



OPEN ACCESS

EDITED AND REVIEWED BY
Valerie Kouskoff,
The University of Manchester,
United Kingdom

*CORRESPONDENCE

Aaron W. James,
✉ awjames@jhmi.edu
Bruno Péault,
✉ bpeault@mednet.ucla.edu
Xinli Zhang,
✉ xzhang@dentistry.ucla.edu

[†]These authors share first authorship

RECEIVED 05 September 2023
ACCEPTED 08 September 2023
PUBLISHED 15 September 2023

CITATION

James AW, Thottappillil N, Péault B and
Zhang X (2023), Editorial: Chondrogenic
potentials, protocols and mechanisms of
mesenchymal progenitor cells.
Front. Cell Dev. Biol. 11:1289438.
doi: 10.3389/fcell.2023.1289438

COPYRIGHT

© 2023 James, Thottappillil, Péault and
Zhang. This is an open-access article
distributed under the terms of the
[Creative Commons Attribution License
\(CC BY\)](https://creativecommons.org/licenses/by/4.0/). The use, distribution or
reproduction in other forums is
permitted, provided the original author(s)
and the copyright owner(s) are credited
and that the original publication in this
journal is cited, in accordance with
accepted academic practice. No use,
distribution or reproduction is permitted
which does not comply with these terms.

Editorial: Chondrogenic potentials, protocols and mechanisms of mesenchymal progenitor cells

Aaron W. James^{1*†}, Neelima Thottappillil^{1†}, Bruno Péault^{2*} and Xinli Zhang^{3*}

¹Department of Pathology, Johns Hopkins University, Baltimore, MD, United States, ²Department of Orthopaedic Surgery, University of California, Los Angeles, Los Angeles, CA, United States, ³School of Dentistry, University of California, Los Angeles, Los Angeles, CA, United States

KEYWORDS

mesenchymal stem cells, chondrogenic differentiation, cartilage regeneration, animal models, clinical application

Editorial on the Research Topic

Chondrogenic potentials, protocols and mechanisms of mesenchymal progenitor cells

From the pivotal observation of the clonogenic nature of bone-forming cells in bone marrow by [Friedenstein \(1990\)](#); [Bianco et al. \(2008\)](#) to its application in thousands of clinical trials (see [ClinicalTrials.gov](https://clinicaltrials.gov)), the history of mesenchymal stem cell research has remained vivid ([Caplan, 1991](#)). Recently, the International Society for Cell & Gene Therapy (ISCT) committee provided a statement to clarify the nomenclature of mesenchymal stem/stromal cells ([Viswanathan et al., 2019](#)). Mesenchymal stem/progenitor cells (MSCs) exist in multiple tissues within our body. These cells when dissociated from the native tissue and cultured *in vitro* show the potential to differentiate into multiple mesodermal cell lineages, suggesting applicability to a myriad of tissue regeneration approaches ([James et al., 2012](#)). Mesenchymal stem cell-based therapy is used in musculoskeletal repair ([James and Péault, 2019](#); [Xu et al., 2021](#)). Even though bone marrow was the first source of MSCs, cells from adipose tissue are presently a major supply of related cells for various applications ([Craig et al., 2022](#)). Collectively coined by the term “adipose stromal vascular fraction derived cells”, they constitute stem cells together with endothelial, immune, and other supporting cells ([Thottappillil et al., 2023](#)). Many reconstructive and regeneration therapies rely on mesenchymal stem cells, but the exact mechanism underlying the broad term “mesenchymal stem cell-mediated tissue regeneration” is not well understood. The role of MSCs in tissue repair can range from complete restorative of damaged tissue architecture to a growth factor secretor and even to an immune modulator ([Scott et al., 2011](#); [Murray and Peault, 2015](#); [Caplan, 2017](#); [Gomez-Salazar et al., 2020](#)). Moreover, mesenchymal progenitors are heterogeneous in their identity and function. One of the common niches for these progenitor cells is the perivascular space of blood vessels, and hence these cells are known as perivascular stem cells or PSCs. PSCs span both pericytes in the microvasculature and adventitial cells around larger vessels ([Crisan et al., 2008](#); [Corselli et al., 2013](#); [James and Péault, 2019](#)). Our recent studies have identified a diversity of perivascular progenitors ([Ding et al., 2020](#); [Xu et al., 2020](#); [Wang et al., 2020](#)).

Mesenchymal progenitor cells can form lineage-specific cells including chondrocytes (Dominici et al., 2006; Li et al., 2016; Hindle et al., 2017). Although MSCs produce fibrocartilage, not hyaline cartilage, several studies show successful regeneration of articular tissue using MSCs. Our recent reviews compile the role of pericytes in cartilage repair and regeneration (James et al., 2017; Negri et al., 2022). Identification of surface markers helps to predict the chondrogenic differentiation of MSCs and perform their isolation from the heterogeneous pool. For instance, receptor tyrosine kinase-like orphan receptor 2 (*ROR2*) was identified as a cell surface marker of MSCs with enhanced capacity for cartilage formation (Dickinson et al., 2017).

