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TOPIC HIGHLIGHT

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Cellular reprogramming and hepatocellular carcinoma development

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Abstract

Hepatocellular carcinoma (HCC) is one of the most common cancers, and is also the leading cause of death worldwide. Studies have shown that cellular reprogramming contributes to chemotherapy and/or radiotherapy resistance and the recurrence of cancers. In this article, we summarize and discuss the latest findings in the area of cellular reprogramming in HCC. The aberrant expression of transcription factors OCT4, KLF4, SOX2, c-MYC, NANOG, and LIN28 have been also observed, and the expression of these transcription factors is associated with unfavorable clinical outcomes in HCC. Studies indicate that cellular reprogramming may play a critical role in the occurrence and recurrence of HCC. Recent reports have shown that DNA methylation, miRNAs, tumor microenvironment, and signaling pathways can induce the expression of stemness transcription factors, which leads to cellular reprogramming in HCC. Furthermore, studies indicate that therapies based on cellular reprogramming could revolutionize HCC treatment. Finally, a novel therapeutic concept is discussed: reprogramming control therapy. A potential reprogramming control therapy method could be developed based on the reprogramming demonstrated in HCC studies and applied at two opposing levels: differentiation and reprogramming. Our increasing understanding and control of cellular programming should facilitate the exploitation of this novel therapeutic concept and its application in clinical HCC treatment, which may represent a promising strategy in the future that is not restricted to liver cancer.

Key words: Reprogramming; Hepatocellular carcinomas; Cancer stem cells; Transcription factor; Therapeutics

Core tip: Cellular reprogramming contributes to chemoresistance and radioresistance and cancer recurrence in hepatocellular carcinoma (HCC). Recent findings on cellular reprogramming in HCC are summarized and discussed, including stemness transcription factors, DNA methylation, miRNAs, tumor microenvironments, and signaling pathways. The novel therapeutic concept of reprogramming control therapy is also described, which may be a promising strategy for HCC therapy in the future.

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INTRODUCTION

Liver cancer is one of the most common tumors worldwide. An estimated 749000 new liver cancer cases and 695000 cancer deaths occurred worldwide in 2008[1]. Half of these cases and deaths were estimated to have occurred in sub-Saharan Africa and Southeast Asia. Among primary liver cancers, hepatocellular carcinoma (HCC) represents the major histological subtype, which accounts for 70%-85% of the total liver cancer burden worldwide[2].

Reports have shown that tumor recurrence[3] and patient survival[4,5] are correlated with HCC differentiation. Based on the Edmondson-Steiner's classification, HCC can be graded from I to Ⅳ: well-differentiated (grade Ⅰ), moderately differentiated (grade Ⅱ), poorly differentiated (grade Ⅲ), and undifferentiated (grade Ⅳ) HCC[6]. The prognosis of poorly differentiated carcinoma is worse than that of well-differentiated carcinoma[4], and the five-year survival of patients with poorly differentiated HCC is significantly worse than that of patients with moderately or well-differentiated HCC[7]. Ample evidence demonstrates that the poor prognosis and low five-year survival with poorly differentiated carcinoma are correlated with the expression of specific genes[4,8,9] and signal pathway activation[10,11], which can increase the resistance to chemotherapeutic drugs and the frequency of HCC recurrence.

Evidence shows that aggressive poorly differentiated human cancers express high levels of embryonic stem cell-like genes, suggesting that reprogramming to a more dedifferentiated state occurs during tumor progression[12]. Moreover, if different reprogramming factors are activated, cancer cells can form well-differentiated and poorly differentiated sarcomas[13]. Poorly differentiated cancers have a higher content of prospectively isolated cancer stem cells than well-differentiated cancers[14]. These data support the view that cancer is a reprogramming-like disease and that cancer stem cells (CSC) may arise through a reprogramming-like mechanism before initiating tumor formation and progression in HCC. Therefore, understanding the role of cellular reprogramming may facilitate the development of new therapeutic strategies for HCC.

