REVIEW

Research progress on the effect of human umbilical cord mesenchymal stem cells (hUC-MSCs) on lung cancer

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ABSTRACT

Lung cancer is one of the most common malignancies with the highest morbidity and mortality in the world, and the existing treatment methods often face challenges such as toxic side effects and drug resistance. Human umbilical cord mesenchymal stem cells (hUC-MSCs) have become a promising new strategy in cancer treatment due to their unique biological characteristics (e.g., self-renewal, multi-differentiation and immune regulation). This paper reviews the mechanism of hUC-MSCs in regulating the proliferation, apoptosis, invasion and metastasis of lung cancer cells and tumor microenvironment, and discusses the dual effect of HUC-MSCs in promoting or inhibiting cancer. In addition, this paper also discusses the engineering transformation strategy of hUC-MSCs as gene and drug carriers, which provides a new research idea and theoretical basis for the development of hUC-MSC-based targeted therapy for lung cancer.

Key Words: Human umbilical cord mesenchymal stem cells (hUC-MSCs), Lung cancer treatment, Tumor microenvironment, Exosome, Genetic engineering technology

1. INTRODUCTION

Lung cancer is one of the most common malignancies in the world, with high morbidity and mortality.[1] Non-small cell lung cancer (NSCLC) is more common, accounting for 85&-90% of all lung malignancies.[2] Over the past few decades, some strategies such as surgery, radiotherapy, chemotherapy, immunotherapy and molecularly targeted therapy have been used to treat lung cancer. Although lung cancer is sensitive to chemotherapy, most of clinically diagnosed lung cancer have progressed to an advanced stage, resulting in poor prognosis and great challenges for clinical treatment.[3,4] Therefore, it is crucial to develop novel cancer treatment strategies to effectively inhibit the progression of tumor cells. With the continuous development of stem cell technology, mesenchymal stem cells have attracted extensive attention due to their unique biological characteristics. At present, mesenchymal stem cells have been applied to the fields of hematological diseases, connective tissue diseases and cardiovascular and cerebrovascular diseases, and have achieved remarkable curative effects. In addition, it has also shown potential therapeutic value in nerve injury repair and myocardial infarction treatment.[5] Therefore, it is of great significance to conduct in-depth research on stem cell therapy and promote its clinical application.

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Human umbilical cord mesenchymal stem cells (hUC-MSC), as an important source of stem cells in clinical research, have many characteristics such as self-renewal, multi-differentiation potential, immune regulation and anti-inflammatory effects, so they have attracted much attention in clinical treatment and become a type of key seed cells. Compared with bone marrow and adipose-derived mesenchymal stem cells, hUC-MSCs have a higher expansion efficiency in vitro, and are easier to be extracted, with low immunogenicity and no ethical controversy, so they have a broader application prospect.[6]

Based on numerous characteristics and advantages of hUC-MSCs, they are expected to become a new strategy for the treatment of lung cancer. However, the specific mechanism of hUC-MSCs in the occurrence and development of lung cancer remains to be clarified.[7] Therefore, this article explores the impact of hUC-MSCs on the occurrence and development of lung cancer and its potential mechanism, which provides a new theoretical basis for the development of hUC-MSC-based targeted therapy strategies for lung cancer.

