Characterization of the Role of MicroRNAs in Hepatic Cancer Stem Cells

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Keywords: MicroRNAs; Cancer stem cells; Liver cancer

Introduction
Liver cancer is the fifth most common cancer in the world, and hepatocellular carcinoma accounts for 75% of liver cancer cases [1,2]. In recent years, although radiotherapy, chemotherapy and surgery have been shown to effectively remove or reduce tumors, the ability to cure malignant tumors and prevent tumor metastasis and recurrence has been limited [3-5]. Studies have shown that the development of hepatocellular carcinoma may be related to HCSCs, which have the CSC characteristics of self-renewal and multi-directional differentiation, increasing the difficulty of liver cancer treatment [6-8]. At present, identification of CSC is the focus of targeted therapy for liver cancer. It has been shown that the cell surface molecular markers of HCSC, including CD133 [9,10], CD90 [11], CD44 [12] and EpCAM [13-15], directly or indirectly promote the occurrence of tumors [16]. Studies have shown that miRNAs, endogenous small molecule containing noncoding RNAs that range from approximately 18 to 30 nt in length, have predominant effects in vivo through inhibition of mRNA degradation or translation. This inhibition results from the complementary or non-fully complementary binding of miRNAs to the 3'UTR of the mRNAs found on target genes [17]. Studies have shown that some miRNAs that play a crucial regulatory role in differentiating CSCs from other tumor cells and that the abnormal expression of these miRNAs is closely related to tumor development. These findings suggest that miRNAs can have roles similar to oncogenes or tumor suppressor genes [18]. Therefore, miRNAs serve as important regulatory factors in CSCs and are of critical importance in studies of CSC characteristics and the treatment of tumors.

The impact of microRNAs in the treatment of hepatocellular carcinoma
miRNAs play important biological roles in HCSCs. HCSC proliferation is regulated by both the bile acid receptor FXR and miRNAs. Studies have shown that GW4064-activated FXR can bind to the miR-122 promoter region at approximately -338 to -325 and promote the expression of miR-122. Following this, miR-122 combines with the target gene IGF-1 and cycling-G1 [19]. In this way, miR-122 inhibits the proliferation of hepatic cancer cells. Moreover, miR-122 enhances glycolysis by negatively regulating the target gene PDK4 and inhibiting the stemness of CD133+ HCSCs, allowing these cells to develop resistance to sorafenib [20]. Bile acid-activated FXR can also bind to the promoter region of miR-22 at -1012 to -1025, facilitating the expression of miR-22, which regulates cyclin A2 to inhibit the proliferation of hepatic cancer cells [21]. miR-125b inhibits liver tumorigenesis by regulating the expression of LIN28B, thereby exerting a tumor-suppressive effect [22]. Moreover, miR-125b inhibits both the proliferation and metastasis of HCSCs and reduces the rate of carcinogenesis by regulating the downstream target genes SMAD2 and SMDA4. Additionally, miR-125b inhibits the Epithelial-Mesenchymal Transition (EMT) of hepatic cancer cells and prevents the EMT caused by drug resistance, migration, and recurrence [23]. miR-150 negatively regulates the expression of cyclin D1 and Bcl-2 by mediating the downstream transcription factor c-myc, which induces the apoptosis of CD133+ HCSCs and inhibits the proliferation and stemness of HCSCs [24]. Because the KIT is a carcinogenic proto-oncogene, it promotes the metastasis and spread of cancer cells, resulting in drug resistance. However, miR-152 inhibits the proliferation of CD133+ Hep3B cells by regulating the downstream target gene KIT [25]. miR-491 blocks the activation of NF-kB by regulating GIT-1 and inhibiting extracellular signal-regulated kinase (ERK), thereby reducing the stemness of HCSCs [26]. miR-148b represses the formation of side population (SP) cells by regulating NRPI and also helps regulate the proliferation, drug resistance, metastasis and angiogenesis of HCSCs [27]. In recent years, studies have shown that EMT plays an important role in tumor invasion and metastasis. Hepatocellular carcinoma cells undergo EMT, and this process is closely related to the invasion and metastasis of hepatocellular carcinoma. miR-148a reduces the stemness of CSCs in hepatic tumor cells by inhibiting the TGF-β/SMAD2 signaling pathways, as SMAD2
The function of microRNAs in carcinogenesis of HCSCs

In liver cancer, miRNAs participate in the signaling related to cell survival in addition to regulating many important transcription factors, enhancing cell proliferation, and maintaining the stemness of CSCs. Therefore, some miRNAs are considered to be carcinogenic. miR-1246 decreases the expression of AXIN2 and GSK3β by activating the Wnt/β-catenin signaling pathway, which in turn promotes the self-renewal, migration, and self-renewal capacity of HCSCs [30]. Studies have shown that miR-200a blocks HCSCs from undergoing the EMT and reduces their invasiveness and metastatic potential [31]. miR-612 attenuates the proliferation, invasion, and metastasis of hepatocarcinoma cells and reduces the ability of these cells to undergo EMT by regulating the downstream target gene AKT2. Recent studies have shown that miR-612 decreases the number of tumor spheres and inhibits the cloning ability, suggesting that miR-612 hinders the multi-directional differentiation ability of tumor cells. miR-612 also blocks the activation of Wnt/β-catenin signaling pathway and inhibits the self-renewal of hepatic cancer cells, thereby reducing the pluripotency of hepatic cancer cells. Furthermore, miR-612 alleviates drug resistance while increasing the sensitivity of tumor cells to 5-Fu and cisplatin. These results suggest that miR-612 plays an important role in regulating the multi-directional differentiation and drug resistance of HCSCs [32]. CD133, a surface marker of HCSC, is expressed in 1-5% of liver cancer cases, but it is not expressed in normal tissue [33]. Studies have shown that miR-142-3p regulates this transmembrane glycoprotein CD133 and thus reduces the self-renewal, migration, proliferation, carcinogenesis and drug resistance capacities of HCSCs [34].

References


Conclusion

In conclusion, studies have shown that miRNAs play important role in regulating the development of tumors by participating in the differentiation, migration and self-renewal of HCSCs (Figure 1). Hence, targeted therapy for tumors that inhibits the metastasis, drug resistance, self-renewal, and multidirectional differentiation of HCSCs using antagonists or by anti-miRNA antisense oligonucleotides that are complementary to miRNAs with oncogene properties is promising.