CELLULAR REPROGRAMMING AND CANCER STEM CELLS

Cancer stem cells

Classical tumor formation theory, *i.e.*, clonal evolution theory, suggests that each cell in a tumor is biological homogeneous[15], whereas the alternative theory considers that the cells within a tumor are not identical, which is also known as tumor heterogeneity[16]. In the alternative theory, all of cell types can arise from a signal cell, known as a CSC, which has the potential for self-renewal and differentiation[17]. Ample evidence supports a major role for the CSC model in tumor heterogeneity. Lapidot *et al*[18] first demonstrated a critical role for CSC in human acute myeloid leukemia, where leukemic stem cells (LSC) initiated human acute myeloid leukemia after transplantation into SCID mice. The existence of LSC prompted further research into other types of cancer. CSC have recently been identified in several solid tumors, including breast, brain, colorectal, pancreas, liver, melanoma, and prostate cancers[19]. CSC possess the properties of normal stem cells, *i.e.*, self-renewal and differentiation. Self-renewal enables CSC to produce another CSC with essentially the same developmental and replication potential, which can increase the capacity for self-protection against drugs, toxins, and radiation. Differentiation involves the production of different types of cancer cells that trigger tumor initiation, maintain tumor growth, and finally form a bulk tumor.

Table 1 Expression of transcription factors in various cancer types

Type of cancer	Transcription factors
Breast cancer	*NANOG*[22], *SOX2*[23], *OCT4*[24] and *KLF4*[22]
Colorectal cancer	*NANOG*[25], *SOX2*[26] and *OCT4*[26]
Gastric cancer	*NANOG*[27], *SOX2*[27] and *OCT3/4*[27]
Hepatic cancer	*NANOG*[28], *SOX2*[29], *OCT4*[29] and *KLF4*[30]
Lung cancer	*NANOG*[31], *SOX2*[32] and *OCT4*[33]
Esophageal cancer	*NANOG*[34], *SOX2*[35], *OCT3/4*[35] and *LIN28*[36]
Ovarian cancer	*OCT4*[37] and *LIN* 28[38]

Cancer development

Studies have shown that reprogramming factors have specific expression signatures in human tumors (Table 1) and that the expression levels of these factors are correlated with the differentiation grades of tumor. Ben-Porath *et al*[12] found that poorly differentiated tumors preferentially overexpressed embryonic stem cell (ESC) genes. Moreover, the activation targets of reprogramming factors, such as *NANOG*, *OCT4*, *SOX*2 and *c-MYC*, are more frequently overexpressed in poorly differentiated tumors than well-differentiated tumors[12]. Chiou *et al*[20] reported that the expression levels of *NANOG*, *OCT4* and *CD133* were correlated with a poor survival prognosis in patients with oral squamous cell carcinoma. Reprogramming factors also play essential roles in maintaining the properties of CSC in tumors. Silencing the expression of Oct-4 in $CD133^+$ lung cancer can significantly inhibit the capacity for self-renewal, enhance $CD133^+$ cell differentiation into $CD133^-$ cells, and reverse the effects of chemotherapy or radiotherapy[21]. These data suggest that reprogramming factors play critical roles in the origin and development of CSC.

Origin of CSC

Studies have shown that the occurrence of CSC is related

to cellular reprogramming, but the origin of CSC remains a conundrum. However, important new evidence has demonstrated that there are two possible routes for CSC emergence.

First, CSC may arise from normal stem cells (SC) that lose the ability to regulate proliferation. Kim *et al*[39] showed that SC are more readily reprogrammed into induced pluripotent stem cells (iPS) compared with somatic cells. *OCT4* and either *KLF4* or *c-MYC* are sufficient to generate iPS from neural SC[39], which suggests that SC can be reprogrammed, and the process may be much easier than reprogramming mature cells. Riggi *et al*[40] successfully reprogrammed mesenchymal SC (MSC) into Ewing sarcoma cancer SC by inducing the expression of the ESC genes *OCT4*, *SOX2* and *NANOG* using the *EWS-FLI1* fusion gene. Chiba *et al*[41] reported that normal SC can be transformed into CSC after overexpressing the *BMI-1* gene, which had the potential for tumor formation.

