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Is Stem Cell Commerce in Small Animal Therapies Scientifically and Morally Justified?

Pinheiro LL[1], de Lima AR[2], Branco É[2].
Author information

Abstract

The lack of clear regulations for the use of veterinary stem cells has triggered the commercialization of unproven experimental therapies for companion animal diseases. Adult stem cells have complex biological characteristics that are directly related to the therapeutic application, but several questions remain to be answered. In order to regulate the use of these cells, well-conducted, controlled scientific studies that generate high-quality data should be performed, in order to assess the efficacy and safety of the intended treatment. This paper discusses the scientific challenges of mesenchymal stem cell therapy in veterinary regenerative medicine, and reviews published trials of adipose-tissue-derived stem cells in companion animal diseases that spontaneously occur.

Front Immunol. 2019 May 8;10:977. doi: 10.3389/fimmu.2019.00977. eCollection 2019.

Metabolism in Human Mesenchymal Stromal Cells: A Missing Link Between hMSC Biomanufacturing and Therapy?

Yuan X[1], Logan TM[2,3], Ma T[1,2].
Author information

Abstract

Human mesenchymal stem cells (hMSCs) are the most commonly-tested adult stem cells in cell therapy. While the initial focus for hMSC clinical applications was to exploit their multi-potentiality for cell replacement therapies, it is now apparent that hMSCs empower tissue repair primarily by secretion of immuno-regulatory and pro-regenerative factors. A growing trend in hMSC clinical trials is the use of allogenic and culture-expanded cells because they are well-characterized and can be produced in large scale from specific donors to compensate for the donor pathological condition(s). However, donor morbidity and large-scale expansion are known to alter hMSC secretory profile and reduce therapeutic potency, which are significant barriers in hMSC clinical translation. Therefore, understanding the regulatory mechanisms underpinning hMSC phenotypic and functional property is crucial for developing novel engineering protocols that maximize yield while preserving therapeutic potency. hMSC are heterogenous at the level of primary metabolism and that energy metabolism plays important roles in regulating hMSC functional properties. This review focuses on energy metabolism in regulating hMSC immunomodulatory properties and its implication in hMSC sourcing and biomanufacturing. The specific characteristics of hMSC metabolism will be discussed with a focus on hMSC metabolic plasticity and donor- and culture-induced changes in immunomodulatory properties. Potential strategies of

modulating hMSC metabolism to enhance their immunomodulation and therapeutic efficacy in preclinical models will be reviewed.

Cancer Cell Int. 2019 May 21;19:139. doi: 10.1186/s12935-019-0855-5. eCollection 2019.

Ally to adversary: mesenchymal stem cells and their transformation in leukaemia.

Sharma M[1], Ross C[1], Srivastava S[2].
Author information

Abstract

Mesenchymal stem cells (MSC) are the key regulators of hematopoiesis. Owing to their dynamic nature; MSC differentiate into various lineages that further constitute the niche which are required for maintenance of the hematopoietic stem cells (HSC). A plethora of growth factors and cytokines secreted by MSC are essential for regulating the homeostasis within the niche in terms of cycling and quiescence of HSC. Additionally, there is a strong evidence suggesting the role of MSC in transformation of the niche to favour survival of leukemic cells. Regulation of HSC by MSC via BMP, Wnt, Notch and Sonic Hedgehog signalling has been well elaborated, however the modulation of MSC by HSC/LSC is yet unresolved. The cross talk between the HSC and MSC via paracrine or autocrine mechanisms is essential for the transformation. There are some reports implicating cell adhesion molecules, growth factors and cytokines; in modulation of MSC function and differentiation. The role of exosome mediated modulation has also been reported in the context of MSC transformation however, much needs to be done to understand this phenomenon in the present context. Similarly, the role of circulating nucleic acids, a well-studied molecular phenomenon in other tumours, requires attention in their potential role in crosstalk between MSC and HSC. This review underlines the current understanding of the physiological and pathophysiological roles of MSC and its transformation in diseased state, laying stress on developing further understanding of MSC regulation for development of the latter as therapeutic targets.

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BMP Signaling in Regulating Mesenchymal Stem Cells in Incisor Homeostasis.

Shi C[1,2], Yuan Y[1], Guo Y[1,3], Jing J[1,4], Ho TV[1], Han X[1], Li J[1,5], Feng J[1], Chai Y[1].
Author information

Abstract

Bone morphogenetic protein (BMP) signaling performs multiple essential functions during craniofacial development. In this study, we used the adult mouse incisor as a model to uncover how BMP signaling maintains tissue homeostasis and regulates mesenchymal stem cell (MSC) fate by mediating WNT and FGF signaling. We observed a severe defect in the proximal region of the adult mouse incisor after loss of BMP signaling in the Gli1+ cell lineage, indicating that BMP signaling is required for cell proliferation and odontoblast differentiation. Our study demonstrates that BMP signaling serves as a key regulator that antagonizes WNT and FGF signaling to regulate MSC lineage commitment. In addition, BMP

signaling in the Gli1+ cell lineage is also required for the maintenance of quiescent MSCs, suggesting that BMP signaling not only is important for odontoblast differentiation but also plays a crucial role in providing feedback to the MSC population. This study highlights multiple important roles of BMP signaling in regulating tissue homeostasis.

