

Peer Review File

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Reviewer A:

Zhantao Deng et al summarized the merits/demerits and the recent progress of hydrogels, stem cell sources, and their combination to apply to cartilage repair in this review. There are some parts of the review were not very clear for me.

Comment 1. In Line 78-79, the authors illustrated that “cell-laden hydrogels can be manufactured by advanced techniques with patient-customized compositions”, please provide more information or references about this technique.

Reply 1: Cell-laden hydrogels can be used to regenerate several kinds of cartilage defect with patient-customized compositions. Xu et al find that supramolecular gelatin hydrogels encapsulated BMSCs and chondrogenic agents (kartogenin and TGF- β 1) promote the regeneration of both hyaline cartilage and subchondral bone(1). Jooybar et al find that when platelet lysate, an autologous and inexpensive source of growth factors was incorporated into hMSCs landed hydrogel, cartilage like extra cellular matrix deposition was induced, collagen type II and proteoglycans were deposited, which resulted ultimately in the formation of a tough dense matrix(2). The two examples above present some of cell-laden hydrogels which manufactured by advanced techniques with patient-customized compositions. Since the length limitation in the main text, two references had been added in the revised manuscript.

Changes in the text: We have modified our text as advised (see Page 5, line 79).

Comment 2. In Line 330-337, this part introduced the modification of MSCs, and may better put it into the paragraph that related to MSCs.

Reply 2: We felt very sorry for the inappropriate expression of MSCs. In line 330-337, this part introduced the modification of BMSCs, which was a kind of MSCs.

We had changed the expression “MSCs” to “BMSCs” in the revised manuscript to avoid misunderstanding.

Changes in the text: We have modified our text as advised (see Page 17-18, line 337-355).

Comment 3. In Figure 2 about the “Ideograph of cartilage repairment by hydrogels”, the 3rd part of the hydrogen injection, it seems the stem cells are already used with hydrogels, which against the description of the context. More explanations should be added in the main manuscript in Line 127 and illustration texts should be added about each figure for a better understanding of this review.

Reply 3: We had revised the 3rd part of Figure 2 (be adjusted to Figure 1 because of deletion of Figure 1) to avoid misunderstanding. The use of stem cell would be more appropriately displayed in Figure 3 (be adjusted to Figure 2 because of deletion of Figure 1). Explanations had been added in the main manuscript in Line 127 and illustration texts had been added each figure.

Changes in the text: We have modified our text as advised (see Page 7, line 128-131 and legends of Figure 1,2).

Comment 4. In Line 386, the abbreviation of VAS needs to be explained.

Reply 4: VAS is the abbreviation of visual analog scale and had been added in the revised manuscript.

Changes in the text: We have modified our text as advised (see Page 19, line 390).

Comment 5. There are format problems in Table 1.

Reply 5: The format of Table 1 has been rearranged.

Changes in the text: We have modified our table as advised (see Table 1)

Comment 6. In the study design column, Table 2, what does, for instance, the “3 group: 6/group” mean? The results should be more precise.

Reply 6: The “3 group: 6/group” mean that there were 3 groups in the selected studies and there were 6 animals for each group. We felt sorry for the unprecise expression in Table 2 and had been rearranged and expressed in a more precise way.

Changes in the text: We have modified our table as advised (see Table 2)

Comment 7. There are several format problems, such as blank spaces between words, singular or plural words, and grammar problems. This article needs further polishing.

Reply 7: The whole manuscript had been thoroughly reviewed and format problems had been revised.

Changes in the text: We have modified our text as advised (see Page 2, line 27; Page 4, line 50; Page 9, line 156, line 166; Page 10, line 186; Page 11, line 216; Page 11, line 229, line 231; Page 14, line 267; Page 15, line 306-308; Page 18, line 367; Page 19, line 385).

Reviewer B:

The authors of this manuscript conducted a comprehensive review of different sources of seed cells and hydrogels for cartilage tissue engineering. It's a very time-consuming and laborious job to accomplish, which deserves my salute.

From the academic point of view, I have no comments about the author's work since every aspect of this field has been regarded in their manuscript. However, from a technical point of view, three suggestions are given below.

Comment 1: First, there are some typo and grammar mistakes in the manuscript, i.e.: line 50, uite osteoarthritis; line 447, spluripotential but hard to direct differentiation. The authors should check carefully when they re-submit the manuscript.

Reply 1: The whole manuscript had been thoroughly reviewed and format problems had been revised.

Changes in the text: We have modified our text as advised (see Page 2, line 27; Page 4, line 50; Page 9, line 156, line 166; Page 10, line 186; Page 11, line 216; Page 11, line 229, line 231; Page 14, line 267; Page 15, line 306-308; Page 18, line 367; Page 19, line 385).

Comment 2: Second, the authors have included a “Methods of literature search” part in the manuscript. It seems to me that this kind of description appears more often in a systematic review or meta-analysis article, instead of a review article. I’m not sure if this is the right way to put it.

Reply 2: We had deleted the paragraph of “Methods of literature search” and “Results of literature search” in the revised manuscript and deleted Figure 1.

Changes in the text: We have modified our text as advised (see Page 6, line 107-124).

Comment 3: Third, the “conclusions and outlook” section is way too long and contains a lot of repeated information. The authors should make it concise and precise.

Reply 3: The “conclusions and outlook” section had been refined to make it more concise and precise.

Changes in the text: We have modified our text as advised (see Page 22-24, line 445-484).