The alternative theory hypothesizes that CSC may be reprogrammed from somatic cells, which acquire the capacities for self-renewal and tumor initiation after genetic lesions. After forcing the expression of exogenous OSKM (OCT4, SOX2, KLF4, MYC) in the human somatic fibroblast line TIG1, Nagata *et al*[42] isolated induced cancer SC (iCSC) from cell populations with the capacity for self-renewal. The lack of a functional RB1 can also trigger reprogramming, which generates cells with the properties of CSC from mouse fibroblasts[43]. Therefore, studies suggest that CSC can be reprogrammed from somatic cells. Moreover, the dedifferentiation of tumor cells may also lead to stemness property of cells. Recent studies suggest that tumor cells could also be a source of CSC. The expression of the reprogramming factors, *OCT4* and *NANOG*, was detected in poorly differentiated lung adenocarcinoma, whereas ectopic expression of *OCT4* and *NANOG* increased the proportion of the CD133-expressing subpopulation, sphere formation, and enhanced drug resistance in lung adenocarcinoma[44]. Similar results were also observed in melanoma and colon cancer[45,46]. For example, exogenous expression of the *OCT4* gene or the transmembrane delivery of OCT4 protein promoted the dedifferentiation of melanoma cells into CSC-like cells by the induced expression of endogenous *OCT4*, *NANOG* and *KLF4*[45]. Su *et al*[46] showed that HT29/CD44$^-$ cells can be reprogrammed into CSC with significantly increased expression levels of *c-MYC*, *STAT3*, *SOX2* and *OCT4* by the CD44-SRC-integrin axis.

CELLULAR REPROGRAMMING OF HCC

Related factors

Transcription factors: Recently, it was demonstrated that forced expression of combinations of four transcription factors, *i.e.*, *OCT4*, *KLF4*, *SOX2*, and *c-MYC* or *OCT4*, *SOX2*, *NANOG* and *LIN28*, can reprogram somatic cells into iPS that closely resemble ESC[47-50]. Increasing evidence has demonstrated that aberrant expression of reprogramming factors may confer primitive and aggressive traits, which are associated with unfavorable clinical outcomes in HCC. *OCT4*, *NANOG* and *SOX2* have been detected in HCC cell lines and in tumor specimens from patients with HCC, and Oct4 could play a significant role in activating the Wnt/β-catenin and transforming growth factor-β (TGF-β) signaling pathways[51]. Huang *et al*[29] demonstrated that SOX2- and OCT4A-positive expression were significantly associated with an aggressive phenotype in HCC. *SOX2* or *OCT4A* are independent prognostic factors for HCC, but the coexpression of *SOX2*/*OCT4A* has the poorest prognosis in HCC[29]. Increased expression of Nanog is also correlated with a poorer clinical outcome in HCC, whereas the overexpression of NANOG in NANOG$^-$ cells increases the capacity for self-renewal by the insulin-like growth factor receptor (IGF1R) signaling pathway in HCC[28]. Of interest, expression of the pluripotent transcription factor KLF4 is decreased or lost in primary HCC[30]. The loss of KLF4 expression is also significantly associated with poor survival in HCC[30]. Evidence suggests that KLF4 is a putative tumor suppressor gene. The enforced restoration of KLF4 expression markedly inhibits cell migration, invasion, and growth *in vitro*, and significantly attenuates tumor growth and metastasis in HCC animal models[30,52]. Reprogramming factors are expressed preferentially in hepatocellular carcinoma SC (HCSC). Expression levels of *CD44*, *OCT4* and *BMI1* were specifically upregulated in CD45$^-$CD90$^+$ cells isolated from the tumor tissues and blood samples of patients with HCC compared with those in CD45$^-$CD90$^+$ cells isolated from normal livers[53]. Ma *et al*[54] found that CD133$^+$ HCC cells expressed consistently higher mRNA levels of β-catenin, *OCT-3/4*, *BMI*, *SMO*, and *NOTCH-1* than CD133$^-$ HCC cells.

DNA methylation: Epigenetic studies have demonstrated that specific DNA methylation patterns, including global hypomethylation and promoter hypermethylation, may be early events in HCC[55]. A genome-wide DNA methylation microarray analysis showed that side population (SP) cells had a different DNA methylation status compared with non-SP cells in HCC[56]. Recent discoveries have shown that DNA methylation is an essential epigenetic mechanism during iPS reprogramming[57]. Demethylating agents and demethylase proteins may activate pluripotent gene promoters, thereby facilitating cellular reprogramming and ultimately enhancing the efficiency of iPS generation. Wang *et al*[58] found that chemoresistant cells exhibited increased expression levels of *OCT4* in HCC, whereas the expression of *OCT4* was regulated by DNA methylation. More recent reports have shown that the expression of OCT4 is associated with the protein level of lipid storage droplet (LSD) in pluripotent cancer cells and human testicular seminoma tissues[59]. CD133 expression is also regulated by DNA methylation in HCC[60]. The elevated expression of CD133 is associated with the demethylation of Line-1 in HCC[60]. More-

