

Dear Editor,

We would like to thank the editor for giving us a chance to resubmit the paper, and also thank the reviewers for giving us constructive suggestions which would help us both in English and in depth to improve the quality of the paper. Now, we show the explanation bellow and hope to meet with your approval. The revised manuscript will be sent to you at the sometime.

Response to reviewer #02446054:

Comments: See document attached

Answer: The related descriptions have been added and modified in order to improve the quality of our manuscript.

Response to reviewer #02446242:

Comments: The review is well written and includes most of the literature on this topic, analyzing the issues and the advantages of MSC treatment of OA.

Answer: Thank you very much for this positive appreciation.

Response to reviewer #00573611:

Comments: In this review article, the authors reviewed the potential applications of mesenchymal stem cells in the preclinical models and clinical applications of osteoarthritis. The authors reviewed the contents of preclinical and clinical trials in the recent 3 years and suggested that intra-articular injection of MSCs can lead to the reduction of index-pain, improve the function and significantly increase the volume of cartilage. Comments This is an interesting review article. The review has some minor concerns as follows: 1. An abbreviation first time used in the text present both the spelled-out version and the short form: AD-MSCs, UC-MSCs, PRP, etc. 2. In Table 1, the authors summarized mesenchymal stem cell preclinical trials in OA animal models from 2015 to 2018, but there is no study on 2015. Moreover, are there any rodents-mouse/rat data for this issue? 3. In Table 2 title: "Summary of MSCs/PRP clinical trials in OA animal models from 2012 to 2018", deleted the description of "in OA animal models", it is the clinical trial. Moreover, there is no study on 2018 in this Table. 4. In the clinical trials, are there any immunosuppressant drugs used?

Answer: Thank you very much for your useful comments. The related changing (point 1 and point 3) has been made.

Point 2: Here, we focus on the comparison of mixed injection and alone injection, so there is a little of pre-clinical trials in OA animal models.

Point 4: Several immunosuppressant drugs are used in the clinical trials, this is mainly for the treatment of rheumatoid arthritis, not including the osteoarthritis. Meanwhile, such as methotrexate and sulfasalazine, which often causes serious adverse reactions in the treatment of arthritis disease.

Response to reviewer #02446277:

Comments: The submitted manuscript summarized the potential applications of mesenchymal stem cells in the preclinical models and clinical applications of osteoarthritis. The authors described the characteristics of MSCs, including their immunomodulatory function, and then continue with examples of therapeutic use of MSC used directly via intra-articular injection, seeded on scaffolds or as source of exosomes. The information included in the manuscript is correct, well presented and very useful, especially the one on MSC clinical trials for osteoarthritis diseases. A major problem is the English. Although the manuscript has a Non-Native Speakers of English Editing Certificate, the English is deficient and many phrases are unclear. Another problem is related to the abbreviation, most of them not being defined at the first time use in the text. Also, there are several orthographical errors like: phrases that ends with comma (page 6), other that starts with lower case (page 4) and other that use capital letter after colon (page 3). In conclusion, proofreading must be seriously considered. Major comments: 1. The phrase: “MSCs can serve as cartilage progenitor cells or regenerative cells to stimulate endogenous cells to be co-cultured with three-dimensional scaffolds and implanted into the target area through joint surgery to repair the damaged cartilage [18]” is unclear. Must be rewritten. 2. Explain what “the connective tissue growth factor” represents (page 4) 3. Explain how scaffold materials can cause graft rejection. I think that scaffold materials can be subject of graft rejection (page 4) 4. The use of immunomodulatory biomaterials is another interesting idea that can be mentioned (eg PMID: 25155610, PMID: 28116128) 5. “Exosomes as communication carriers” (page 4); most probably it is “Exosomes are communication carriers” 6. Please verify the following sentence: “Accordingly, microRNA may be vital to mediate MSCs exosomes in the treatment of OA” (page 4). It is unclear. 7. “Exosome activates enzymes promotes tissue repair” (page 5); the time of the verb promote is inappropriate 8. Define the abbreviation the first time you use it in the text (eg. Page 4: PLGA, PEG, PLA, PGA; Page 5: AD-MSC, HA, PRP; Table 5: ICRS, VAS, IKDC, WOMAC, VAS, SF-36, SASK, OOS, OARSI; Table 4: VAS, ICOAP, LEQUESNE) 9. Incorrect / unclear sentence “MSCs can be activated by inflammatory factors, thereby making secrete PGE2, IDO, NO and other factors directly or indirectly suppress immune cells [40] (page 6). 10. There are several orthographical errors like: phrases that ends with comma (page 6), other that starts with lower case (page 4) and other that use capital letter after colon (page 3). 11. Unclear phrases: “Mixed injection means that MSCs combined with growth factor, cytokines and scaffolds for implantation, and the efficacy is improved by implantation of MSCs mixed with them.” “If the PRP combined with MSCs (...) for treating knee osteoarthritis, which can create a better microenvironment for MSCs growth (...), promote the synthesis of cartilage matrix and improve the therapeutic effect of stem cells in knee arthritis (page 7) 12. Table 2: a clinical trial cannot be on animal models. It can be referred as pre-clinical trial trials or non-clinical models.

