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Exosomes Derived from Dental Pulp Stem Cells Show Different Angiogenic and Osteogenic Properties in Relation to the Age of the Donor

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Abstract

Craniofacial tissue reconstruction still represents a challenge in regenerative medicine. Mesenchymal stem cell (MSC)-based tissue engineering strategies have been introduced to enhance bone tissue repair. However, the risk of related complications is limiting their usage. To overcome these drawbacks, exosomes (EXOs) derived from MSCs have been recently proposed as a cell-free alternative to MSCs to direct tissue regeneration. It was hypothesized that there is a correlation between the biological properties of exosomes derived from the dental pulp and the age of the donor. The aim of the study was to investigate the effect of EXOs derived from dental pulp stem cells of permanent teeth (old donor group) or exfoliated deciduous teeth (young donor group) on MSCs cultured in vitro. Proliferation potential was evaluated by doubling time, and commitment ability by gene expression and biochemical quantification for tissue-specific factors. Results showed a well-defined proliferative influence for the younger donor aged group. Similarly, a higher

commitment ability was detected in the young group. In conclusion, EXOs could be employed to promote bone regeneration, likely playing an important role in neo-angiogenesis in early healing phases.

Life (Basel)
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Human Amniotic Mesenchymal Stem Cells and Fibroblasts Accelerate Wound Repair of Cystic Fibrosis Epithelium

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Free PMC article

Abstract

Cystic fibrosis (CF) airways are affected by a deranged repair of the damaged epithelium resulting in altered regeneration and differentiation. Previously, we showed that human amniotic mesenchymal stem cells (hAMSCs) corrected base defects of CF airway epithelial cells via connexin (CX)43-intercellular gap junction formation. In this scenario, it is unknown whether hAMSCs, or fibroblasts sharing some common characteristics with MSCs, can operate a faster repair of a damaged airway epithelium. A tip-based scratch assay was employed to study wound repair in monolayers of CFBE14o- cells (CFBE, homozygous for the *F508del* mutation). hAMSCs were either co-cultured with CFBE cells before the wound or added to the wounded monolayers. NIH-3T3 fibroblasts (CX43+) were added to wounded cells. HeLa cells (CX43-) were used as controls. γ-irradiation was optimized to block CFBE cell proliferation. A specific siRNA was employed to downregulate CX43

expression in CFBE cells. CFBE cells showed a delayed repair as compared with wt-CFTR cells (16HBE41o-). hAMSCs enhanced the wound repair rate of wounded CFBE cell monolayers, especially when added post wounding. hAMSCs and NIH-3T3 fibroblasts, but not HeLa cells, increased wound closure of irradiated CFBE monolayers. CX43 downregulation accelerated CFBE wound repair rate without affecting cell proliferation. We conclude that hAMSCs and fibroblasts enhance the repair of a wounded CF airway epithelium, likely through a CX43-mediated mechanism mainly involving cell migration.

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Characterisation of Extracellular Vesicles from Equine Mesenchymal Stem Cells

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Abstract

Extracellular vesicles (EVs) are nanosized lipid bilayer-encapsulated particles secreted by virtually all cell types. EVs play an essential role in cellular crosstalk in health and disease. The cellular origin of EVs determines their composition and potential therapeutic effect. Mesenchymal stem/stromal cell (MSC)-derived EVs have shown a comparable therapeutic potential to their donor cells, making them a promising tool for regenerative medicine. The therapeutic application of EVs circumvents some safety concerns associated with the transplantation of viable, replicating cells and facilitates the quality-controlled production as a ready-to-go, off-the-shelf biological therapy. Recently, the International Society for Extracellular Vesicles (ISEV) suggested a set of minimal biochemical, biophysical and functional standards to define extracellular vesicles and their functions to improve

standardisation in EV research. However, nonstandardised EV isolation methods and the limited availability of cross-reacting markers for most animal species restrict the application of these standards in the veterinary field and, therefore, the species comparability and standardisation of animal experiments. In this study, EVs were isolated from equine bone-marrow-derived MSCs using two different isolation methods, stepwise ultracentrifugation and size exclusion chromatography, and minimal experimental requirements for equine EVs were established and validated. Equine EVs were characterised using a nanotracking analysis, fluorescence-triggered flow cytometry, Western blot and transelectron microscopy. Based on the ISEV standards, minimal criteria for defining equine EVs are suggested as a baseline to allow the comparison of EV preparations obtained by different laboratories.

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Bone Marrow MSC Secretome Increases Equine Articular Chondrocyte Collagen Accumulation and Their Migratory Capacities

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Abstract

Equine osteoarthritis (OA) leads to cartilage degradation with impaired animal well-being, premature cessation of sport activity, and financial losses. Mesenchymal stem cell (MSC)-based therapies are promising for cartilage repair, but face limitations inherent to the cell itself. Soluble mediators and extracellular vesicles (EVs) secreted by MSCs are the

alternatives to overcome those limitations while preserving MSC restorative properties. The effect of equine bone marrow MSC secretome on equine articular chondrocytes (eACs) was analyzed with indirect co-culture and/or MSC-conditioned media (CM). The expression of healthy cartilage/OA and proliferation markers was evaluated in eACs (monolayers or organoids). In vitro repair experiments with MSC-CM were made to evaluate the proliferation and migration of eACs. The presence of nanosized EVs in MSC-CM was appraised with nanoparticle tracking assay and transmission electron microscopy. Our results demonstrated that the MSC secretome influences eAC phenotype by increasing cartilage functionality markers and cell migration in a greater way than MSCs, which could delay OA final outcomes. This study makes acellular therapy an appealing strategy to improve equine OA treatments. However, the MSC secretome contains a wide variety of soluble mediators and small EVs, such as exosomes, and further investigation must be performed to understand the mechanisms occurring behind these promising effects.