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Extemporaneous Preparation of Injectable and Enzymatically Degradable 3D Cell Culture Matrices from an Animal-Component-Free Recombinant Protein Based on Human Collagen Type I.

Kamata H[1], Ashikari-Hada S[2], Mori Y[1], Azuma A[1], Hata KI[1,2].
Author information

Abstract

Injectable hydrogels are considered important to realize safe and effective minimally invasive therapy. Although animal-derived natural polymers are well studied, they typically lack injectability and fail to eliminate the potential risks of immunogenic reactions or unknown pathogen contamination. Despite extensive research activities to explore ideal injectable hydrogels, such state-of-the-art technology remains inaccessible to non-specialists. In this article, the design of a new injectable hydrogel platform that can be extemporaneously prepared from commercially available animal-component-free materials is described. The hydrogels can be prepared simply by mixing mutually reactive aqueous solutions without necessitating specialized knowledge or equipment. Their solidification time can be adjusted by choosing proper buffer conditions from immediate to an extended period of time, that is, few or several tens of minutes depending on the concentration of polymeric components, which not only provides injectability, but enables 3D encapsulation of cells. Mesenchymal stromal/stem cells can be encapsulated and cultured in the hydrogels at least for 2 weeks by traditional cell culture techniques, and retrieved by collagenase digestion with cell viability of approximately 80%. This hydrogel platform accelerates future cell-related research activity

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Cartilage tissue engineering combining microspheroid building blocks and microneedle arrays.

Grogan SP[1], Dorthé EW[1], Glembotski NE[1], Gaul F[1,2], D'Lima DD[1].
Author information

Abstract

Purpose: Scaffold-free cartilage tissue engineering circumvents issues with scaffold seeding, potential toxicity response, and impaired host integration. However, precisely controlling and maintaining a scaffold-free construct shape have been challenging. We explored the feasibility of microneedle arrays to print tissue using cellular microspheroids as building blocks. **Materials and Methods**: Human embryonic-derived mesenchymal stem cells or infrapatellar fat pad mesenchymal stem cells were used

to create microspheroids of 500 µm in diameter, which were assembled on microneedle arrays in a predefined arrangement using a robotic system under computer vision. Microspheroids on microneedles were cultured to permit fusion into a tissue construct. Infrapatellar fat pad mesenchymal stem cell constructs were either implanted into chondral defects created in human osteoarthritic cartilage explants or maintained on the microneedle array for 3 weeks. Embryonic-derived mesenchymal stem cell constructs were designed to be press-fit into 3 mm subchondral defects in New Zealand White rabbits and maintained for up to 8 weeks to assess retention, early tissue repair, and more mature cartilage regeneration. **Results**: Microspheroids of both cell types fused together in culture to form neotissues of predefined shape and size. Infrapatellar fat pad mesenchymal stem cell neotissues expressed high levels of chondrogenic genes and integrated with the surrounding osteoarthritic host cartilage. Embryonic-derived mesenchymal stem cell constructs generated chondrogenic neotissue *in vivo* as early as 2 weeks and more mature tissue by 8 weeks with increased glycosaminoglycan deposition. **Conclusions**: We constructed defined scaffold-free shapes by bioprinting and fusing microspheroids. Proof of concept was shown in the repair of *ex vivo* osteoarthritic human cartilage and *in vivo* rabbit osteochondral (OC) defects.

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Knockdown of NANOG Reduces Cell Proliferation and Induces G0/G1 Cell Cycle Arrest in Human Adipose Stem Cells.

Pitrone M[1], Pizzolanti G[2,3], Coppola A[4], Tomasello L[5], Martorana S[6], Pantuso G[7], Giordano C[8,9].
Author information