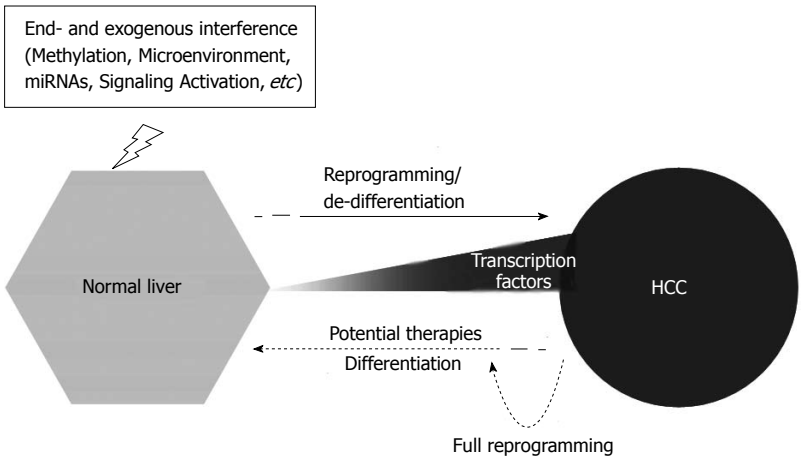

Figure 1 The process of cellular reprogramming and potential therapies in hepatocellular carcinoma. The endogenous and exogenous interferences such as DNA methylation, microenvironment factors, microRNAs (miRNAs) and signaling activation (see text for details) could induce the reprogramming of hepatic cells and stem/progenitor cells, result in tumor initiation, an excess of self-renewal and chemo/radio-resistance, and form HCC. Reversely, the differentiation induction including demethylation, miRNAs, RNAi and signaling inhibition, will be the potential therapies for HCC. Additionally full reprogramming induction might offer us a novel way to treat HCC. The reprogramming approach would help to induce the partially reprogrammed cells to transform in full reprogrammed cells, like induced pluripotent stem cells, which can be induced to various types of differential somatic cells. HCC: Hepatocellular carcinoma.

over, TGF-β-1 can inhibit the expression of DNA methyltransferases (DNMT)1 and DNMT3β, thereby leading to significant demethylation in the CD133 promoter-1 in $CD133^-$ Huh7 cells[61]. Studies of MSC have shown that methylation of the tumor suppressor genes, *HIC1* and *RASSF1A*, is sufficient to successfully reprogram the MSC into cancer stem/initiating cells[62]. These studies suggest that the demethylation of reprogramming factors and/or methylation of tumor suppressor genes contribute to reprogramming in HCC and to the origination of HCSC.

MicroRNAs: MicroRNAs (miRNAs) are well-characterized regulators of development and differentiation[63]. Studies have demonstrated that specific miRNAs have high expression levels in ESC and that they play a critical role in the control of pluripotency-related genes[64,65]. The clusters of miRNA-302s/367s[66] or miRNA-302s/369s/200c[67] can directly reprogram mouse and human somatic cells to pluripotency and increase the expression levels of OCT4 and SOX2. Studies have shown that miRNA-302 is a direct target of OCT4 and SOX2 in human ESC[68], whereas miRNA-302 and OCT4/SOX2 may work as a positive feedback system in cellular reprogramming. Moreover, the reprogramming miRNA-302 is highly expressed in a rare subpopulation of glioma cell lines. miR-302 expression causes tumorsphere formation and significant upregulation of pluripotent genes[69]. Results indicate that miRNAs participate in the neoplastic transformation of HCSC in HCC. In total, 68 miRNAs have been found to be overexpressed, whereas 10 miRNAs were underexpressed in a SP of HCC cells compared with fetal liver cells[70]. miRNA can also regulate the expression of cancer SC markers in HCC. OCT4 was regulated by miRNA-145 in T3A-A3, which are CSC-like cells[71], whereas miRNA-148 attenuated the expression of CD90 and CD44 in HCC[72]. miRNA-181 family members were highly expressed in (epithelial cell adhesion molecule$^+$ ($EpCAM^+AFP^+$) HCC cells, and the inhibition of miRNA-181 led to a reduction in the quantity of $EpCAM^+$ HCC cells and their tumor-initiating ability[73]. These reports suggest that miRNAs are potential factors in the reprogramming of HCC (Figure 1).