The goal of the present Research Topic was to emphasize the chondrogenic potential of mesenchymal progenitor cells in culture, and mechanisms to *in vivo* applications. The Research Topic includes four articles that provide ideas on defining the heterogeneous nature of mesenchymal progenitor cells and efficiently using them for cartilage regeneration.

The original research by Ghabriel et al. aims to identify markers that can be used together with the International Society for Cellular Therapy (ISCT) minimum criteria to define mesenchymal stromal/stem cells. In the present study, the authors carried out a comparative analysis of publicly available single-cell RNA sequencing datasets of MSCs derived from different tissues in both humans and mice. The authors hypothesize that there exists a relationship between protein homeostasis (proteostasis) and mesenchymal stem cell function. Computationally, the study finds six members of proteasomal machinery are promising additional stemness-related markers for accurately validating the identity of MSCs.

Another study by Magallanes et al. focuses on the fate of Gli1+ mesenchymal stem cells post-knee injury in mice. Their results indicate that Gli1+ cells get activated, expand, and differentiate into fibrotic cells in surgically induced knee arthrofibrosis, and significantly contribute to the osteoblast pool during trauma-induced heterotopic ossification. Moreover, the study establishes a novel mouse model for studying post-traumatic knee injury, which can be applied to study other cell populations in the injured joint.

The mini-review by Liu et al. updates the relevance of mesenchymal stem cell therapies to articular cartilage regeneration in large animals. The authors comprehensively present the pros and cons of MSC treatment in large animals ranging from pigs to dogs. They conclude that MSC-based studies for articular cartilage regeneration are to be conducted in either ruminants or pigs, mainly because of anatomical/biomechanical similarity with humans. The mini-review also includes the major tissue engineering strategies for optimized

application of MSCs for regenerating cartilage. The authors interestingly point out that there is relevance in the choice of autologous, allogenic, or xenogenic MSCs, which shape the success of cartilage regeneration in large animals.

Another study by Ren et al. directs to the clinical application of adipose stromal vascular fraction (SVF) to treat human knee osteoarthritis. In detail, the article explains the clinical phase I/II trial using MSCs to treat cartilage degeneration in six patients with both knee cartilage defects I-II due to osteoarthritis. Liposuction was performed on the same patient to extract SVF. Postoperatively for 24 weeks, a novel 3D MRI imaging and spatial alignment method was used to evaluate quantitative and qualitative cartilage regeneration in these patients. Conclusively, the authors found that clinical phase I/II application of stromal vascular fraction enhanced cartilage regeneration. The study also provides novel protocols and data for phase-III clinical trials to further test the efficacy of SVF-based cartilage regeneration.

The studies described here contribute to expanding current knowledge on mesenchymal stem cells and cartilage regeneration. Several promising ideas, disease models and protocols were discussed, hoping to improve the health of patients with degenerated cartilage in the future.

Author contributions

AJ: Writing—original draft, Writing—review and editing. NT: Writing—original draft, Writing—review and editing. BP: Writing—review and editing. XZ: Writing—review and editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

- Bianco, P., Robey, P. G., and Simmons, P. J. (2008). Mesenchymal stem cells: revisiting history, concepts, and assays. *Cell. Stem Cell.* 2 (4), 313–319. doi:10.1016/j.stem.2008.03.002
- Caplan, A. I. (1991). Mesenchymal stem cells. *J. Orthop. Res.* 9 (5), 641–650. official publication of the Orthopaedic Research Society. doi:10.1002/jor.1100090504
- Caplan, A. I. (2017). Mesenchymal stem cells: time to change the name!. *Stem Cells Transl. Med.* 6 (6), 1445–1451. doi:10.1002/sctm.17-0051
- Corselli, M., Crisan, M., Murray, I. R., West, C. C., Scholes, J., Codrea, F., et al. (2013). Identification of perivascular mesenchymal stromal/stem cells by flow cytometry. *Cytom. Part A* 83 (8), 714–720. the journal of the International Society for Analytical Cytology. doi:10.1002/cyto.a.22313
- Craig, D. J., James, A. W., Wang, Y., Tavian, M., Crisan, M., and Péault, B. M. (2022). Blood vessel resident human stem cells in health and disease. *Stem Cells Transl. Med.* 11 (1), 35–43. doi:10.1093/stcltm/szab001
- Crisan, M., Yap, S., Casteilla, L., Chen, C. W., Corselli, M., Park, T. S., et al. (2008). A perivascular origin for mesenchymal stem cells in multiple human organs. *Cell. Stem Cell.* 3 (3), 301–313. doi:10.1016/j.stem.2008.07.003
- Dickinson, S. C., Sutton, C. A., Brady, K., Salerno, A., Katopodi, T., Williams, R. L., et al. (2017). The Wnt5a receptor, receptor tyrosine kinase-like orphan receptor 2, is a predictive cell surface marker of human mesenchymal stem cells with an enhanced capacity for chondrogenic differentiation. *Stem Cells* 35 (11), 2280–2291. doi:10.1002/stem.2691

