

**Rebuttal Letter (Point-by-point response):**

We would like to thank the reviewers and editorial office for their constructive feedback and valuable comments and suggestions. These remarks are highly valued and appreciated, and they will be taken into consideration to improve the quality of our manuscript.

**Reviewer #1**

1. **The reviewer suggested to combine some specific data or examples in the introduction of mesenchymal stem cells to osteoarthritis analgesic mechanism.**

Response:

We thank the reviewer for the critical evaluation of our manuscript. Four paragraphs containing specific examples on osteoarthritis analgesic mechanisms were added on pages 15-16, as highlighted in the revised manuscript.

2. **The reviewer suggested to change "analgesia" to "analgesic mechanism" in the key words.**

Response:

Thank you for your suggestion. We changed the word accordingly.

3. **The reviewer requested more details on the paracrine factor-mediated mechanism and the exosome-mediated mechanism on analgesia.**

Response:

Thank you for this valuable comment. We highlighted more details on the paracrine factor-mediated mechanism and the exosome-mediated mechanism on analgesia on pages 10-11 as seen in the revised version of the manuscript.

Reviewer #2

1. **The reviewer requested to emphasize the mechanisms of osteoarthritis pain by listing individual molecular causes and explain how these causes are improved by MSC or MSC-derived EV.**

Response:

Thank you for your valuable comment. We clarified the individual molecular mechanisms of osteoarthritis pain on pages 4-5, in the “Pain in OA” section of the manuscript. In addition, we explained the effects of MSCs on such mechanisms on pages 15-16 and 19, in the “Proposed mechanisms of analgesia of MSCs in OA” section.

2. **The reviewer requested a schematic illustration to the readability of the review.**

Response:

We would like to thank the reviewer for this comment. We prepared a schematic illustration that was added to the manuscript. The scheme summarizes the proved and proposed mechanisms of analgesic effects of MSCs in OA. This should improve the clarity and readability of our work.

One more time, we want to thank the reviewers and the editorial office for the helpful comments. Based on your critical comments, we believed that the scientific content of our manuscript has been improved significantly.