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A functional autophagy pathway is essential for BMP9-induced osteogenic differentiation of mesenchymal stem cells (MSCs)

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Free PMC article

Abstract

Mesenchymal stem cells (MSCs) are capable of differentiating into bone, cartilage and adipose tissues. We identified BMP9 as the most potent osteoinductive BMP although detailed mechanism underlying BMP9-regulated osteogenesis of MSCs is indeterminate. Emerging evidence indicates that autophagy plays a critical role in regulating bone homeostasis. We investigated the possible role of autophagy in osteogenic differentiation induced by BMP9. We showed that BMP9 upregulated the expression of multiple autophagy-related genes in MSCs. Autophagy inhibitor chloroquine (CQ) inhibited the osteogenic activity induced by BMP9 in MSCs. While overexpression of ATG5 or ATG7 did not enhance osteogenic activity induced by BMP9, silencing *Atg5* expression in MSCs effectively diminished BMP9 osteogenic signaling activity and blocked the expression of the osteogenic regulator Runx2 and the late marker osteopontin induced by BMP9. Stem cell implantation study revealed that silencing *Atg5* in MSCs profoundly inhibited ectopic

bone regeneration and bone matrix mineralization induced by BMP9. Collectively, our results strongly suggest a functional autophagy pathway may play an essential role in regulating osteogenic differentiation induced by BMP9 in MSCs. Thus, restoration of dysregulated autophagic activity in MSCs may be exploited to treat fracture healing, bone defects or osteoporosis.

Bone
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Expression profiling of mitochondria-associated microRNAs during osteogenic differentiation of human MSCs

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Abstract

Small non-coding microRNAs (miRNAs) have the ability to target and bind to many mRNAs within the cytosol resulting in reduced protein expression and modulation of a number of cellular pathways and networks. In addition to the cytosol, miRNAs have been identified in other cellular compartments and organelles, including the mitochondria. While a few mitochondria-associated miRNAs (mitomiRs) are predicted to be derived from the mitochondrial genome, the majority appear to be transcribed from nuclear DNA and somehow transported into the mitochondria. These findings raise interesting questions about why miRNAs are located in the mitochondria and if they play a role in regulating processes within these organelles. Previously published work from our laboratory showed that miR-181a/b can regulate osteogenesis, in part, by enhancing mitochondrial metabolism. In other published studies, miR-181 paralogs and many other miRNAs have been identified in mitochondrial extracts derived from common cell lines and specific primary cells and tissues. Taken together, we were motivated to identify mitomiR expression profiles during in vitro osteogenesis. Specifically, we obtained RNA from purified mitochondrial extracts of human bone marrow-derived mesenchymal

stem/stromal cells (MSCs) and from whole cell extracts of MSCs at day 0 or following osteogenic induction for 3, 7 and 14 days. Utilizing Affymetrix GeneChip™ miRNA 4.0 arrays, mitomiR expression signatures were determined at each time point. Based on the Affymetrix detection above background algorithm, the total number of miRNAs detected in MSC mitochondria extracts was 527 (non-induced MSCs), 627 (day 3 induced), 372 (day 7 induced) and 498 (day 14 induced). In addition, we identified significantly differentially-expressed mitomiRs at day 7 and day 14 of osteogenic induction when compared to day 0 (fold change ≥1.5; adjusted p value <0.05). In general, the most pronounced and highly significant changes in mitomiR expression during osteogenesis were observed at the day 7 time point. Interestingly, most miRNAs found to be differentially-expressed in mitochondria extracts did not show significantly altered expression in whole cell extracts at the same time points during osteoblast differentiation. This array study provides novel information on miRNAs associated with the mitochondria in MSCs during differentiation toward the osteoblast phenotype. These findings will guide future research to identify new miRNA candidates that may function in regulating mitochondrial function and/or bone formation, homeostasis or repair.

PLoS One
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Novel low shear 3D bioreactor for high purity mesenchymal stem cell production

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Free PMC article

Abstract

Bone marrow derived human Mesenchymal Stem Cells (hMSCs) are an attractive candidate for regenerative medicine. However, their harvest can be invasive, painful, and expensive, making it difficult to supply the enormous amount of pure hMSCs needed for future allogeneic therapies. Because of this, a robust method of scaled bioreactor culture must be designed to supply the need for high purity, high density hMSC yields. Here we test a scaled down model of a novel bioreactor consisting of an unsubmerged 3D printed Polylactic Acid (PLA) lattice matrix wetted by culture media. The growth matrix is uniform, replicable, and biocompatible, enabling homogenous cell culture in three dimensions. The goal of this study was to prove that hMSCs would culture well in this novel bioreactor design. The system tested resulted in comparable stem cell yields to other cell culture systems using bone marrow derived hMSCs, while maintaining viability (96.54% ±2.82), high purity (>98% expression of combined positive markers), and differentiation potential

Animals (Basel)

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The Effect of a 7 Year-Long Cryopreservation on Stemness Features of Canine Adipose-Derived Mesenchymal Stem Cells (cAD-MSC)