Microenvironment: Microenvironment plays a role in HCC, although its role during cellular reprogramming remains unclear. Hypoxia is a well-known characteristic of the tumor microenvironment, including HCC. In the emerging field of induced pluripotency, Yoshida *et al*[74] have shown that hypoxia can significantly improve the generation of iPS colonies following reprogramming. Seven hypoxia-related prognostic genes, *i.e.*, *CCNG2*, *EGLN3*, *ERO1L*, *WDR45L*, *FGF21*, *MAT1A* and *RCL1*, which were dysregulated in HCC, were associated with chronic hypoxia, and were correlated with a poor prognosis in HCC[75]. *CCNG2*[76] and *EGLN3*[77] were upregulated in CSC, whereas MAT1A deficiency increases the expression of $CD133^+$ HCSC[78]. Mathieu *et al*[79] showed that hypoxia by hypoxia-inducible factor (HIF) could induce a hESC-like transcriptional program, including induction of the reprogramming factors, *OCT4*, *NANOG*, *SOX2*, *KLF4*, *cMYC* and miRNA-302, in 11 cancer cell types, including HCC. Haraguchi *et al*[80] reported that CD13 is a marker for semiquiescent CSC in human liver cancer cell lines, where the expression of CD13 is accompanied by the expression of carbonic anhydrase 9 (CA9), a hypoxia marker in HCC.

The tumor environment is always characterized by inflammation. Interleukin (IL)-6, an inflammatory cytokine, led to HCC from an IL-6-driven transformed SC with inactivated TGF-β signaling[81]. Moreover, a subset of highly chemoresistant and invasive HSC were screened that had aberrant expression levels of cytokine IL-6 and TWIST. The secretion of IL-6 and TWIST can significantly increase the expression levels of let-7 and miR-181, which contribute to chemoresistance and cell invasion in HCC[82].

Both of Hepatitis B virus (HBV) and Hepatitis C virus (HCV) are the major etiological agents of chronic liver disease and HCC. *In vitro* and *in vivo* studies have shown that OCT4, NANOG, KLF-4, β-catenin and (EpCAM) are activated by HBx, and the upregulated expression of multiple stem genes demonstrates that HBx contributes to hepatocarcinogenesis, at least partly, by promoting changes in gene expression, which are characteristics of CSC[83]. Moreover, HCV can also induce the cancer stem cell-like signatures in cell culture and mouse

model.

Signaling pathways

Reprogramming is likely to induce drastic molecular changes that involve the upregulation of pluripotent genes and the repression of differentiation genes. Thus, signaling pathways have profound effects on the reprogramming of somatic cells into iPS[84]. A class comparison analysis showed that 793 genes were differentially expressed in hepatic stem cell-like HCC (HpSC-HCC) and mature hepatocyte-like HCC (MH-HCC)[85]. A pathway analysis indicated that differentially expressed genes were significantly associated with SC signaling pathways, including Wnt/β-catenin, TGF-β and ERK/MAPK signaling[85]. These results suggest that signaling pathways have significant effects on cell reprogramming in HCC.

Wnt/β-catenin: It is well-known that Wnt/β-catenin signaling can control ESC self-renewal and the maintenance of stemness[86], and it also regulates the expression of *ESC* genes[87]. Furthermore, it may contribute to the reprogramming of somatic cells in pluripotent cells[88]. Yamashita *et al*[89] identified a novel prognostic HCC subtype based on EpCAM expression, which resembled hepatic progenitor cells with activated stem cell markers and Wnt/β-catenin signaling. The expression of EpCAM was associated with the activation of Wnt/β-catenin signaling[89]. Similar results were reported by Yang *et al*[90] who found that $OV6^+$ cancer cells could endogenously activate Wnt/β-catenin signaling in HCC. Expression of OV6 increases after the activation of Wnt/β-catenin signaling, whereas inhibition of Wnt/β-catenin signaling leads to a decrease in the proportion of $OV6^+$ cells in HCC[90]. Moreover, the activation of Wnt/β-catenin signaling could be inhibited by silencing the expression of *OCT4*, with a reduction in *WNT-10b* and β-*catenin* and an increase in TCF3[51]. These results indicate that Wnt/β-catenin signaling may be an essential part of cellular reprogramming and the maintenance of stem-like characteristics in HCC.

