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Exosomes derived from mesenchymal stem cells as therapeutic agents for Hepatocellular Carcinoma

Wenjing Liu, Beijing Chen, Shuang Li

Institute of basic medicine, Shanghai University of Medicine & Health Sciences. Shanghai, 201318, China.

Correspondence

Shuang Li, PhD.

Institute of basic medicine, Shanghai University of Medicine & Health Sciences. Shanghai, 201318, China

E-mail:alyssa@bjmu.edu.cn; lis@sumhs.edu.cn

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Mesenchymal stem cells (MSCs), the major stem cells for cell therapy, widely exist in most tissues of the body and are easy to obtain. In addition to multi-directional differentiation potential and self-renewal, MSCs also have the characteristics to migrate the injured site and regulate immune responses. Because tumors are considered as "never healing wounds", MSCs have become an ideal carrier for tumor targeted therapy [1]. Exosomes are small vesicles (30-150nm) containing complex lipid, RNAs and proteins. All types of eukaryotic cells can secrete exosomes, and exosomes naturally exist in body fluids, including blood, saliva, urine, cerebrospinal fluid and milk. Exosomes can protect bioactive molecules from extracellular degradation and deliver them to recipient cells in a highly specific manner to exert cell-to-cell communication effect [2]. Similar to exosomes in general, MSCs derived exosomes carry complex cargo, and are therefore well equipped to exert intercellular signal transduction to cope with external pressure. Compared with MSC, the exosomes derived from MSCs have lower immunogenicity and lower risk of tumor formation which make MSCs-exosomes an ideal delivery system for cancer therapy [3, 4]. Hepatocellular carcinoma (HCC) is the sixth common cancer type in the world. And HCC is the fifth most lethal tumor with the characteristics of high malignancy, fast growth, wide metastasis and high recurrence rate. Many studies have proved the effectiveness and safety of MSCs derived exosomes in the treatment of HCC.

The use of targeted drugs greatly improves the survival of patients, like sorafenib, doxorubicin, etc. But due to the drug resistance, the therapeutic effect is not ideal and the response rate is not high. The expression level of some genes in hepatocellular carcinoma cells will change during chemotherapy, which will affect the downstream signal pathways or target molecules, and eventually lead to the enhancement of drug resistance [5]. Some studies use exosomes as vectors to transfer antagonistic genes to drug resistance cells to reverse the drug resistance. Exosomes from BM-MSCs were modified to up-regulate the drug-sensitivity to sorafenib, via transporting exosomal siGRP78 to sorafenib resistant HCC cells to down regulate the expression of GRP78 which expression increase sorafenib resistance. Both in vitro and in vivo studies found that after treatment with exosomes contain siGRP78 inhibit the growth and invasion of the cancer cells [6]. Evidence indicates that miR-122 can modulate the sensitivity of HCC cells to doxorubicin and sorafenib. Transfect miR-122 to adipose tissue-derived MSC (AMSCs) can be obtained exosomes with the high level of miR-122, the exosomal miR-122 regulate the expression of miR-122-target genes in HCC cells and increase the sensitivity to chemotherapeutic agents [7]. Transmitted AMSCs with miR-199a lentivirus and obtained exosomes can transfer miR-199a delivery to HCC cells to enhance the chemosensitivity by targeting mTOR and subsequently inhibited the mTOR pathway [8]. The human umbilical cord mesenchymal stem cell (HucMSC) derived exosomes elevated miR-451a can down-regulated the target gene, ADAM10, in HCC cells and consequently suppresses the paclitaxel resistance and HCC proliferation [9]. Exosomes as vectors can wrap these easily degradation RNAs or functional molecules and can effectively deliver these cargos to increase the sensitivity to cancer drugs and reverse the drug resistance of HCC.

In the tumor microenvironment, cancer cells, cytokines, immune cells, non tumor cells and extracellular matrix constitute a dynamic system. The imbalance of the microenvironment produces growth factors, cytokines and chemokines to participate in immunosuppression, so as to promote the progress of HCC. Cancer-associated fibroblasts-mediated HCC tumor progression is partially related to the loss of antitumor miR-320a in the exosomes, both in vitro and in vivo studies revealed that miR-320a as an antitumor miRNA by regulating its direct downstream target [10]. HCC patient serum exosomes contained significantly less HMGN1 which loaded into human dendritic cells (DCs) can augment human DC immunogenicity [11]. In mice tumorigenesis

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experiments, treatment with exosomes contain FAM138B, the exosomal FAM138B as miR-765 sponge to reduce the expression of miR-765 and in consequence decreased the tumor volume, and inhibited the ratio of tumor weight to body weight [12]. These data provide potential treatment options to overcome progression. And MSC derived exosomes can be easily modified as carriers to transfer these functional factors.

Exosomes are ideal functional carriers, which are widely distributed in body fluids. Exosomes have the advantages of escaping the host immune system, easy access to recipient cells, protect contents from degradation and so on. In addition, exosomes carry a large number of bioactive substances, have the ability to regulate signal pathways, and have more advantages in drug loading. At present, exosomes are involved in HCC progression and reversing drug resistance by carrying specific molecules such as anticancer genes and inflammatory regulators. The pathogenesis of hepatocellular carcinoma is not completely clear. There are great differences in the treatment strategies for HCC, and should be individualized. Therefore, researchers must establish a biomarker-panel and determine a personalized treatment by analyzing the biomarkers of each patient. The exosomes derived from mesenchymal stem cells are more abundant and easy to be artificially modified. Therefore, the exosomes derived from mesenchymal stem cells have attracted more and more attention in the treatment of liver cancer.

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