- Ding, L., Vezzani, B., Khan, N., Su, J., Xu, L., Yan, G., et al. (2020). CD10 expression identifies a subset of human perivascular progenitor cells with high proliferation and calcification potentials. *Stem Cells* 38 (2), 261–275. doi:10.1002/stem.3112
- Dominici, M., Le Blanc, K., Mueller, L., Slaper-Cortenbach, I., Marini, F., Krause, D., et al. (2006). Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy* 8 (4), 315–317. doi:10.1080/14653240600855905
- Friedenstein, A. J. (1990). "Osteogenic stem cells in bone marrow," in *Bone and mineral research*. Editors J. N. M. Heersche and J. A. Kanis (Amsterdam: Elsevier), 243–272.
- Gomez-Salazar, M., Gonzalez-Galofre, Z. N., Casamitjana, J., Crisan, M., James, A. W., and Péault, B. (2020). Five decades later, are mesenchymal stem cells still relevant? *Front. Bioeng. Biotechnol.* 8, 148. doi:10.3389/fbioe.2020.00148
- Gomez-Salazar, M. A., Wang, Y., Thottappillil, N., Hardy, R. W., Alexandre, M., Höller, F., et al. (2023). Aldehyde dehydrogenase, a marker of normal and malignant stem cells, typifies mesenchymal progenitors in perivascular niches. *Stem Cells Transl. Med.* 12 (7), 474–484. doi:10.1093/stcltm/szad024
- Hindle, P., Khan, N., Biant, L., and Péault, B. (2017). The infrapatellar fat pad as a source of perivascular stem cells with increased chondrogenic potential for regenerative medicine. *Stem Cells Transl. Med.* 6 (1), 77–87. doi:10.5966/sctm.2016-0040
- James, A. W., and Péault, B. (2019). Perivascular mesenchymal progenitors for bone regeneration. *J. Orthop. Res.* 37 (6), 1221–1228. official publication of the Orthopaedic Research Society. doi:10.1002/jor.24284
- James, A. W., Zara, J. N., Corselli, M., Chiang, M., Yuan, W., Nguyen, V., et al. (2012). Use of human perivascular stem cells for bone regeneration. *J. Vis. Exp. JoVE* (63), e2952. doi:10.3791/2952
- James, A. W., Hindle, P., Murray, I. R., West, C. C., Tawonsawatruk, T., Shen, J., et al. (2017). Pericytes for the treatment of orthopedic conditions. *Pharmacol. Ther.* 171, 93–103. doi:10.1016/j.pharmthera.2016.08.003
- Li, C. S., Zhang, X., Péault, B., Jiang, J., Ting, K., Soo, C., et al. (2016). Accelerated chondrogenic differentiation of human perivascular stem cells with NELL-1. *Part A* 22 (3-4), 272–285. doi:10.1089/ten.TEA.2015.0250
- Murray, I. R., and Péault, B. (2015). Q&A: mesenchymal stem cells - where do they come from and is it important? *BMC Biol.* 13, 99. doi:10.1186/s12915-015-0212-7
- Negri, S., Li, Z., Wang, Y., Cherief, M., Qin, Q., Xu, J., et al. (2022). The role of pericytes in the articular environment—A review. *Curr. Tissue Microenviron. Rep.* 3, 77–82. doi:10.1007/s43152-022-00041-8
- Scott, M. A., Nguyen, V. T., Levi, B., and James, A. W. (2011). Current methods of adipogenic differentiation of mesenchymal stem cells. *Stem Cells Dev.* 20 (10), 1793–1804. doi:10.1089/scd.2011.0040
- Thottappillil, N., Gomez-Salazar, M., Xu, M., Qin, Q., Xing, X., Xu, J., et al. (2023). ZIC1 dictates osteogenesis versus adipogenesis in human mesenchymal progenitor cells via a Hedgehog dependent mechanism. *Stem Cells*, sxad047. doi:10.1093/stmcls/sxad047
- Viswanathan, S., Shi, Y., Galipeau, J., Krampera, M., Leblanc, K., Martin, I., et al. (2019). Mesenchymal stem versus stromal cells: international society for cell and Gene therapy (ISCT[®]) mesenchymal stromal cell committee position statement on nomenclature. *Cytotherapy* 21 (10), 1019–1024. doi:10.1016/j.jcyt.2019.08.002
- Wang, Y., Xu, J., Meyers, C. A., Gao, Y., Tian, Y., Broderick, K., et al. (2020). PDGFR α marks distinct perivascular populations with different osteogenic potential within adipose tissue. *Stem Cells* 38 (2), 276–290. doi:10.1002/stem.3108
- Xu, J., Wang, Y., Hsu, C. Y., Negri, S., Tower, R. J., Gao, Y., et al. (2020). Lysosomal protein surface expression discriminates fat-from bone-forming human mesenchymal precursor cells. *eLife* 9, e58990. doi:10.7554/eLife.58990
- Xu, J., Wang, Y., Gomez-Salazar, M. A., Hsu, G. C., Negri, S., Li, Z., et al. (2021). Bone-forming perivascular cells: cellular heterogeneity and use for tissue repair. *Stem Cells Dayt. Ohio* 39 (11), 1427–1434. doi:10.1002/stem.3436