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Microvesicles derived from human bone marrow mesenchymal stem cells promote U2OS cell growth under hypoxia: the role of PI3K/AKT and HIF-1α.

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Author information

Abstract

Studies have demonstrated that mesenchymal stem cells (MSCs) can promote tumor growth, and MSC microvesicles (MVs) are very important in the tumor microenvironment and information transfer between cells during tumorigenesis and development. However, the potential effects and mechanisms of MSC-MVs on tumor growth are still controversial. Here in this study, we investigated the roles and effects of human bone marrow MSC-MVs (hBMSC-MVs) on human osteosarcoma (U2OS) cell growth under hypoxia in vitro and in vivo. BMSC-MVs were harvested and purified by ultracentrifugation. U2OS cells were treated with different concentrations of hBMSC-MVs under hypoxia. Cell viability and migration was measured by MTT test, transwell invasion assay and scratch migration assay. The expression of the signaling molecules of AKT, VEGF, GLUT1 and Bax, cleaved-caspase3 in U2OS cells cultured with MVs under hypoxia was determined by western blot. U2OS/siHIF-1α or U2OS/NC cells mixed with/without MVs were subcutaneously injected into nude mice; the tumor size and weight were detected. We found that hBMSC-MVs promoted U2OS cell proliferation and migration under hypoxia in vitro, and that was partially associated with the PI3K/AKT and HIF-1α pathways. MVs co-injected with U2OS cells promoted tumor growth in a mouse xenograft model. siHIF-1α transfection reversed these changes to some extent. The function of hBMSC-MVs on U2OS cell progression and tumor growth was associated with PI3K/AKT and HIF-1α pathway under hypoxia. These findings support a new mechanism suggesting the contribution of MSC-MVs to tumor growth.

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PDGF enhances the protective effect of adipose stem cell-derived extracellular vesicles in a model of acute hindlimb ischemia.

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Abstract

We previously have shown that platelet-derived growth factor (PDGF) modulates the biological activity of extracellular vesicles released by adipose-derived mesenchymal stem cells (ASC-EVs). ASC-EVs may interact with blood and vessel cells by transferring proteins and nucleic acids and regulate their functions. In this study, we investigated immunomodulatory activity and protection from acute hindlimb ischemia of EVs released by PDGF-stimulated ASC (PDGF-EVs). PDGF treatment of ASC changed

protein and RNA composition of released EVs by enhancing the expression of anti-inflammatory and immunomodulatory factors. In vitro, control EVs (cEVs) derived from non-stimulated ASC increased the secretion of both the IL-1b, IL-17, IFNγ, TNFα pro-inflammatory factors and the IL-10 anti-inflammatory factor, and enhanced the in vitro peripheral blood mononuclear cell (PBMC) adhesion on endothelium. In contrast, PDGF-EVs enhanced IL-10 secretion and induced TGF-β1 secretion by PBMC. Moreover, PDGF-EVs stimulated the formation of T regulatory cells. In vivo, PDGF-EVs protected muscle tissue from acute ischemia, reduced infiltration of inflammatory cells and increased T regulatory cell infiltration in respect to cEVs. Our results suggest that PDGF-EVs are enriched in anti-inflammatory and immunomodulatory factors and induced in PBMC an enhanced production of IL-10 and TGF-β1 resulting in protection of muscle from acute ischemia in vivo

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Human bone marrow contains high levels of extracellular vesicles with a tissue-specific subtype distribution.

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Abstract

INTRODUCTION:

Extracellular vesicles (EV) are shed from a broad variety of cells and play an important role in activation of coagulation, cell to cell interaction and transport of membrane components. They are usually measured as circulating EV in peripheral blood (PB) and other body fluids. However, little is known about the distribution, presence and impact of EV and their subpopulations in bone marrow (BM). In our study, we focused on the analysis of different EV subtypes in human BM as compared to EV subsets in PB.

METHODS:

EV in BM and PB from 12 healthy stem cell donors were measured by flow-cytometry using Annexin V and cell-specific antibodies for hematopoietic stem cells, leucocytes, platelets, red blood cells, and endothelial cells. Additionally, concentrations of tissue factor-bearing EV were evaluated.

RESULTS:

High numbers of total EV were present in BM (median value [25-75 percentile]: 14.8 x109/l [8.5-19.3]). Non-significantly lower numbers of total EV were measured in PB (9.2 x109/l [3.8-14.5]). However, distribuation of EV subtypes showed substantial differences between BM and PB: In PB, distribution of EV fractions was similar as previously described. Most EV originated from platelets (93.9%), and only few EV were derived from leucocytes (4.5%), erythrocytes (1.8%), endothelial cells (1.0%), and hematopoietic stem cells (0.7%). In contrast, major fractions of BM-EV were derived from red blood cells or erythropoietic cells (43.2%), followed by megacaryocytes / platelets (27.6%), and by leucocytes as well as their progenitor cells (25,7%); only low EV proportions originated from endothelial cells and

hematopoietic stem cells (2.0% and 1.5%, respectively). Similar fractions of tissue factor-bearing EV were found in BM and PB (1.3% and 0.9%).

CONCULSION:

Taken together, we describe EV numbers and their subtype distribution in the BM compartment for the first time. The tissue specific EV distribution reflects BM cell composition and favours the idea of a BM-PB barrier existing not only for cells, but also for EV.

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Bone marrow-derived mesenchymal stromal cell: what next?

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Abstract

Bone marrow mesenchymal stromal cell (MSC) is a potential alternative in regenerative medicine and has great potential in many pathologic conditions including kidney disease. Although most of the studies demonstrate MSC efficiency, the regenerative potential may not be efficient in all diseases and patients. Stem cell feasibility is modified by donor characteristics as gender, age, diet, and health status, producing both positive and negative results. The conditioning of MSC can potentiate its effects and modify its culture medium (CM). In current practices, the cell-free treatment is gaining notable attention, while MSC-conditioned CM is being applied and studied in many experimental diseases, including, but not limited to, certain kidney diseases. This may be the next step for clinical trials. Studies in stem cell CM have focused mainly on extracellular vesicles, nucleic acids (mRNA and microRNA), lipids, and proteins presented in this CM. They mediate regenerative effects of MSC in a harmonic manner. In this review, we will analyze the regenerative potential of MSC and its CM as well as discuss some effective techniques for modifying its fractions and improving its therapeutic potential. CM fractions may be modified by hypoxic conditions, inflammation, lipid exposition, and protein growth factors. Other possible mechanisms of action of stem cells are also suggested. In the future, the MSC paracrine effect may be modified to more closely meet each patient's needs.