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Mesenchymal stromal cells from Shwachman-Diamond syndrome patients fail to recreate a bone marrow niche in vivo and exhibit impaired angiogenesis.

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Abstract

Shwachman-Diamond syndrome (SDS) is a rare multi-organ recessive disease mainly characterised by pancreatic insufficiency, skeletal defects, short stature and bone marrow failure (BMF). As in many other BMF syndromes, SDS patients are predisposed to develop a number of haematopoietic malignancies, particularly myelodysplastic syndrome and acute myeloid leukaemia. However, the mechanism of cancer predisposition in SDS patients is only partially understood. In light of the emerging role of mesenchymal stromal cells (MSCs) in the regulation of bone marrow homeostasis, we assessed the ability of MSCs derived from SDS patients (SDS-MSCs) to recreate a functional bone marrow niche, taking advantage of a murine heterotopic MSC transplant model. We show that the ability of semi-cartilaginous pellets (SCPs) derived from SDS-MSCs to generate complete heterotopic ossicles in vivo is severely impaired in comparison with HD-MSC-derived SCPs. Specifically, after in vitro angiogenic stimuli, SDS-MSCs showed a defective ability to form correct networks, capillary tubes and vessels and displayed a marked decrease in VEGFA expression. Altogether, these findings unveil a novel mechanism of SDS-mediated haematopoietic dysfunction based on hampered ability of SDS-MSCs to support angiogenesis. Overall, MSCs could represent a new appealing therapeutic target to treat dysfunctional haematopoiesis in paediatric SDS patients.

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Umbilical cord-derived mesenchymal stem cells can inhibit the biological functions of melanoma A375 cells.

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Author information

Abstract

Tumor tropism is an important property of mesenchymal stem cells (MSCs) that has been used in tumor-targeting therapies. However, the effects of MSCs on tumors remain controversial. The aim of the present study was to investigate the effects of MSCs on A375 melanoma cells. Umbilical cord-derived mesenchymal stem cells (UCMSCs) were co-cultured with A375 cells. MTT and Transwell assays were used to assess cell proliferation and invasion, while flow cytometry was performed to detect the apoptosis and the cell cycle distribution of A375 cells. The expression levels of kinases were

assayed by western blotting and fluorescence analysis was conducted to detect cytoskeletal rearrangement. The results clearly indicated that UCMSCs could inhibit the proliferation, induce apoptosis and suppress the invasion of A375 cells. Mechanistic studies revealed decreased expression of several kinases (AKT, STAT3 and mTOR) and UCMSCs were also found to promote cytoskeletal rearrangement in A375 cells. These results confirmed that UCMSCs exert antitumor effects on melanoma A375 cells.

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Point-of-care treatment of focal cartilage defects with selected chondrogenic mesenchymal stromal cells - an in vitro proof-of-concept study.

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Abstract

Due to the poor self-healing capacities of cartilage, innovative approaches are a major clinical need. The use of in vitro expanded MSCs in a two-stage approach is accompanied by cost, time and personnel-intensive GMP production. A one-stage intra-operative procedure could overcome these drawbacks. The aim was to prove the feasibility of a point-of-care concept for the treatment of cartilage lesions using defined MSC subpopulations in a collagen hydrogel without prior MSC monolayer expansion. We tested four single marker candidates (MSCA-1, W4A5, CD146, CD271) for their effectiveness of separating colony-forming units of ovine MSCs via magnetic cell separation. The most promising surface marker with regard to the highest enrichment of colony-forming cells was subsequently used to isolate a MSC subpopulation for the direct generation of a cartilage graft composed of a collagen type I hydrogel without the propagation of MSCs in monolayer. We observed that separation with CD271 sustained the highest enrichment of colony-forming units. We then demonstrated the feasibility of generating a cartilage graft with an unsorted bone marrow mononuclear cell fraction and with a characterized CD271 positive MSC subpopulation without the need for a prior cell expansion. A reduced volume of 6.25% of the CD271 positive MSCs was needed to achieve the same results regarding chondrogenesis compared to the unseparated bone marrow mononuclear cell fraction, drastically reducing the number of non-relevant cells. This study provides a proof-of-concept and reflects the potential of an intra-operative procedure for direct seeding of cartilage grafts with selected CD271 positive cells from bone marrow.

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Adipose-derived mesenchymal stem cells release microvesicles with procoagulant activity.

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Abstract

Extracellular vesicles are produced by a number of different cell types, among them mesenchymal stromal/stem cells (MSC) of different sources. It has been shown that extracellular vesicles of MSC exert similar therapeutic effects as the cells themselves. Here, we isolated and characterized extracellular vesicles produced by adipose-derived MSC (adMSC) in vitro upon stimulation with the proinflammatory substances lipopolysaccharide (LPS) and tumor necrosis factor (TNF). We found that the number of vesicles produced by adMSC does not change upon stimulation of the cells with LPS and TNF. Furthermore, adMSC-derived extracellular vesicles exert procoagulant activity independent of previous stimulation with LPS or TNF. We found evidence that the vesicles induce coagulation via both the intrinsic and the extrinsic pathway of coagulation.