ML 23-20 (15/06/2020)

Front Cell Dev Biol
. 2020 May 25;8:353.
doi: 10.3389/fcell.2020.00353. eCollection 2020.

Exosomes Secreted by Adipose-Derived Mesenchymal Stem Cells Foster Metastasis and Osteosarcoma Proliferation by Increasing COLGALT2 Expression

Yan Wang[1], Yijing Chu[2], Kun Li[3], Guoqing Zhang[1], Zhu Guo[1], Xiaolin Wu[1], Chensheng Qiu[1], Yan Li[2], Xin Wan[2], Jing Sui[2], Dan Zhang[4], Hongfei Xiang[1], Bohua Chen[1]
Affiliations expand

- PMID: 32523950

- PMCID: PMC7262406

- DOI: 10.3389/fcell.2020.00353

Free PMC article

Abstract

Objectives: Homosapien collagen beta (1-O) galactosyl transferase 2 (COLGALT2) is an important enzyme during collagen glycosylation, yet its biological functions in cancer are incompletely understood. Our previous study revealed that in the osteosarcoma microenvironment, adipose-derived mesenchymal stem cells (ADSCs) demonstrate cancer-promoting effects, but the exact mechanisms remain unclear. The aim of this study was to investigate the role of COLGALT2 in the osteosarcoma-fostering effects of ADSCs.

Materials and methods: In this study, we compared COLGALT2 expression between primary and metastatic osteosarcoma tissues and found that metastatic tissues expressed significantly higher COLGALT2 levels. Then, we isolated and identified exosomes secreted by ADSCs. Additionally, we assessed the roles of ADSC exosomes and COLGALT2 in the osteosarcoma-promoting effects of ADSCs.

Results: Our results showed that ADSC exosomes could foster the invasion, migration, and proliferation of osteosarcoma cells, together with increasing COLGALT2 expression. COLGALT2 inhibition in MG63 cells suppressed the ADSC exosome-mediated fostering of osteosarcoma cell invasion, migration and proliferation *in vitro*. Conversely, COLGALT2 overexpression promoted U-2OS cell invasion, migration and proliferation *in vitro*. Additionally, COLGALT2 inhibition attenuated metastasis and tumor growth, and ADSC exosomes promoted tumor progression, as demonstrated in a nude mouse model of osteosarcoma.

Conclusion: According to these data, ADSC exosomes foster osteosarcoma progression by increasing COLGALT2 expression in osteosarcoma cells.

Keywords: Homo sapiens collagen beta (1-O)galactosyltransferase 2; adipose-derived mesenchymal stem cells; exosomes; metastasis; osteosarcoma.

Stem Cells 2020 Jun 14.
doi: 10.1002/stem.3245. Online ahead of print.

Canonical Notch Signaling Is Required for Bone Morphogenetic Protein-mediated Human Osteoblast Differentiation

Yadav Wagley[1], Alessandra Chesi[2 3], Parker K Acevedo[1], Sumei Lu[2], Andrew D Wells[2 4], Matthew E Johnson[2 3], Struan F A Grant[2 3 5 6 7 8], Kurt D Hankenson[1]
Affiliations expand

- PMID: 32535942

- DOI: 10.1002/stem.3245

Abstract

Osteoblast differentiation of bone-marrow derived human mesenchymal stem cells (hMSC) can be induced by stimulation with either canonical Notch ligand, Jagged1, or bone morphogenetic proteins (BMP). However, it remains elusive how these two pathways lead to the same phenotypic outcome. Since Runx2 is regarded as a master regulator of osteoblastic differentiation, we targeted Runx2 with siRNA in hMSC. This abrogated both Jagged1 and BMP2 mediated osteoblastic differentiation, confirming the fundamental role for Runx2. However, while BMP stimulation increased Runx2 and downstream Osterix protein expression, Jagged1 treatment failed to upregulate either, suggesting that