2. Regulatory mechanism of hUC-MSCs on lung cancer cells

2.1 Dual regulatory effects of hUC-MSCs on lung cancer cell proliferation and apoptosis

Recent studies have found that hUC-MSCs can act on lung cancer cells by directly fusing with lung cancer cells or secreting a large number of cytokines. The researchers confirmed that hUC-MSCs have a dual role in inhibiting proliferation and promoting apoptosis on lung cancer cells through CCK-8 method, flow cytometry, tumor volume measurement, and tumor tissue section analysis. For instance, some studies have shown that when hUC-MSCs are co-cultured with A549 cells, the proliferation rate of A549 cells is significantly reduced, with the apoptosis rate significantly increased, and the cell cycle is significantly blocked in the G1 phase. Further studies have found that the transcriptional levels of CyclinD1 and Bcl-2 of PI3K/AKT signaling pathway molecules are downregulated, while the transcriptional levels of BAX are upregulated. These results show that hUC-MSCs inhibit the proliferation of A549 cells and promote their apoptosis by inhibiting the PI3K/AKT signaling pathway.[8] By co-culturing hUC-MSCs with A549 cells, it was found that hUC-MSCs were able to fuse with lung cancer cells, resulting in A549 cell cycle arrest at G0/G1 phase. By co-culturing hUC-MSCs with A549 cells, Yuan Y et al. have found that hUC-MSCs are able to fuse with lung cancer cells, resulting in A549 cell cycle arrest at G0/G1 phase. The study further shows that hUC-MSCs can induce the apoptosis of A549 cells by downregulating the expression of Bcl-2, Caspase-7, β-catenin and C-myc, while upregulating EphA5.[9] In addition, miRNAs contained in hUC-MSC-derived exosomes (Exos) also affect the occurrence and development of lung cancer cells by acting on target genes in lung cancer cells. Dong L et al. established an in-vivo experiment of a xenograft model, first pretreating lung adenocarcinoma (LUAD) cells with CM-Dil-labeled hUC-MSC-Exos in vitro, and then injecting LUAD cells subcutaneously into nude mice, measuring tumor size and observing tumor tissue sections, the results showed that hUC-MSC-Exos promoted tumor growth by directly affecting LUAD cells. They also co-cultured hUC-MSC-Exos with H1299 cells, and the results showed that hUC-MSC-Exos promoted the proliferation of H1299 cells and inhibited apoptosis. Then, the miR-410 genea in hUC-MSC-Exos were knocked out, indicating that the decrease in miR-410 expression could increase the expression of its target gene PTEN, which inhibited the growth of LUAD cells.[10] Guo Q et al. also confirmed in vivo and in vitro experiments that miR-130b-3p in hUMSC-Exos activates the NFE2L2/TXNRD1 pathway by downregulating FOXO3, thereby promoting lung cancer cell proliferation and inhibiting apoptosis.[11]

2.2 Complex network regulation of hUC-MSCs on the invasion and metastasis of lung cancer cells

In recent years, researchers have also found that hUC-MSCs secrete a large number of cytokines and act on lung cancer cells. Through transwell, immunohistochemical staining, and cell migration-related protein expression detection, hUC-MSCs can inhibit or promote the invasion and metastasis of lung cancer cells. For instance, Li Chai et al. co-cultured hUC-MSCs with H1299 cells, and the results showed that hUC-MSCs can inhibit the invasion ability of lung cancer cell H1299 through the PI3K/AKT/STAT3 signaling pathway and induce cell apoptosis. However, hUC-MSCs did not show significant effects on the proliferation and cell cycle progression of H1299 cells.[12] In addition, in-vitro experiments have found that hUC-MSC-exo containing miR-320a can inhibit the proliferation, invasion and migration of H1299 and H460 cells and accelerate their apoptosis by regulating the miR-320a/SOX4/Wnt/β-catenin signaling pathway.[13] Zhao X et al. have found that hUC-MSC-exo-treated A549 cell co-culture plays a dual role, hUC-MSCs can promote A549 cell epithelial-mesenchymal transition (EMT), invasion and migration by activating Smad2/3, Akt/GSK-3β, MAPK and NF-κb in the TGF-β1 signaling pathway, but inhibit lung cancer cell proliferation and promote apoptosis, and its specific molecular mechanism still needs further study.[14] In addition, after hUC-MSCs and A549 cells were injected into nude mice under the armpit, the growth rate of subcutaneous xenografts in nude mice was significantly accelerated, and

hUC-MSCs were malignantly differentiated by HE staining, and immunohistochemical staining showed that liver metastases of lung cancer occurred in nude mice, with β-catenin and E-cadherin up-regulated. The results of this study show that HUC-MSCs can promote the growth and metastasis of lung cancer xenografts, but the specific mechanism has not been fully clarified.[15]