TGF-β: TGF-β signaling pathway has been reported in many cellular processes in adult organisms and the developing embryo, including cell growth, differentiation, apoptosis, and homeostasis. Ichida *et al*[91] demonstrated that TGF-β signaling is involved with cellular reprogramming. The inhibition of TGF-β signaling can promote the completion of reprogramming by the induction of Nanog[91]. Recent studies have shown that the TGF-β signaling pathway can regulate cellular reprogramming in HCC. HCSC exhibit the unexpected loss of Transforming growth factor beta receptor Ⅱ, which could lead to inactivation of the TGF-β signaling pathway[81]. Toll-like receptor 4/NANOG-dependent tumor-initiating stem-like cells (TICs) were also detected with an inactivated TGF-β signaling pathway. Restoration of the TGF-β signaling pathway can inhibit the expression of pluripotent genes, including *NANOG*, *CD133*, *OCT4* and *SOX2*, as well as tumorigenesis and abrogate the chemoresistance of TICs[92].

Mitogen-activated protein kinase/ERK kinase: The mitogen-activated protein kinase/ERK kinase (MAPK/ERK) signaling pathway has been detected in mouse ESC[93]. During reprogramming, the inhibition of MAPK/ERK could promote the transformation of pre-iPS into ground state pluripotent SC, which are cells associated with inhibition of the glycogen synthase kinase-3 (GSK3) signaling pathway[94]. It has been reported that $CD133^+$ HCC exhibit a substantial increase in MAPK/ERK pathway activation[95,96] and that activation of the MAPK/ERK pathway can enhance proliferation, tumor angiogenesis, and initiate tumors in $CD133^+$ HCC. Moreover, MAPK inhibition using the MAPK kinase 1 (MEK1) inhibitor PD98059 leads to a significant increase in TGF-β-induced apoptosis in $CD133^+$ HCC[97].

In addition to these signaling pathways, the BMI-1 and Insulin-like growth factor-1 signal pathways also play key roles during cellular reprogramming in HCC. BMI-1 expression was highly correlated with the CSC phenotype in $CD133^+$ HCC cells, and a modification in BMI-1 expression resulted in a similar change in the maintenance of a CD133 subpopulation in HCC[98]. Insulin-like growth factor (IGF2) and IGF1R can be upregulated in $NANOG^+$ CSC, and a specific inhibitor of IGF1R signaling may significantly inhibit self-renewal and NANOG expression in HCSC, thereby indicating that IGF1R signaling participates in NANOG-mediated cellular reprogramming in HCC[28].

POTENTIAL THERAPIES BASED ON CELLULAR REPROGMMING

The detection and treatment of HCC have greatly improved with the advances in medicine; however, HCC remains largely incurable due to tumor recurrence. Conventional anticancer approaches, surgical resection, chemotherapy, and radiotherapy are primarily directed at bulk tumor populations. However, these strategies are frequently ineffective because of resistance to drugs and/or radiation[99]. Increasing evidence indicates that cellular reprogramming is involved with self-renewal, drug and/or radiation resistance, and tumorigenicity in HCC, and the concept of using precancerous cells and their progeny, CSC, in cancer therapy could provide unique insights into early cancer diagnosis, treatment, and preventive therapy[100]. Cellular reprogramming could also be a potentially useful therapeutic target in HCC.