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Free PMC article

Abstract

Mesenchymal stem cells (MSCs) are used in therapy in animal models and veterinary medicine, due to their capacity of inducing tissue regeneration and immunomodulation. Their clinical application requires a ready off-the-shelf amount of viable therapeutics doses. For this purpose, it is useful to cryopreserve MSCs to gain a ready and controlled source of abundant autologous stem cells. We evaluated the effect of 7 years cryopreservation using 10% dimethyl sulfoxide (DMSO) with different fetal bovine serum (FBS) concentrations (from 10 to 90%) on different passages of MSCs isolated from canine adipose tissue (cAD-MSCs). The study aimed to evaluate the most adequate cell passage and FBS percentage for the long-term cryopreservation of cells by maintaining the stemness features. Phenotype morphology, cell viability, osteogenic and adipogenic differentiation potentials, proliferative potential and expression of pluripotency markers were analyzed in thawed cells and compared with fresh ones. We demonstrated that cells cryopreserved with at least 80% FBS maintain unaltered the stemness characteristics of the freshly isolated cells. In particular, cells of P0-P1 passages have to be expanded in vitro and subsequently cryopreserved and cells of P2-P4 passages should be considered in the studies on therapeutic application and in vitro study of cAD-MSCs.

Animals (Basel)

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Chicken Mesenchymal Stem Cells and Their Applications: A Mini Review

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Free article

Abstract

Mesenchymal stem cells (MSCs) are multipotent progenitor cells that adhere to plastic; express the specific markers CD29, CD44, CD73, CD90, and CD105; and produce cytokines and growth factors supporting and regulating hematopoiesis. MSCs have capacity for differentiating into osteocytes, chondrocytes, adipocytes, and myocytes. They are useful for

research toward better understanding the pathogenic potential of the infectious bursal disease virus, mineralization during osteogenesis, and interactions between MSCs as a feeder layer to other cells. MSCs are also important for immunomodulatory cell therapy, can provide a suitable strategy model for coculture with pathogens causing dermatitis disorders in chickens, can be cultured in vitro with probiotics and prebiotics with a view to eliminate the feeding of antibiotic growth promoters, and offer cell-based meat production. Moreover, bone marrow-derived MSCs (BM-MSCs) in coculture with hematopoietic progenitor/stem cells (HPCs/HSCs) can support expansion and regulation of the hematopoiesis process using the 3D-culture system in future research in chickens. MSCs' several advantages, including ready availability, strong proliferation, and immune modulatory properties make them a suitable model in the field of stem cell research. This review summarizes current knowledge about the general characterization of MSCs and their application in chicken as a model organism.

Stem Cell Rev Rep

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Metabolomic Applications in Stem Cell Research: a Review

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Abstract

This review describes the use of metabolomics to study stem cell (SC) characteristics and function, excluding SCs in cancer research, suited to a fully dedicated text. The interest in employing metabolomics in SC research has consistently grown and emphasis is, here, given to developments reported in the past five years. This text informs on the existing methodologies and their complementarity regarding the information provided, comprising untargeted/targeted approaches, which couple mass spectrometry or nuclear magnetic resonance spectroscopy with multivariate analysis (and, in some cases, pathway analysis

and integration with other omics), and more specific analytical approaches, namely isotope tracing to highlight particular metabolic pathways, or in tandem microscopic strategies to pinpoint characteristics within a single cell. The bulk of this review covers the existing applications in various aspects of mesenchymal SC behavior, followed by pluripotent and neural SCs, with a few reports addressing other SC types. Some of the central ideas investigated comprise the metabolic/biological impacts of different tissue/donor sources and differentiation conditions, including the importance of considering 3D culture environments, mechanical cues and/or media enrichment to guide differentiation into specific lineages. Metabolomic analysis has considered cell endometabolomes and exometabolomes (fingerprinting and footprinting, respectively), having measured both lipid species and polar metabolites involved in a variety of metabolic pathways. This review clearly demonstrates the current enticing promise of metabolomics in significantly contributing towards a deeper knowledge on SC behavior, and the discovery of new biomarkers of SC function with potential translation to in vivo clinical practice.

Antibiotics (Basel)

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Microfluidic Tools for Enhanced Characterization of Therapeutic Stem Cells and Prediction of Their Potential Antimicrobial Secretome

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Free article

Abstract

Antibiotic resistance is creating enormous attention on the development of new antibiotic-free therapy strategies for bacterial diseases. Mesenchymal stromal stem cells (MSCs) are the most promising candidates in current clinical trials and included in several cell-therapy protocols. Together with the well-known immunomodulatory and regenerative potential of the MSC secretome, these cells have shown direct and indirect anti-bacterial effects. However, the low reproducibility and standardization of MSCs from different sources are the current limitations prior to the purification of cell-free secreted antimicrobial peptides and exosomes. In order to improve MSC characterization, novel label-free functional tests, evaluating the biophysical properties of the cells, will be advantageous for their cell profiling, population sorting, and quality control. We discuss the potential of emerging microfluidic technologies providing new insights into density, shape, and size of live cells, starting from heterogeneous or 3D cultured samples. The prospective application of these technologies to studying MSC populations may contribute to developing new biopharmaceutical strategies with a view to naturally overcoming bacterial defense mechanisms.