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Extracellular vesicles from bone mesenchymal stem cells transport microRNA-206 into osteosarcoma cells and target NRSN2 to block the ERK1/2-Bcl-xL signaling pathway

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Abstract

Osteosarcoma (OS) is a kind of malignant tumor originating from mesenchymal tissue Bone mesenchymal stem cells-derived extracellular vesicles (BMSCs-EVs) can play important roles in OS. This study investigated the mechanism of BMSCs-EVs on OS. BMSC surface antigens and adipogenic and osteogenic differentiation were detected by flow cytometry, and oil red O and alizarin red staining. EVs were isolated from BMSCs by differential centrifugation and identified by transmission electron microscopy, nanoparticle tracking analysis, and Western blot (WB). miR-206 and neurensin-2 (NRSN2) levels in human osteoblast hFOB 1.19 or OS cells (143B, MG-63, Saos2, HOS) were detected by RT-qPCR. Human OS cells with lower miR-206 levels were selected and treated with BMSCs-EVs or pSUPER-NRSN2. The uptake of EVs by 143B cells, cell proliferation, apoptosis, invasion, and migration were detected by immunofluorescence, 5-ethynyl-2'-deoxyuridine (EdU) and colony formation assays, flow cytometry, scratch test, and transwell assays. The binding sites between miR-206 and NRSN2 were predicted by Starbase database and verified by dual-luciferase assay. The OS xenograft model was established and treated by BMSCs-EVs. Tumor growth rate and volume, cell proliferation, and p-ERK1/2, ERK1/2, and

Bcl-xL levels were detected by vernier caliper, immunohistochemistry, and WB. BMSCs-EVs were successfully extracted. miR-206 was diminished and NRSN2 was promoted in OS cells. BMSCs-EVs inhibited proliferation, migration, and invasion, and promoted apoptosis of OS cells. BMSCs-EVs carried miR-206 into OS cells. Inhibition of miR-206 in EVs partially reversed the inhibitory effect of EVs on malignant behaviors of OS cells. miR-206 targeted NRSN2. Overexpression of NRSN2 reversed the inhibitory effect of EVs on OS cells. NRSN2 activated the ERK1/2-Bcl-xL pathway. BMSC-EVs inhibited OS growth in vivo. In summary, BMSC-EVs targeted NRSN2 and inhibited the ERK1/2-Bcl-xL pathway by carrying miR-206 into OS cells, thus inhibiting OS progression.

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Tumor-Homing of Mesenchymal Stem Cells Infected with Oncolytic Virus in a Canine Patient

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Abstract

Intravenous administration of oncolytic adenovirus (OAds) can be challenging, although various vehicles for the delivery of the virus to the tumor have been described. The efficacy of mesenchymal stem cells (MSCs) as a virus vehicle has been reported in mouse models and canine and human patients, but the actual action mechanism has never been described in patients. It is of importance to determine whether MSCs infected with OAds can reach the tumor and release the virus in a clinical setting. For this purpose, GFP-labeled

MSCs were infected with an OAd and inoculated into a companion dog diagnosed with spontaneous lung carcinoma. Forty-eight hours later, the tumor was excised and analyzed microscopically by flow cytometry for GFP fluorescence detection, and a cellular culture was established. Peripheral blood samples were taken to quantify the oncolytic adenovirus by qRT-PCR. Green fluorescence cells detected in the cellular culture by microscopy and flow cytometry revealed 0.69% GFP-positive cells in the tumor. OAd in peripheral blood was confirmed by qRT-PCR during follow-up. For the first time, the tumoral-homing capacity of OAds infected-MSC has been confirmed in a clinical setting, helping to explain the clinical response mechanism, whose efficacy was previously reported in canine and human patients.