Furthermore, several studies have shown that activation of the STAT3 signaling pathway promotes the expression of CD133 through induction of transcription and the maintenance of CD133+ CSC stemness.^{53,54} Maehara et al. found that AMPK-CEBP β signaling plays an important role in regulating the expression of CD133 and self-renewal of CD133+ liver CSCs.⁵⁵ Many studies have reported a correlation between the JNK signaling pathway and CSCs, however, the role of JNK signaling in CSCs remains unclear.⁵⁶ Tong et al. found that *p*-JNK was preferentially expressed in CD133+ HCC cells, and that activation of the JNK pathway promoted characteristics associated with CD133+ CSCs.⁵⁷ In contrast, Jin et al. demonstrated that the expression of JNK-associated signaling molecules was inversely correlated to CD133 expression, and that CD133+ CSCs have high metastatic capacity due to inhibition of the JNK signaling transduction pathway.²¹ Thus, further studies are needed to elucidate these disputed functions related to JNK signaling in CSCs. Furthermore, the role of TGF- β signaling in CSCs remains controversial due to its complex functions in the development of cancer. It has been demonstrated that TGF- β can enhance the expression of CD133 and impart an aggressive EMT phenotype.⁵⁸⁻⁶¹ Interestingly, a study by Chen et al. revealed that the inhibition of the TGF- β pathway through the activation of TLR4/

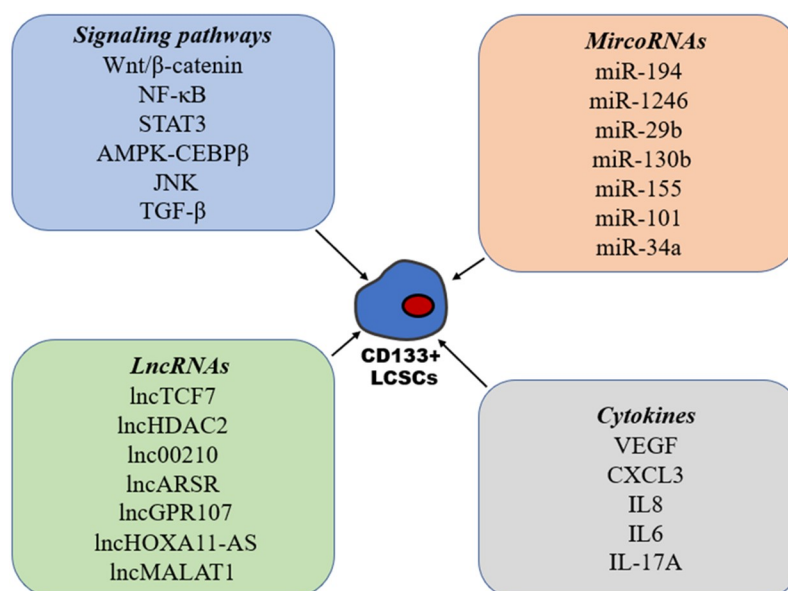


Figure 1. The molecular mechanism that regulates the stemness of CD133+ liver cancer stem cells.

NANOG exhibited enhanced tumorigenesis and chemoresistance in CD133+ CSCs.⁶²

MircoRNAs

There is accumulating evidence linking microRNAs (miRNAs) to the regulation of CSC stemness, including CD133+ LCSCs (Figure 1). Ran et al. found that miR-194 decreased remarkably in CD133+ LCSCs, and that interference of miR-194 facilitated the self-renewal of CD133+ LCSCs by targeting Ras-related C3 botulinum toxin substrate 1 (RAC1).⁶³ MiR-1246 has been found to be overexpressed in CD133+ LCSCs, which may play an important role in CSCs stemness via suppression of AXIN2 and GSK3 β expression, and the constitutive activation of the Wnt signaling pathway.⁴⁸ A study by Bai et al. revealed that miR-29b could directly bind with CD133 to regulate the expression of CD133, and that miR-29b is responsible for CD133+ cell stemness both in vitro and in vivo.⁶⁴ Using miRNA expression profiling of CD133+ and CD133- cells, Ma et al. found that miR-130b was overexpressed in CD133+ spheres; they also demonstrated that miR-130b was involved in self renewal, tumorigenicity, and chemoresistance in CD133+ cells and this was achieved by targeting TP53INP1.⁶⁵ MiR-155 was also demonstrated to regulate the expression of CD133 by targeting TP53INP1 in HCC cells.⁶⁶ Using miRNA microarray analysis, Ma et al. found that miR-101 expression was downregulated in CD133+ liver CSCs. Furthermore, increasing the miR-101 expression markedly inhibited CD133+ CSC proliferation, and their tumorigenesis by targeting AXNA2,⁶⁷ and a recent study showed that miR-34a plays an important role in the maintenance of CD133+ LCSC stemness via FOXM1.⁶⁸

