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Characterization of the Role of MicroRNAs in Hepatic Cancer Stem Cells

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Abstract

Liver cancer is one of the most malignant tumors and is prone to relapse, metastasis and drug resistance. These phenomena can be explained by the existence of cancer stem cells (CSCs). CSCs have a strong ability to proliferate, are highly carcinogenic, exhibit multi-directional differentiation, develop drug resistance, and play critical roles in tumor radiotherapy, chemotherapy and tumor recurrence. miRNAs exert effects on oncogenes and tumor suppressor genes. There are distinctive miRNA expression profiles in different types of tumors, and these profiles are closely related to tumorigenesis, differentiation, metastasis and prognosis. Studies have shown that miRNAs are abnormally expressed in hepatocellular carcinoma and have important regulatory effects on the self-renewal and differentiation of hepatic cancer stem cells (HCSCs) as well as on the initiation of tumorigenesis. Therefore, it is critical to understand the impact of miRNAs in HCSC and the associated molecular mechanisms to develop new methods for the clinical diagnosis and treatment of liver cancer.

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-myb, 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 restrains the formation of side population (SP) cells by regulating NRP1 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

is the target gene of miR-148a [28]. It was also reported that miR-148a inhibits the proliferation, migration and invasion of tumor stem cell-like hepatocellular carcinoma subtypes through a miR-148a-ACVR1/BMP regulatory loop, revealing new prognostic markers and therapeutic targets for hepatocellular carcinoma [29]. Additionally, researchers have shown that miR148a not only inhibits EMT but also reduces the expression of CD90 and CD44 and restrains the migration 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 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].

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 and metastasis of HCSCs [35]. Studies have shown that miR-155 is up-regulated in tumors and down-regulation of miR-155 can inhibit the formation of CSCs. Because TP53IPN1 is a tumor suppressor gene that regulates the cell cycle and induces apoptosis, miR-155, which targets the TP53INP1 gene, boosts the proliferation and self-renewal capacity of HCSCs [36]. FXR plays an important role in liver regeneration and helps prevent the development of liver cancer in addition to inhibiting the proliferation of HCSCs. It has been shown that miR-421 promotes the proliferation and metastasis of hepatoma cells by negatively regulating FXR. These findings suggest that miR-421 plays an important role in regulating FXR and promoting the development of hepatocellular carcinoma [37]. In recent years, studies have shown that tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) has an anti-cancer effect and can induce cancer cells apoptosis without causing damage to normal tissue [38]. PTEN is a tumor suppressor gene, a natural inhibitor of PI3K and a negative regulator of Akt [39]; hence, PTEN inhibits the formation of tumors by blocking activation of the PI3K-Akt signaling pathway. However, knockdown of miR-25 leads to up-regulation of PTEN and activation of the PTEN-PI3K-Akt-Bad signaling pathway, thus enhancing the sensitivity of HCSCs to TRAIL-induced apoptosis [40].

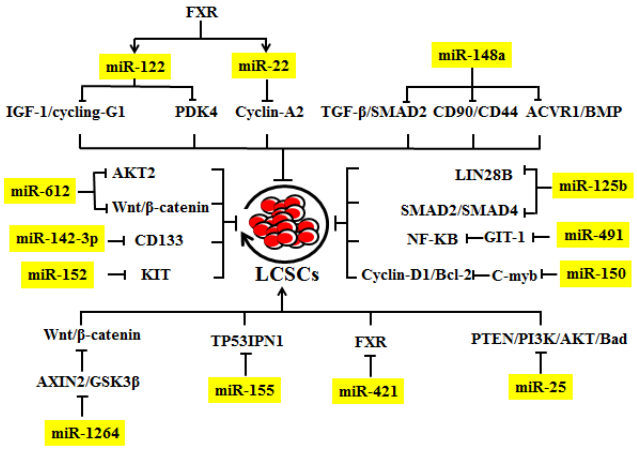

Figure 1: microRNAs play a vital role in the formation, differentiation, migration, and self-renewal of HCSCs; microRNAs can have an inhibitory effect by negatively regulating the expression of target genes that cause liver cancer, or they can promote the occurrence and development of tumors by positively regulating the expression of target genes.

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.

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