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Nanoparticle encapsulated CQ/TAM combination harmonizes with MSCs in arresting progression of severity in AP mice through iNOS (IDO) signaling

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Abstract

Background: Sever acute pancreatitis (SAP) is a critical disease with high mortality, and lack of clinically available treatments with specificity and effectiveness. Bone marrow derived mesenchymal stem cells (BMSCs) exhibited moderate effect on AP which needs further improvement.

Methods: Pancreatic infiltrating lymphocytes were analyzed to demonstrate the intervention of BMSCs on inflammatory cell infiltration of AP. Gene silencing with siRNA and small molecule inhibitor were utilized to determine the key effector molecule of BMSCs on AP. Pharmacological regulation and nanotechnology were introduced to further ameliorate BMSCs action.

Results: It was revealed that BMSCs prevent the progression of acute pancreatitis (AP) by reducing recruitment of macrophages, neutrophils and CD4+T cells in the lesion site. The pivotal role of chemokine-iNOS-IDO axis for BMSCs to intervene AP was confirmed. Compared with any single drug, Chloroquine/Tamoxifen combination together with IFN-γ pronouncedly up-regulated the transcription of several MSC immune regulators such as COX-2, PD-L1, HO-1 especially iNOS/IDO. As expected, BMSCs and human umbilical cord mesenchymal stem cells (UMSCs) pretreated with CQ/TAM/IFN-γ exerted enhanced intervention in AP and SAP mice. Moreover, pretreatment with CQ-LPs/TAM-NPs combination not only counteracted MSCs proliferation inhibition induced by free drugs but also enhanced their efficacy.

Conclusion: Under the background of rapid progress in MSCs clinical translation, this study focuses on the urgent clinical issue and initiates an original mechanism-based strategy to promote intervention on severity progression of SAP, which promises its clinical translation in future.

Lab Invest

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Bone mesenchymal stem cell-derived extracellular vesicles containing NORAD promote osteosarcoma by miR-30c-5p

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Abstract

Osteosarcoma is a bone tumor that often affects children, adolescents and young people. Non-coding RNA activated by DNA damage (NORAD) can promote the proliferation of cancer cells in multiple tumors. Thus, the current study set out to explore the role of NORAD derived from extracellular vesicles (EVs) of bone mesenchymal stem cells (BMSCs) in osteosarcoma. First, NORAD was highly expressed in osteosarcoma cells and tissues, which might be associated with the progression and metastasis of osteosarcoma. We

isolated EVs from the characterized BMSCs, and found that NORAD was transferred from BMSCs to osteosarcoma cells via EVs in the co-culture system. Consequently, NORAD delivered by BMSC-derived EVs promoted the proliferation and invasion of osteosarcoma cells. Subsequently, bioinformatics analyses suggested potential binding relationship between NORAD and microRNA-30c-5p (miR-30c-5p) as well as between miR-30c-5p and Krueppel-like factor 10 (KLF10), and the results of which were further verified by dual luciferase reporter gene assay, RNA immunoprecipitation, and RNA pull-down assay. Mechanistically, NORAD acted as a sponge of miR-30c-5p and up-regulated the expression of KLF10 where miR-30-c-5p mimic declined the effect induced by NORAD on cancer cells. The osteosarcoma cells were injected into mice to develop tumor growth and metastasis models. In these two models, injection of BMSC-EVs elevated NORAD expression and KLF10 but reduced miR-30c-5p expression, whereby suppressing tumor growth and lung metastasis. To conclude, BMSC-EVs deliver NORAD to osteosarcoma cells to regulate the miR-30c-5p/KLF10 axis, thereby accelerating the progression and metastasis of osteosarcoma.

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Lack of tumorigenesis and protumorigenic activity of human umbilical cord mesenchymal stem cells in NOD SCID mice

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Abstract

Background: The tumorigenesis of infused umbilical cord mesenchymal stem cells (UC-MSCs) is being preclinically evaluated.

Methods: We observed tumor formation in NOD SCID mice after a single subcutaneous injection of hUC-MSCs and the effect of these cells on tumor growth in tumor-bearing mice. Three generations (P5, P7, and P10) of hUC-MSCs (1×10^7) from two donors (hUC-MSC1 and hUC-MSC2) were inoculated subcutaneously into NOD SCID mice. Subcutaneous transplantation models were established in NOD SCID mice with human cervical cancer HeLa cells (solid tumor) and human B cell lymphoma Raji cells (hematological tumor). Then, the animals were euthanized, gross dissection was performed, and tissues were collected. Various organs were observed microscopically to identify pathological changes and tumor metastasis.

Results: In the tumorigenesis experiment, no general anatomical abnormalities were observed. In the tumor promotion experiment, some animals in the HeLa groups experienced tumor rupture, and one animal died in each of the low- and medium-dose hUC-MSC groups. The results may have occurred due to the longer feeding time, and the tumor may have caused spontaneous infection and death. Pathological examination revealed no metastasis to distant organs in any group. In the Raji tumor model, some animals in each group experienced tumor rupture, and one animal in the medium-dose hUC-MSC group died, perhaps due to increased tumor malignancy. Thus, hUC-MSCs neither promoted nor inhibited tumor growth. No cancer cell metastasis was observed in the heart, liver, spleen, lungs, kidneys or other important organs, except that pulmonary venule metastasis was observed in 1 animal in the model group.

Conclusions: Injected hUC-MSCs were not tumorigenic and did not significantly promote or inhibit solid or hematological tumor growth or metastasis in NOD SCID mice.

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A Subset of Osteosarcoma Bears Markers of CXCL12-Abundant Reticular Cells

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Abstract

Currently, the cell of origin for osteosarcoma or other primary skeletal tumors is largely unknown. Recent reports identifying specific cell types comprising bone now newly enable investigation of this topic. Specifically, CXC motif chemokine 12 (CXCL12)-abundant reticular (CAR) cells are a specific skeletal stromal cell type that orchestrate the bone marrow microenvironment through cross-talk with hematopoietic and endothelial cells and a likely candidate cell of origin for at least a subset of primary skeletal tumors. Here, we analyze osteosarcomas via immunohistochemistry for known markers of CAR cells such as leptin receptor (LEPR), B-cell factor 3 (EBF3), CXCL12, and platelet-derived growth factor receptor alpha (PDGFRA). A large proportion of high-grade tumors expressed LEPR, PDGFRA, and EBF3 but not CXCL12. These data raise the hypothesis that CAR cells are the cell of origin of this osteoblastic osteosarcoma subset, a finding with implications for the cellular oncogenesis of primary osteosarcoma and the development of effective targeted therapies