LncRNAs

Currently, there is a tremendous amount of work exploring the involvement of long noncoding RNAs (lncRNAs) in CD133+ LCSC self-renewal (Figure 1). Using transcriptome microarray analysis, Wang et al. identified lncTCF7 to be highly expressed in HCC tumors and CD133+ CD13+ cells and was also involved in CD133+ CD13+ LCSC self-renewal.³⁸ A separate study by the same group identified a further lncRNA termed lncHDAC2 by conducting a transcriptome microarray analysis of CD13+ CD133+ cells and CD13- CD133- cells, and found that this lncRNA was able to promote the self-renewal of liver CD13+ CD133+ CSCs.³⁷ A further transcriptome microarray analysis, by Fu et al., identified lnc00210 as being overexpressed in CD133+ cells and found that it played an important role in CD133+ LCSC self-renewal.⁶⁹ Yang et al. showed that lncARSR expression was increased in CD133+ LCSCs, and that this lncRNA when silenced caused inhibition of the self-renewing capacity of CD133+ LCSCs.⁷⁰ LncGPR107 was also highly expressed in HCC and CD133+ LCSCs, where it regulates the self-renewal of CD133+ CSCs through GPR107.⁷¹ A study by Guo et al. demonstrated that CD133+ cells showed high expression of lncHOXA11-AS, and that its silencing suppressed the self-

renewal and tumorigenicity of CD133+ cells in vivo.⁷² A recent study further indicated that silencing lncMALAT1 downregulates β -catenin expression and attenuates CD133+ HCC cell populations.⁷³

Cytokines

It is generally accepted that CSCs reside in a particular niche microenvironment, which has a complex architecture consisting of endothelial cells, fibroblastic cells, immune cells, an extracellular matrix, and a variety of cytokines.⁷⁴ Cytokines have an important role in determining the characteristics of CSCs in both an autocrine or paracrine manner (Figure 1). Liu et al. demonstrated that vascular endothelial growth factor (VEGF) increased the proportion of CD133+ CSCs and enhanced their capacity for self-renewal via activation of the VEGF receptor (VEGFR2).⁷⁵ Furthermore, the expression of CXCL3 in HCC cells is positively correlated with CD133, and CXCL3 plays an important role in CD133+ LCSCs maintenance via MAPK signaling.⁷⁶ Kahraman et al. found that IL8 expression was increased significantly upon Sorafenib treatment in CD133+/EpCAM+ LCSCs and that IL8 inhibition with the inhibitor reparixin or siRNA, repressed the characteristics of LCSCs, and increased their sensitivity to sorafenib.²⁶ A recent study also indicated that IL6-mediated inflammatory programs and enhanced the metastatic capacity of CD133+ LCSCs via constitutive activation of TAK1-NF- κ B signaling, and that this program reacts to deficient TGF β signaling.⁷⁷ Finally, it has been found that IL-17A secreted from lymphatic endothelial cells promotes self-renewal and the immune escape of CD133+ LCSCs through upregulation of PD-L1.⁷⁸