Answer: Your suggestion is very useful for us. The related description (Point 1~2 and Point 4~12) has been changed.

Point 3: Use of MSCs seeded on the scaffold in articular cartilage repair may cause happening of the host immunological rejection response, but also weakens the regenerative cell migration into the scaffolds. Additional literature mentioned the scaffolds with lower concentration gave comparatively higher increment of MHC-II expression and allogeneic lymphocytes proliferation. Moreover, grafts are associated to pain, infection, tissue death at the donor site and immunological rejection.

Response to reviewer #00609434:

Comments: The manuscript from Wang et al. is a very useful review describing the application of MSC cell therapies to the treatment of osteoarthritic diseases. This review is really interesting and updated in its collection and description of current knowledge and clinical protocols exploring the therapeutic use of MSCs from various sources on cartilage degenerative pathologies in animal models and humans. I find it absolutely worthy of publication although in some chapters there are English syntax errors and the punctuation has to be revised before publication. In the following, the points to be revised: Page 4 lines 6-9: “Accordingly, it has been studied that connective tissue growth factor is loaded into scaffolds to assist cartilage repair and increase the degree of integration of new cartilage units with surrounding tissues [20, 21]”. What is “connective tissue growth factor”? The mentioned literature (20, 21) does not fit with the description given by the Authors, which by the way, is not clear. Page 4 lines 27-29 “Exosomes as communication carriers between cells, which primarily delivering various mRNA, microRNA, DNA proteins, lipids and other bioactive substances [24]”. Please correct the syntax of the sentence, it lacks the main verb. Page 5 lines 1-3: “The increase in enzyme activity is proportional to the loss of normal equilibrium, i.e., exosome activates enzymes promotes tissue repair and regeneration by restoring homeostasis during injury and disease”. Please correct “exosome activates enzymes promotes...” because it’s not clear the meaning and it’s grammatically wrong. Page 6 page 2-4: “MSCs can be activated by inflammatory factors, thereby making secrete PGE2, IDO, NO and other factors directly or indirectly suppress immune cells [40]”. Please write in correct English. Page 6 lines 14-15: “The supernatant cultured with MSCs stimulated by INF- γ and IL-1 β can increase the expression of arginine, IDO and nitric oxide synthase (iNOS) in macrophages,”. Did the authors mean “The supernatant from MSCs stimulated by INF...”? Please write in correct English. Page 6 lines 24-26: “It has been reported that cytokines secreted MSCs can target with synovial membrane and chondrocytes, so as to regulate anabolic and catabolic factors, or to induce the molecules expression of anti-inflammatory and chondrogenic [49].” Please write in correct English. Page 6 lines 30-32:” Barry and Murphy consider that [50] the function of mesenchymal stem cells actually originates from its paracrine mechanism, the repairing of damaged cartilage was used cells which primarily comes from the joint itself, and only a small number of foreign cells are involved during repairing, though the joint surface was repaired after the injection of mesenchymal stem cells”. Please write in correct English. Page 7 lines 6-7:” Mixed injection means that MSCs combined with growth factor, cytokines and scaffolds for implantation, and the efficacy is improved by implantation of MSCs mixed with them”. Please write it correctly. Page 7 lines 15-18:” If the PRP combined with MSCs (adipose mesenchymal stem cells: AD-MSCs/vascular stroma of adipose tissue: SVF) for treating knee osteoarthritis, which can create a better microenvironment for MSCs growth (promote the blood supply, reduce the local inflammatory response), promote the synthesis of cartilage matrix and improve the therapeutic effect of stem cells in knee arthritis [52-54]”. Please correct all the sentence because it is not possible to understand its meaning. Page 7, Table 2 title: “Summary of MSCs/PRP clinical trials in OA

animal models from 2012 to 2018.” Please revise the title because they are clinical studies and not animal models.

Answer: We appreciate your comments and considered your comments for the improvement of this manuscript. The related information (page 4 lines 6-9; page 4 lines 27-29; page 5 lines 1-3; page 6 lines 2-4; page 6 lines 14-15; page 6 lines 24-26; page 6 lines 30-32; page 7 lines 6-7; page 7 lines 15-18; page 7 table 2 title) has been corrected.

Here we submit a new version of our manuscript with the title “Application of mesenchymal stem cells therapy in the treatment of osteoarthritis of the knee: a concise review”, which has been modified according to the reviewers’ suggestions. We have revised the manuscript according to your kind advices and referee’s detailed suggestions. We sincerely hope this manuscript will be finally acceptable to be published on Word journal of stem cell. Thank you very much for all your help and looking forward to hearing from you soon.

Yours sincerely,

Dr. Hao YU, PhD, Doctor

Cell Products of National Engineering Research Center
National Stem Cell Engineering Research Center, Tianjin 300457, China
E-mail: yuhao-wuhan@hotmail.com