Int J Mol Sci

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Extracellular Vesicles Released from Stem Cells as a New Therapeutic Strategy for Primary and Secondary Glomerulonephritis

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Abstract

Current treatment of primary and secondary glomerulopathies is hampered by many limits and a significant proportion of these disorders still evolves towards end-stage renal disease. A possible answer to this unmet challenge could be represented by therapies with

stem cells, which include a variety of progenitor cell types derived from embryonic or adult tissues. Stem cell self-renewal and multi-lineage differentiation ability explain their potential to protect and regenerate injured cells, including kidney tubular cells, podocytes and endothelial cells. In addition, a broad spectrum of anti-inflammatory and immunomodulatory actions appears to interfere with the pathogenic mechanisms of glomerulonephritis. Of note, mesenchymal stromal cells have been particularly investigated as therapy for Lupus Nephritis and Diabetic Nephropathy, whereas initial evidence suggest their beneficial effects in primary glomerulopathies such as IgA nephritis. Extracellular vesicles mediate a complex intercellular communication network, shuttling proteins, nucleic acids and other bioactive molecules from origin to target cells to modulate their functions. Stem cell-derived extracellular vesicles recapitulate beneficial cytoprotective, reparative and immunomodulatory properties of parental cells and are increasingly recognized as a cell-free alternative to stem cell-based therapies for different diseases including glomerulonephritis, also considering the low risk for potential adverse effects such as maldifferentiation and tumorigenesis. We herein summarize the renoprotective potential of therapies with stem cells and extracellular vesicles derived from progenitor cells in glomerulonephritis, with a focus on their different mechanisms of actions. Technological progress and growing knowledge are paving the way for wider clinical application of regenerative medicine to primary and secondary glomerulonephritis: this multi-level, pleiotropic therapy may open new scenarios overcoming the limits and side effects of traditional treatments, although the promising results of experimental models need to be confirmed in the clinical setting.

Front Immunol

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Bone Marrow Niches and Tumour Cells: Lights and Shadows of a Mutual Relationship

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Abstract

The bone marrow (BM) niche is the spatial structure within the intra-trabecular spaces of spongious bones and of the cavity of long bones where adult haematopoietic stem cells (HSCs) maintain their undifferentiated and cellular self-renewal state through the intervention of vascular and nervous networks, metabolic pathways, transcriptional and epigenetic regulators, and humoral signals. Within the niche, HSCs interact with various cell types such as osteoblasts, endothelial cells, macrophages, and mesenchymal stromal cells (MSCs), which maintain HSCs in a quiescent state or sustain their proliferation, differentiation, and trafficking, depending on body needs. In physiological conditions, the BM niche permits the daily production of all the blood and immune cells and their admittance/ingress/progression into the bloodstream. However, disruption of this delicate microenvironment promotes the initiation and progression of malignancies such as those included in the spectrum of myeloid neoplasms, also favouring resistance to pharmacological therapies. Alterations in the MSC population and in the crosstalk with HSCs owing to tumour-derived factors contribute to the formation of a malignant niche. On the other hand, cells of the BM microenvironment cooperate in creating a unique milieu favouring metastasization of distant tumours into the bone. In this framework, the pro-tumorigenic role of MSCs is well-documented, and few evidence suggest also an anti-tumorigenic effect. Here we will review recent advances regarding the BM niche composition and functionality in normal and in malignant conditions, as well as the therapeutic implications of the interplay between its diverse cellular components and malignant cells.

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Heterogeneity of In Vitro Expanded Mesenchymal Stromal Cells and Strategies to Improve Their Therapeutic Actions

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Abstract

Beneficial properties of mesenchymal stromal cells (MSCs) have prompted their use in preclinical and clinical research. Accumulating evidence has been provided for the therapeutic effects of MSCs in several pathologies, including neurodegenerative diseases, myocardial infarction, skin problems, liver disorders and cancer, among others. Although MSCs are found in multiple tissues, the number of MSCs is low, making in vitro expansion a required step before MSC application. However, culture-expanded MSCs exhibit notable differences in terms of cell morphology, physiology and function, which decisively contribute to MSC heterogeneity. The changes induced in MSCs during in vitro expansion may account for the variability in the results obtained in different MSC-based therapy studies, including those using MSCs as living drug delivery systems. This review dissects the different changes that occur in culture-expanded MSCs and how these modifications alter their therapeutic properties after transplantation. Furthermore, we discuss the current strategies developed to improve the beneficial effects of MSCs for successful clinical implementation, as well as potential therapeutic alternatives.