Clinical significance of CD133 in HCC

According to our current thinking, the characteristics of CSCs should be closely correlated with patient prognosis. Thus, detection of liver CSCs might contribute to a more accurate prediction of prognosis in HCC patients. Several studies have shown that high CD133 expression in HCC was an independent risk factor for the overall survival (OS) and relapse-free survival (RFS) rates in these patients.⁷⁹⁻⁸² A separate study has indicated that CD133 expression was an independent prognostic factor for OS, and a highly accurate prognostic factor in patients with stage I disease in HCC.⁸³ CSC biomarkers are expressed heterogeneously, and the positive rate of a single biomarker in cancers is always low. Thus, it is reasonable to assume that applying a set of CSC biomarkers may be more sensitive and specific than employing a single marker to predict prognosis in cancer patients. Based on Cox regression, Yang et al. used a simplified model including the CSC markers CD133, CD44, nestin and angiogenesis microvessel density (MVD) markers and found that these were a good independent predictor of OS and RFS, regardless of the α -fetoprotein (AFP) level, tumor stage, or recurrence time in HCC.⁸⁴ Based on CD133 immunostaining and serum AFP levels, Dai et al. subclassified HCC cases into four subtypes and found that when compared to CD133+ AFP- HCC, CD133

– AFP+ HCC and CD133– AFP– HCC, only CD133+ AFP+ HCC was associated with a relatively poor prognosis.⁸⁵ Several studies have found that the PTEN–/CD133+ group had shorter OS and RFS times when compared to the PTEN–/CD133–, PTEN+/CD133+ and PTEN+/CD133– groups in HCC.^{86,87}

The clinical significance of CD133 in the response to various treatments for HCC was also explored. It has been reported that high expression of CD133 was linked to a poor response to sorafenib, suggesting that CD133 may be a predictive biomarker for the nature of the response to sorafenib treatment in HCC.⁸⁸ A further study showed that CD133 expression was related to the response to sorafenib; however, the association was not statistically significant for CD133 alone. Furthermore, they also found that the levels of CD133 and CD90 expression were associated with the clinical response to sorafenib.⁸⁹ By studying resected livers from HCC patients during transplantation, CD133 was found to be an independent risk factor associated with increased recurrence and a worsening OS.^{90,91} Further studies with greater sample sizes and a longer follow-up period are required to elucidate the real clinical associations between CD133 and HCC.

Therapeutic strategies targeting CD133 in HCC

As mentioned above, CD133 is functionally important for LCSCs, making it an attractive therapeutic target. There have been therapeutic advances in the field of CD133+ LCSCs (Figure 2).

Antibody

Monoclonal antibody targeting CSC markers in neoplasia is an attractive option for a novel therapeutic approach. A study by Chen et al. determined the effect of a monoclonal antibody directed against CD133 (CD133mAb) LCSCs in HCC cells, and found that treatment with CD133mAb inhibited spheroid and colony formation, suppressed xenografted tumor growth and

promoted chemotherapy efficacy.⁹² Antibody-drug conjugates (ADC) have developed to recognize tumor-associated antigens and to release cytotoxic payloads to specific subsets of tumor cells.⁹³ One such study used a murine anti-human CD133 antibody (AC133) conjugated to a cytotoxic drug, monomethyl auristatin F (MMAF), to inhibit the growth of Hep3B tumors in SCID mice.⁹⁴ They also found AC133-vcMMAF treatment caused elimination of most CD133+ cells within the tumors investigated.⁹⁴

Aptamers

Aptamers are small single-stranded DNA or RNA oligomers which form unique tertiary structures that bind to target molecules. Compared to antibodies, aptamers have low immunogenicity, low toxicity, and are chemically stable.⁹⁵ One study used a CD133 aptamer A15 conjugated with salinomycin-loaded nanoparticles. Once internalized, into CD133+ HCC cells, the salinomycin was released to the cytoplasm and cells were destroyed.⁹⁶ Zhou et al. developed a specific aptamer against CD133 (CD133-apt) that was loaded with the anticancer drug, doxorubicin (CD133-apt-Dox), which inhibited the self-renewal capacity of liver CSCs and attenuated their stemness phenotypes in vitro and in vivo.⁹⁷

T-cell therapy

Chimeric antigen receptor (CAR) T cells have been engineered to express synthetic antigen receptors that are specific to tumor surface antigens.⁹⁸ CART cells directed toward CD133,

(CART-133) were tested in a clinical trial by Wang et al. They found encouraging antitumor activity from CART-133 for the treatment of HCC patients with advanced and CD133+ tumors.⁹⁹ Results from a recent clinical trial have shown an important therapeutic potential for CART-133 cell therapy in patients with advanced HCC.¹⁰⁰