Inhibition of reprogramming

Methylation: Given the essential role of DNA methylation during cellular reprogramming in HCC, DNA methylation may be a therapeutic target in HCC. Enhancer of zeste homolog 2 (EZH2) is a histone methyltransferase that catalyzes the addition of methyl groups to H3K27, and the blocking of H3K27 methylation leads to a sig-

nificant reduction in TF-induced reprogramming[101]. 3-deazaneplanocin A, an S-adenosylhomocysteine hydrolase inhibitor, is an efficient inhibitor of the function of EZH2, which reduces the levels of H3K27 me3 in HCC cells, thereby reducing the number of $EpCAM^+$ cells and the self-renewal capacity of these cells[102]. Lysine-specific histone demethylase 1 (LSD1) is a histone demethylase, and specific small bioactive inhibitors of LSD1 can enhance H3K4 methylation, derepress epigenetically suppressed genes, and inhibit the proliferation of pluripotent cancer cells, including teratocarcinoma, embryonic carcinoma, seminoma, and ESC[59]. All these studies suggest that methylation of histone 3 may be a potential target in HCC therapy.

miRNA: It is known that miRNAs are involved with the reprogramming of HCC and that they directly regulate the expression of reprogramming factors; however, miRNA can also act as a barrier during reprogramming. Evidence suggests that miRNA-34 is a reprogramming suppression miRNA, which can repress the expression of pluripotent genes, including *NANOG*, *SOX2* and *MYCN*[103]. The expression of pluripotent genes in HCC can also be downregulated by miRNAs. miRNA-145 can directly target OCT4 to arrest the cell cycle and inhibit the tumor growth of T3A-A3[71]. Moreover, miRNAs can regulate self-renewal, differentiation, and chemoresistance in HCSC. The inhibition of let-7 increases the chemosensitivity to sorafenib and doxorubicin by directly targeting SOCS-1 and Caspase-3, whereas silencing of miR-181 expression leads to a reduction in the motility and invasion by directly targeting RASSF1A, TIMP3, and nemo-like kinase in $CD133^+$ HCC[82]. Zhang *et al*[104] demonstrated that overexpression of miR-150 downregulates c-Myb protein levels and leads to a significant reduction in $CD133^+$ cells, which is accompanied with significant inhibition of cell growth and tumorsphere formation. Ma *et al*[105] reported that antagonizing miR-130b reduces the resistance to chemotherapeutic agents, leads in the loss of *in vivo* tumorigenicity, and inhibits self-renewal in $CD133^+$ TICs through TP53INP1 silencing.

Silencing of transcription factors

Using chemotherapeutic drugs to select chemoresistant cancer cells in HCC, Wang *et al*[58] showed that chemoresistant cells exhibit CSC features with dramatically increased Oct4 levels and a highly activated OCT4-TCL1-AKT-ABCG2 pathway. OCT4 knockdown and/or AKT pathway inhibition can reduce the resistance to chemotherapy both *in vitro* and *in vivo*[58]. Oikawa *et al*[106] focused on Sal-like protein 4 (SALL4) and found that elevated expression of SALL4 in tumors is associated with poor survival in HCC. The silencing of SALL4 expression significantly inhibits *in vitro* and *in vivo* tumor growth with increased differentiation[106]. Yamashita *et al*[85] suggested that RNAi-mediated knockdown of EpCAM can reduce self-renewal, tumorigenicity, migration, and drug resistance in HCC cells. Haraguchi *et al*[80] demonstrated that CD13 could ROS-induced DNA damage after genotoxic chemotherapy or radiation stress and protect cells from apoptosis. The combination of a CD13 inhibitor and the genotoxic chemotherapeutic agent fluorouracil (5-FU) drastically reduces the tumor volume in mouse xenograft models[80].

Regulating signaling pathways

Reports have shown that the abnormal activation and/or inhibition of signaling pathways in CSC, as well as the regulation of signal pathways, may be effective approaches to HCC therapy. Yamashita *et al*[89] found that TCF/β-catenin binding inhibitors were much more sensitive to $EpCAM^+$ HCC than $EpCAM^-$ HCC, and they significantly inhibited the growth of $EpCAM^+$ HCC. $CD133^+$ HCC cells that survived chemotherapy had increased preferential expression levels of proteins involved with the AKT/PKB and BCL-2 pathways. AKT/PKB pathway-related cell survival proteins significantly reduce after treatment with an AKT1 inhibitor. Coincubation of an AKT1 inhibitor with DOX or 5-FU almost completely inhibits the preferential survival effect induced by $CD133^+$ cells in HCC[107]. HCSC also exhibit an inactivated TGF-β signaling pathway[81]. A $CD133^+$ population demonstrated significant resistance to TGF-β induced apoptosis compared with $CD133^-$ cells in HCC, whereas the MEK1 inhibitor PD98059 leads to a significant increase in TGF-β-induced apoptosis in $CD133^+$ cells[97].

