

Reviewer #1

Comment 1

Manuscript titled "Update on mesenchymal stem cell therapies for cartilage disorders" deals an important issue of medical biology and cartilage repair. The present editorial provide an update on the recent advancements on the field of stem cell therapy for cartilage defects. This editorial is well presented, formulated, written, interesting and fit very well with the remit and purpose of this journal but it is less innovative and updated. Moreover, there are some minor and major concerns that need to be addressed before recommending publication.

Reply to the reviewer: We thank the reviewer for the kind comments and the comprehensive description of the work presented. We included some updated information as requested and we addressed all minor and major concerns

Comment 2

Please reformulate better the aim in the abstract, adding also the clinical relevance of this study to help better readers understand.

Reply to the reviewer: We thank the reviewer for this suggestion. We reformulated the aim in the abstract and we added the clinical relevance of the study. We also have updated the language of our abstract to focus the scope of this review to focal cartilage defects.

Comment 3

Please reformulate the text, it must be improved because is poor in important recent information related to the treated, presented topic. Please strengthen the paragraphs of this editorial adding more details and recent interesting information to help better readers understand the last innovative approaches in this research arena regarding: osteoarthritis, new biomarkers (β -Defensin-4, lubricin) expressed in cartilage and in menisci fibrocartilage, mechanical loading, chondrosenescence, tissue engineering, MSC and prospective. I recommend to see the following recent and interesting papers and comment them to stay to the study topic:

- Osteoarthritis and new biomarkers expressed in cartilage and in menisci fibrocartilage: β -Defensin-4 (HBD-4) is expressed in chondrocytes derived from normal and osteoarthritic cartilage encapsulated in PEGDA scaffold. Acta Histochem. 2012 Dec;114(8):805-12.
- Expression of β -defensin-4 in "an in vivo and ex vivo model" of human osteoarthritic knee meniscus. Knee Surg Sports Traumatol Arthrosc. 2012 Feb;20(2):216-22.
- Lubricin is expressed in chondrocytes derived from osteoarthritic cartilage encapsulated in poly (ethylene glycol) diacrylate scaffold. Eur J Histochem. 2011;55(3):e31.

- Acute injury affects lubricin expression in knee menisci: an immunohistochemical study. *Ann Anat.* 2013 Mar;195(2):151-8.
- Mechanical loading: The Effect of Mechanical Loading on Articular Cartilage. *J. Funct. Morphol. Kinesiol.* 2016, 1, 154-161.
- Chondrosenescence: Chondrosenescence: definition, hallmarks and potential role in the pathogenesis of osteoarthritis. *Maturitas.* 2015 Mar;80(3):237-44.
- Physical activity ameliorates cartilage degeneration in a rat model of aging: a study on lubricin expression. *Scand J Med Sci Sports.* 2015 Apr;25(2):e222-30.
- Age-related degeneration of articular cartilage in the pathogenesis of osteoarthritis: molecular markers of senescent chondrocytes. *Histol Histopathol.* 2015 Jan;30(1):1-12.
- Tissue engineering, MSC and prospective: Mesenchymal stem cells from adipose tissue which have been differentiated into chondrocytes in three-dimensional culture express lubricin. *Exp Biol Med (Maywood).* 2011 Nov;236(11):1333-41.
- Chondrocyte and mesenchymal stem cell-based therapies for cartilage repair in osteoarthritis and related orthopaedic conditions. *Maturitas.* 2014 Jul;78(3):188-98.
- New perspectives for articular cartilage repair treatment through tissue engineering: A contemporary review. *World J Orthop.* 2014 Apr 18;5(2):80-8.

Reply to the reviewer: We thank the reviewer for suggesting these interesting studies. We made an effort to include as much as possible of the suggested work in the text. However, since our paper deals with the current state of stem cells in focal cartilage defect repair, we feel that inclusion of some of the papers that focus on the treatment and detection of OA potentially exceeds the scope of this editorial and they were not possible to be included.

Comment 6

In the conclusion please specify the clinical relevance of your work, the rational of this work, innovation, limitations, your personal view and some important suggestions for the scientific community.

Reply to the reviewer: We thank the reviewer for this comment, we modified the future perspectives and conclusion sections accordingly.

Comment 7

Please refresh and update the references list, is too poor.

Reply to the reviewer: We thank the reviewer for this comment; we updated our reference list.

Reviewer #2

Comment 1

The manuscript summarizes recent advances in the field of MSCs in local cartilage defects.

Minor points:

- Abstract, line 3 from bottom: in the field
- Page 4, line 2 from top: bone marrow
- Page 6, line 1 from top: its function is utilized..
- Page 6, line 4 from top: result in recruitment..
- Page 11, line 6 from bottom: Please consider changing: For this reason TO: However,
- Page 12, line 1 from top: fluorescein-labeled
- Page 13, line 11 from top: Synovial MSCs ,cultured in autologous human serum, arthroscopically implanted in 10 patients with single cartilage defect showed promising results.50. At 3-year follow up...
- Page 14, line 6 from bottom: terms
- Page 15, line 4 from top: please consider changing: to be correlated TO: to be included

Reply to the reviewer: We thank the reviewer for the kind comments. We incorporated all suggestions in the text.

Reviewer #3

Comment 1

The m/s is very good and can be accepted for publication.

The authors must correct an error in the last line of the m/s, in page 17, as follows: "...the treatment plan should be based on the characteristics of the patient."

Reply to the reviewer: We thank the reviewer for the kind comments. We incorporated all suggestions in the text.