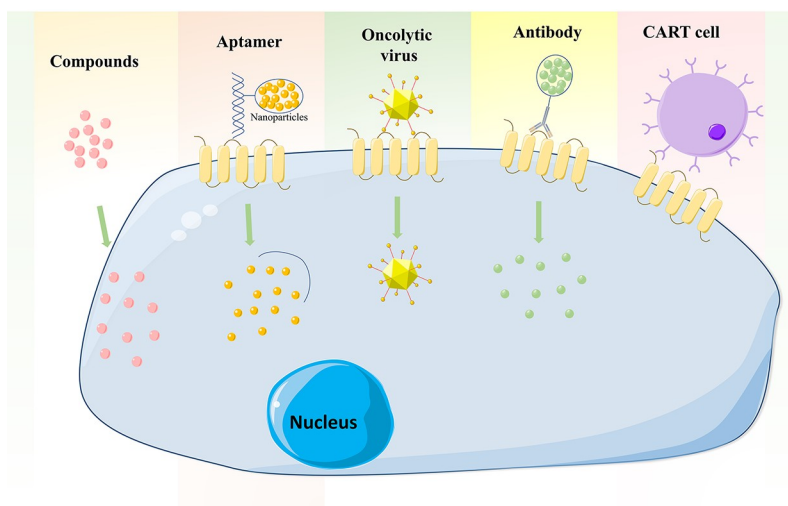


Figure 2. Therapeutic strategies targeting CD133 in HCC, including antibodies, aptamers, CAR T cells, oncolytic viruses and some drugs or compounds.

CD133-targeted viruses

A growing body of evidence has demonstrated that oncolytic viruses can efficiently eliminate CSCs in many types of cancer, including HCC CSCs. Bach et al. generated CD133-targeted viruses using oncolytic measles virus, which selectively eliminate CD133+ HCC cells and exerted strong antitumoral effects on tumor growth subcutaneously or in a multifocal cancer model in NOD/SCID mice.¹⁰¹ Another study, by Terai et al., developed a mutated version of Herpes simplex virus-1 (HSV-1), which was transcriptionally targeted against CD133+ HCC cells, and the virus showed a robust inhibitory activity against tumor growth and invasiveness.¹⁰²

Drugs and compounds

A study by Song et al. revealed that treatment with sulfasalazine (SASP) sensitizes CD133+ HCC to chemotherapies by decreasing the levels of glutathione (GSH), and suggested that a combination of SASP and conventional chemotherapy may effectively overcome resistance in HCC.¹⁰³ Using highthroughput screening, Song et al. identified oxytetracycline as exhibiting a significant inhibition of the CD133+ population. They also demonstrated that oxytetracycline suppresses stemness and malignancies in HCC cells through destabilization of CD133 in CD133+ HCC cells.¹⁰⁴ Ye et al. found that osthole reversed the resistance of CD133+ HCC cells to cisplatin through inhibited AKT/Bad/Bcl-2 pathway via the increase of PTEN expression.¹⁰⁵ Zhang et al. indicated that As2O3 induced CD133+ HCC CSC differentiation and inhibited recurrence after radical resection and prolonged survival in a mouse model.¹⁰⁶ Research by Song et al. demonstrated that chromenopyrimidinone (CPO) effectively suppressed stemness and malignancies caused by CD133+ cells in vitro and in vivo, by inducing degradation of CD133.¹⁰⁷

Conclusion

CD133 is one of the most frequently used cell surface markers for the detection and isolation of CSCs from HCC. In the past two decades, there have been numerous studies relating to CD133 + LCSCs, and many novel and controversial views have emerged. The confirmation that CSC heterogeneity has led to an increasing number of researchers combining CD133 with other markers for the identification of LCSCs. CD133 is not just a surface marker of stem cells in HCC, its expression also plays an important role in signal transduction involved in the maintenance of stemness in liver CSCs.

Here, we have summarized the relevant mechanisms that regulate the stemness of CD133+ cells, including signaling pathways, non-coding RNA and the cellular microenvironment. Beyond the molecular mechanisms of CSCs, the expression of CD133+ in tumors contributes to the accuracy of prognosis in HCC patients. Although increasing studies suggest that CD133-targeted-based therapies could be a novel promising option for the treatment of HCC (Figure 2), they currently remain far removed from clinical applications for their controversial

specificity.

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Disclosure statement

All authors declare that they have no conflict of interests.

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