canonical Notch signals require basal Runx2 expression. To fully understand the transcriptomic profile of differentiating osteoblasts, RNA sequencing was performed in cells stimulated with BMP2 or Jagged1. There was common upregulation of ALPL and extracellular matrix genes, such as ACAN, HAS3, MCAM, and OLFML2B. Intriguingly, genes encoding components of Notch signaling (JAG1, HEY2 and HES4) were among the top 10 genes upregulated by both stimuli. Indeed, ALPL expression occurred concurrently with Notch activation and inhibiting Notch activity for up to 24 hours after BMP administration with DAPT (a gamma secretase inhibitor) completely abrogated hMSC osteoblastogenesis. Concordantly, RBPJ (Recombination Signal Binding Protein for Immunoglobulin Kappa J Region, a critical downstream modulator of Notch signals) binding could be demonstrated within the ALPL and SP7 promoters. As such, siRNA mediated ablation of RBPJ decreased BMP-mediated osteoblastogenesis. Finally, systemic Notch inhibition using diabenzazepine (DBZ) reduced BMP2-induced calvarial bone healing in mice supporting the critical regulatory role of Notch signaling in BMP-induced osteoblastogenesis. © AlphaMed Press 2020 SIGNIFICANCE STATEMENT: While BMPs are potent osteoblastogenic agents, the role for Notch signaling in osteoblastogenesis has been controversial. In addition to activating canonical SMAD protein, BMPs also lead to increased Notch receptor processing, Notch target gene expression, and Notch ligand Jagged1 upregulation. Blocking canonical Notch signaling ablates BMP-induced osteoblastogenesis but not BMP signaling. Given that Jagged1 stimulation alone drives osteoblastic differentiation of hMSCs, and that loss-of-function mutations in the Jagged1 gene causes low bone mass and osteopenia in humans, decreases in Jagged1 ligand during osteoblastogenesis may contribute to reduced bone formation by affecting activity of classical osteoanabolic factors, such as BMP.

FASEB J

. 2020 Jun 13.
doi: 10.1096/fj.202000629R. Online ahead of print.

Resident Mesenchymal Vascular Progenitors Modulate Adaptive Angiogenesis and Pulmonary Remodeling via Regulation of Canonical Wnt Signaling

Megan E Summers[1], Bradley W Richmond[2], Swapna Menon[3], Ryan M Sheridan[4], Jonathan A Kropski[2], Sarah A Majka[1], M Mark Taketo[5], Julie A Bastarache[2], James D West[2], Stijn De Langhe[6], Patrick Geraghty[7], Dwight J Klemm[8,9], Hong Wei Chu[1], Rachel S Friedman[10], Yuankai K Tao[3], Robert F Foronjy[7], Susan M Majka[1,9,10,11]
Affiliations expand

- PMID: 32533805

- DOI: 10.1096/fj.202000629R

Abstract

Adaptive angiogenesis is necessary for tissue repair, however, it may also be associated with the exacerbation of injury and development of chronic disease. In these studies, we demonstrate that lung mesenchymal vascular progenitor cells (MVPC) modulate adaptive angiogenesis via lineage trace, depletion of MVPC, and modulation of β-catenin expression. Single cell sequencing confirmed MVPC as multipotential vascular progenitors, thus, genetic depletion resulted in alveolar simplification with reduced adaptive angiogenesis. Following vascular endothelial injury, Wnt activation in MVPC was sufficient to elicit an emphysema-like phenotype characterized by increased MLI, fibrosis, and MVPC driven adaptive angiogenesis. Lastly, activation of Wnt/β-catenin signaling skewed the profile of human and murine MVPC toward an adaptive phenotype. These data suggest that lung MVPC drive angiogenesis in response to injury and regulate the microvascular niche as well as subsequent distal lung tissue architecture via Wnt signaling.

Cells

. 2020 Jun 10;9(6):E1444.
doi: 10.3390/cells9061444.

Tracking of Infused Mesenchymal Stem Cells in Injured Pulmonary Tissue in *Atm*-Deficient Mice

Patrick C Baer[1], Julia Sann[1], Ruth Pia Duecker[2], Evelyn Ullrich[3,4,5], Helmut Geiger[1], Peter Bader[3], Stefan Zielen[2], Ralf Schubert[2]
Affiliations expand