2.3 Regulatory role of hUC-MSCs in tumor microenvironment

The tumor microenvironment is a complex network system composed of many components, including tumor cells, immune cells, stromal cells, vascular system, extracellular matrix and signaling molecules. These components interact to jointly regulate tumor progression.[16] hUC-MSCs affect the progression of lung cancer by regulating the tumor microenvironment. For instance, IL-24 secreted by hUC-MSCs can directly inhibit the formation of endothelial cell tubes or inhibit the expression of growth factor VEGF, affect the angiogenesis of lung cancer cells, thereby inhibiting tumor growth, metastasis and immune escape.[17] It was also found that in the hypoxic environment, the expression level of hypoxia-inducing factor (HIF-1α) was increased in the hUC-MSC-treated A549 cells, which activated the JAKSTAT3 pathway, thereby promoting the proliferation and migration of A549 cells and inhibiting apoptosis, which aggravated the negative effects of hypoxia.[18]

3. Engineered transformation and targeted delivery strategies

Recent studies have shown that by means of engineered transformation of hUC-MSCs, they can be developed as delivery carriers of gene cytokines or chemokines to achieve targeted tumor therapy, which has become a new and efficient treatment strategy. For instance, Chen Shijun et al. used lentiviral transfection to transfect IFN-β genes into hUC-MSCs. hUC-MSCs can secrete biologically active IFN-β in vitro, significantly inhibiting the proliferation, migration and cloning ability of A549 and H226 cells.[19] Further studies showed that after interferon-β (IFN-β) genes were introduced into hUC-MSCs through lentiviral vectors and IFN-β-MSCs were injected into A549 lung cancer tumor-bearing mice through the tail vein, the IFN-β gene-modified hUC-MSCs could migrate to A549 lung cancer cells in a targeted manner, significantly inhibiting the growth of tumor cells and inducing their apoptosis, avoiding the damage to internal organs caused by interferon-β alone.[20] In addition, a trimer TRAIL (ISZ-STRail) can be formed by introducing an isoleucine zipper (ISZ) at the N-terminal of the soluble TRAIL (sTRAIL). ISZ-sTRAIL is specifically delivered to the tumor site by using hUC-MSCs, which can significantly enhance its anti-tumor activity. This targeted therapy system showed excellent apoptosis-induced and anti-tumor effects in mouse xenograft models, and no significant side effects were observed.[21] hUC-MSCs with overexpression of miR-198 can significantly inhibit the expression of c-MET genes and reduce the activity of MAPK in the downstream of HFC-MET signaling pathway, thus effectively inhibiting the migration and invasion of NSCLC. In addition, this treatment reduces vascular permeability and inhibits the occurrence of malignant pleural effusion (MPE) in mouse tumor models.[22]

hUC-MSCs are used as drug carriers in tumor treatment, and also show a potential therapeutic prospect. Studies have shown that the combination of hUC-MSCs and paclitaxel (PTX) can significantly inhibit the proliferation and invasion of A2780 cancer stem cells in ovarian cancer and promote their apoptosis in the in-vitro experiments.[23] However, at present, the research on the anti-tumor effect of hUC-MSCs combined with drugs on lung cancer is still relatively limited, and there is a lack of in-vitro and in-vivo experiments for systematic verification. Further research is needed in the future to explore its potential application in the treatment of lung cancer. In addition, the long-term safety of engineered cells, the efficiency of drug delivery and large-scale preparation are still major challenges for clinical conversion.

4. Conclusion

In conclusion, hUC-MSCs can promote and inhibit the proliferation, apoptosis, invasion and metastasis of lung cancer cells. The mechanism mainly relies on hUC-MSCs and their exosomes to deliver a variety of bioactive substances to the target cells, including proteins, cytokines, mRNA and miRNA, so as to play a regulatory role. However, the specific mechanism is more complex, and the dual effect of hUC-MSCs and their exosomes on tumors may be regulated by various factors, such as cell source, culture conditions and cross-talk between hUC-MSCs and tumor cells.[24] Therefore, it is necessary to further study the mechanism of hUC-MSCs in the occurrence and development of lung cancer, and clarify the regulatory functions and effects of related signaling pathways, so as to provide a theoretical basis for exploring new strategies for lung cancer treatment.

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Authors contributions

Yan Zhang contributed to the literature research, organization and manuscript drafting; Xingyang Pang contributed to the literature collection and manuscript drafting; Yonggang Li contributed to the manuscript revision; Yanwei Guo con-

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