Abstract

The core components of regenerative medicine are stem cells with high self-renewal and tissue regeneration potentials. Adult stem cells can be obtained from many organs and tissues. *NANOG*, *SOX2* and *OCT4* represent the core regulatory network that suppresses differentiation-associated genes, maintaining the pluripotency of mesenchymal stem cells. The roles of *NANOG* in maintaining self-renewal and undifferentiated status of adult stem cells are still not perfectly established. In this study we define the effects of downregulation of *NANOG* in maintaining self-renewal and undifferentiated state in mesenchymal stem cells (MSCs) derived from subcutaneous adipose tissue (hASCs). hASCs were expanded and transfected in vitro with short hairpin Lentivirus targeting *NANOG*. Gene suppressions were achieved at both transcript and proteome levels. The effect of *NANOG* knockdown on proliferation after 10 passages and on the cell cycle was evaluated by proliferation assay, colony forming unit (CFU), qRT-PCR and cell cycle analysis by flow-cytometry. Moreover, *NANOG* involvement in differentiation ability was evaluated. We report that downregulation of *NANOG* revealed a decrease in the proliferation and differentiation rate, inducing cell cycle arrest by increasing *p27*/*CDKN1B* (Cyclin-dependent kinase inhibitor 1B) and *p21*/*CDKN1A* (Cyclin-dependent kinase inhibitor 1A) through *p53* and regulate *DLK1*/*PREF1*. Furthermore, *NANOG* induced downregulation of *DNMT1*, a major DNA methyltransferase responsible for maintaining methylation

status during DNA replication probably involved in cell cycle regulation. Our study confirms that *NANOG* regulates the complex transcription network of plasticity of the cells, inducing cell cycle arrest and reducing differentiation potential.

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Melatonin-pretreated adipose-derived mesenchymal stem cells efficeintly improved learning, memory, and cognition in an animal model of Alzheimer's disease.

Nasiri E[1], Alizadeh A[2], Roushandeh AM[3], Gazor R[1], Hashemi-Firouzi N[4], Golipoor Z[5,6].
Author information

Abstract

Currently, mesenchymal stem cells (MSCs) based therapy has extensive attraction for Alzheimer's disease (AD). However, low survival rate of MSCs after transplantation is a huge challenging. The current study aimed to improve adipose-derived MSCs (AD-MSCs)-based therapy by their pre-treatment with melatonin (MT) 'a well-known antioxidant' in an animal model of AD. In this study, after isolating rat AD-MSCs from the epididymal white adipose tissues, the cells were pretreated with 5μM of MT for 24 hours. Forty male Wistar rats were randomly allocated to control, sham, amyloid-beta (Aβ) peptide, AD-MSCs and MT-pretreated ADMSCs groups. The novel object recognition, passive avoidance test, Morris water maze and open field test were performed two months following the cell transplantation. The rats were sacrificed 69 days following cell therapy. The brain tissues were removed for histopathological analysis and also immunohistochemistry was performed for two Aβ1-42 and Iba1 proteins. It has been revealed that both AD-MSCs and MT-AD-MSCs migrated to brain tissues after intravenous transplantation. However, MT-ADMSCs significantly improved learning, memory and cognition compared with AD-MSCs ($P<0.05$). Furthermore, clearance of Aβ deposition and reduction of microglial cells were significantly increased in the MT-ADMSCs compared with AD-MSCs. Although stem cell therapy has been introduced as a promising strategy in neurodegenerative diseases, however, its therapeutic properties are limited. It is suggested that pretreatment of MSCs with melatonin partly would increase the cells efficiency and consequently could decrease AD complication including memory and cognition.

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Desktop-stereolithography 3D printing of a radially oriented extracellular matrix/mesenchymal stem cell exosome bioink for osteochondral defect regeneration.

Chen P[1,2], Zheng L[1,2,3], Wang Y[1,2], Tao M[1,2], Xie Z[1,2], Xia C[1,2], Gu C[1,2], Chen J[1,2], Qiu P[1,2], Mei S[1,2], Ning L[1,2], Shi Y[1,2], Fang C[1,2], Fan S[1,2], Lin X[1,2].
Author information

Abstract

Mitochondrial dysfunction and oxidative stress damage are hallmarks of osteoarthritis (OA). Mesenchymal stem cell (MSC)-derived exosomes are important in intercellular mitochondria

communication. However, the use of MSC exosomes for regulating mitochondrial function in OA has not been reported. This study aimed to explore the therapeutic effect of MSC exosomes in a three dimensional (3D) printed scaffold for early OA therapeutics. **Methods**: We first examined the mitochondria-related proteins in normal and OA human cartilage samples and investigated whether MSC exosomes could enhance mitochondrial biogenesis *in vitro*. We subsequently designed a bio-scaffold for MSC exosomes delivery and fabricated a 3D printed cartilage extracellular matrix (ECM)/gelatin methacrylate (GelMA)/exosome scaffold with radially oriented channels using desktop-stereolithography technology. Finally, the osteochondral defect repair capacity of the 3D printed scaffold was assessed using a rabbit model. **Results**: The ECM/GelMA/exosome scaffold effectively restored chondrocyte mitochondrial dysfunction, enhanced chondrocyte migration, and polarized the synovial macrophage response toward an M2 phenotype. The 3D printed scaffold significantly facilitated the cartilage regeneration in the animal model. **Conclusion**: This study demonstrated that the 3D printed, radially oriented ECM/GelMA/exosome scaffold could be a promising strategy for early OA treatment.