- PMID: 32531978

- DOI: 10.3390/cells9061444

Free article

Abstract

Pulmonary failure is the main cause of morbidity and mortality in the human chromosomal instability syndrome Ataxia-telangiectasia (A-T). Major phenotypes include recurrent respiratory tract infections and bronchiectasis, aspiration, respiratory muscle abnormalities, interstitial lung disease, and pulmonary fibrosis. At present, no effective pulmonary therapy for A-T exists. Cell therapy using adipose-derived mesenchymal stromal/stem cells (ASCs) might be a promising approach for tissue regeneration. The aim of the present project was to investigate whether ASCs migrate into the injured lung parenchyma of *Atm*-deficient mice as an indication of incipient tissue damage during A-T. Therefore, ASCs isolated from luciferase transgenic mice (mASCs) were intravenously transplanted into *Atm*-deficient and wild-type mice. Retention kinetics of the cells were monitored using in vivo bioluminescence imaging (BLI) and completed by subsequent verification using quantitative real-time polymerase chain reaction (qRT-PCR). The in vivo imaging and the qPCR results demonstrated migration accompanied by a significantly longer retention time of transplanted mASCs in the lung parenchyma of *Atm*-deficient mice compared to wild type mice. In conclusion, our study suggests incipient damage in the lung parenchyma of *Atm*-deficient mice. In addition, our data further demonstrate that a combination of luciferase-based PCR together with BLI is a pivotal tool for tracking mASCs after transplantation in models of inflammatory lung diseases such as A-T.

NPJ Microgravity

. 2020 Jun 1;6:16.
doi: 10.1038/s41526-020-0106-z. eCollection 2020.

Feasibility, Potency, and Safety of Growing Human Mesenchymal Stem Cells in Space for Clinical Application

Peng Huang[1,2], Athena L Russell[1,2], Rebecca Lefavor[1,2], Nisha C Durand[1,2], Elle James[1,2], Larry Harvey[3], Cuiping Zhang[1,2], Stefanie Countryman[4], Louis Stodieck[4], Abba C Zubair[1,2]
Affiliations expand

- PMID: 32529028
- PMCID: PMC7264338
- DOI: 10.1038/s41526-020-0106-z

Free PMC article

Abstract

Growing stem cells on Earth is very challenging and limited to a few population doublings. The standard two-dimensional (2D) culture environment is an unnatural condition for cell growth. Therefore, culturing stem cells aboard the International Space Station (ISS) under a microgravity environment may provide a more natural three-dimensional environment for stem cell expansion and organ development. In this study, human-derived mesenchymal stem cells (MSCs) grown in space were evaluated to determine their potential use for future clinical applications on Earth and during long-term spaceflight. MSCs were flown in Plate Habitats for transportation to the ISS. The MSCs were imaged every 24-48 h and harvested at 7 and 14 days. Conditioned media samples were frozen at -80 °C and cells were either cryopreserved in 5% dimethyl sulfoxide, RNAprotect, or paraformaldehyde. After return to Earth, MSCs were characterized to establish their identity and cell cycle status. In addition, cell proliferation, differentiation, cytokines, and growth factors' secretion were assessed. To evaluate the risk of malignant transformation, the space-grown MSCs were subjected to chromosomal, DNA damage, and tumorigenicity assays. We found that microgravity had significant impact on the MSC capacity to secrete cytokines and growth factors. They appeared to be more potent in terms of immunosuppressive capacity compared to their identical ground control. Chromosomal, DNA damage, and tumorigenicity assays showed no evidence of malignant transformation. Therefore, it is feasible and potentially safe to grow MSCs aboard the ISS for potential future clinical applications.

Stem Cells

. 2020 Jun 11.
doi: 10.1002/stem.3242. Online ahead of print.

Stem Cell Homing: From Physiology to Therapeutics

Jane L Liesveld[1], Naman Sharma[1], Omar S Aljitawi[1]
Affiliations expand

- PMID: 32526037

- DOI: 10.1002/stem.3242

Abstract

Stem cell homing is a multi-step endogenous physiologic process which is also utilized by exogenously administered hematopoietic stem and progenitor cells (HSPCs). This multi-step process involves cell migration and is essential for hematopoietic stem cell transplantation. The process can be manipulated to enhance ultimate engraftment potential, and understanding stem cell homing is also important to the understanding of stem cell mobilization. Homing is also of potential importance in the recruitment of marrow mesenchymal stem and stromal cells (MSCs) to sites of injury and regeneration. This process is less understood but assumes importance when these cells are utilized for repair purposes. In this review, the process of HSPC and MSC homing is examined as are methods to enhance this process. © AlphaMed Press 2020 SIGNIFICANCE STATEMENT: Stem cell homing is essential for successful hematopoietic stem cell transplantation, so understanding how to enhance and refine it has clinical significance. Examination of he homing of mesenchymal stromal cells to sites of tissue injury has assumed importance as these cells are now being used increasingly in therapeutic settings.