Differentiation induction

Given that the formation of tumors involves various cancer cells that differentiate from CSC, it is expected that CSC will become less malignant if forced to differentiate into mature cells. Tang *et al*[81] demonstrated that IL-6 can drive the differentiation of HCC from hepatic stem/progenitor cells with inactivated TGF-β signaling. Chow *et al*[108] found that MYC-driven tumors contains a subset of cells (SP cells), which are characterized by Hoechst 33342 efflux. SP tumor cells exhibit markers of hepatic stem cells and chemoresistance, whereas chemoresistance is lost when SP tumor cells differentiate into non-SP tumor cells[108]. This suggests that the differentiation of hepatic CSC may be a possible therapeutic approach. Recently, Yamashita *et al*[109] identified an oncostatin M (OSM) receptor in $EpCAM^+$ HCSC. OSM treatment induced hepatocytic differentiation in $EpCAM^+$ HCSC with a reduction of SC-related gene expression and an increase in albumin expression. Furthermore, a combined treatment with OSM and 5-FU eliminated HCSC and non-CSC subpopulations in an efficient manner[109]. A recent study showed that bone morphogenetic protein 4, a critical molecule in hepatogenesis and hepatic stem cell differentiation, can also promote differentiation and inhibit self-renewal in $CD133^+$ HCSC with a high exogenous dose[110].

Full reprogramming induction

iPS can be generated from normal tissues by the expression of defined transcription factors, as well as from malignant cells[111]. After transformation with four ectopic

reprogramming factors, *i.e.*, OCT4, KLF4, SOX2 and c-MYC, the chronic myeloid leukemia (CML) cell line KBM7 could be reprogrammed into iPS[112]. Moreover, Kumano *et al*[113] induced iPS in samples isolated from patients with CML sensitive to imatinib. This report was the first example of the reprogramming of human primary cancer cells into iPS. In principle, CSC can also be reprogrammed into iPS using four or less reprogramming factors. Kim *et al*[39] showed that iPS could be reprogrammed from adult neural SC using only two reprogramming factors. This indicates that the number of reprogramming factors could be reduced using somatic cells that express appropriate levels of complementary factors endogenously. Studies have shown that HCSC exhibit the endogenous expression of *SOX2*, *C-MYC*, *NANOG* and *OCT4*, and that these endogenous reprogramming factors could facilitate the reprogramming of CSC into iPS, which may reduce the recurrence of HCC.

PERSPECTIVE

In this study, we reviewed the expression of transcription factors detected in HCC and summarized the complex mechanisms that contribute to cellular reprogramming in HCC, which then lead to the acquisition and maintenance of self-renewal and stemness features by a population of cancer cells, thereby resulting in the generation of HCSC. There are numerous potential applications of cellular reprogramming in regenerative medicine and cancer therapy. However, we showed that the knowledge obtained through studies of the molecular and cellular mechanisms that underlie reprogramming in HCC will also have deep implications for our understanding and the treatment of HCC, as well as other types of cancer. Furthermore, we also should refine the theory for application since the non-stem cell mediated, mature hepatocyte-derived HCC emerged in mice[114-116].

Recognizing the role of cellular reprogramming in HCC suggests a novel therapeutic concept: reprogramming control therapy. Based on reprogramming in HCC studies, a possible reprogramming control therapy could be developed that targets two opposing: differentiation (or dereprogramming) and reprogramming (or dedifferentiation). The differentiation approach would focus on the differentiation of reprogrammed cells in HCC. Reprogrammed cells exhibit stem cell-like characteristics, including the expression of stemness genes and the activation of specific signaling pathways. Modifications of gene expression and/or signaling pathways could induce the reprogrammed cells to differentiate into mature somatic cells with impaired self-renewal and reversed chemoresistance and/or radioresistance. The reprogramming approach would help to induce the partially reprogrammed cells in HCC to transform in full reprogrammed cells, such as iPS, which can be redifferentiated into various types of mature cells. *In vitro* experiments and mice model studies have shown that these theoretical therapeutic approaches may have applications in future HCC therapy. Increased knowledge and control of cellular programming could lead to the development of this novel therapeutic concept and its application in clinical HCC therapy, which may be a promising strategy in the future.

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