First of all, I am very grateful to the esteemed reviewers for their suggested changes to this article. Here are my responses.

1. I've added the last section about the strengths and limitations of my proposed perspective.

And the title has been revised.

2. I have added some relevant data.

3. I have modified it to read "We provide a synthesis of the new approach"

4. i have added paragraphs in the introduction i have added some references.

5. I have written out the relationship between this translocation and the title of this section miRNA. Here it refers to IVD .

6. it has been modified to gene

7 Here is my mistake, I have revised the duplication .

8. what I want to express is that urolithic acid, urushiolic acid, does not exist as an exosome

of MSCs, he just assists MSCs. I have revised this natural paragraph.

9. I have revised it to be more understandable

10. I have revised the mistakes .

11. i have explained the abbreviations that appear for the first time this time .

12. I have analyzed this natural paragraph in more depth and cited the appropriate review articles.

13. I have explained the acronyms LI and ROS.

14. In the section on future directions, I have elaborated in more detail.

15. I have revised the grammar and content of this article in detail.

1. I have revised this piece in detail for grammar, spelling and punctuation .

2. I have addressed your question about the source and the differences in the function and behavior of MSCs.

3. I have included a brief description of current clinical studies or commercial products on

MSC repair of disc metaplasia.

1. I have changed the title accordingly.

2. Because this article is mainly about the therapeutic effect of MSCs. It does not mention preparation methods, so I have only briefly mentioned some preparation methods in the article. I have summarized the effects of MSCs in a table.

3. I have briefly described the effect of the route and location of administration of stem cells on the therapeutic efficacy of stem cells.

4. in the text, I have added a section on relevant allogeneic MSCs.

5. I have included corresponding studies on how to improve native MSCs in this review.

6. i have summarized all miRNAs, lncRNAs and cytokines in a table.

Finally, once again, thank you very much for taking time out of your busy schedule to revise this article.

Dear Journal Editor-in-Chief：

First of all, we would like to thank you for reviewing our manuscript in your busy schedule and providing valuable suggestions for revision. I have benefited greatly from your insights.

The following are the responses to your revisions.

1):**The current version of the manuscript did not thoroughly analyze the literature and develop novel themes. Nor did the authors point out the problems and offer any specific solutions. Instead, the authors blended the facts from different sources without defining the boundaries of scientific terminology. For example, The authors did not take up the peer-reviewer critiques to revise their title: "How to enhance the ability of mesenchymal stem cells to alleviate intervertebral disc degeneration," to reflect their content.**

My answer: The main purpose of this film review is to summarize the experience of our predecessors, to provide some references for our colleagues who are currently doing basic research, and to summarize the current status of stem cell therapy for intervertebral discs, as well as what other limitations we still need to break through, and we need to think accordingly based on this. After the last revision, I have followed the last revision to change the title to "How to enhance the ability of mesenchymal stem cells to alleviate intervertebral disc degeneration ".

2):**Another example of blended facts in a compound concept is "MSCs," as reviewer 1 specifically pointed out: "2-Despite similar phenotypes and the common mechanisms of tissue regeneration, the source of MSCs can play a crucial role in their therapeutic effects. Studies have shown that diversity in the microenvironment of MSCs and, subsequently, the expression of different genes lead to differences in their function and behavior. So, it has been suggested that tissue-matched MSCs may increase the efficacy of their regenerative effects."**

My answer: It is true that stem cells from different sources have effects that are not entirely consistent. According to the last revision, I need to make a brief explanation in the text. I have made the changes in the text, which are in the INTRODUCTION on page four. "Mesenchymal stem cells (MSCs), a class of pluripotent stem cells with the capacity for self-renewal and the ability to differentiate into a variety of tissues in vitro, were first mentioned in 1970 in guinea pig bone marrow[2]. Isolation and culture of MSCs from human bone marrow was first described in 1992. Since then, MSCs have been isolated and cultured from different human tissues, such as fat, amniotic membrane, gingiva, thymus, and placenta. MSCs from different sources differ in phenotype and function[3], for example, in solving the problem of intervertebral disc (ID) withdrawal, umbilical cord-derived MSCs have a greater capacity for cell proliferation and osteogenesis than bone marrow-derived MSCs[4]"

3):**No specific connection was found between the text and the abstract: e.g., "The current aim of stem cell therapy is to replace the aged and metamorphosed cells in the ID and to increase the content of the extracellular matrix" (Abstract) did not connect to**

the main text. The second example: "The treatment of disc degeneration with stem cells has achieved good efficacy, with an efficacy rate of almost 70%, and the current challenge is how to improve this efficacy" (abstract), did NOT flow into deeply elaborating the statement in the main text. Third example: "Here, we reviewed current treatments for disc degeneration and summarize studies on stem cell vesicles, enhancement of therapeutic effects when stem cells are mixed with related substances, and improvements in the efficacy of stem cell therapy by adjuvants under adverse conditions (abstract)." What did they mean "enhancement of effects?" How much did the authors enhance from 70% to what percentage of effects? Any follow-up elaboration? Fourth example: "The new approaches and ideas for stem cell treatment of disc degeneration" – How did the authors define "new approaches?"

My answer: I sincerely thank you, Editor-in-Chief, for your suggestions.

1,It may be that I did not explicitly address stem cell therapies in a specific natural paragraph alone. However, there are many other references to stem cells' ability to reduce inflammation (i.e., reduce pain) by inhibiting the senescence of nucleus pulposus cells in the intervertebral discs and increasing the ECM content (e.g., exosomes from stem cells can inhibit the expression of matrix metalloproteinases, which promotes nucleus pulposus cell proliferation and maintains the extracellular matrix homeostasis as mentioned in the text), for example, in the first natural paragraph on page 6, the second natural paragraph on page 7, and so on. etc.

2-3, Regarding the editor's question about how much I was able to increase the effectiveness of this treatment, I was unable to get an accurate figure to explain to the editor. What I want to express in the article is that there are studies that show that stem cell therapy for intervertebral discs can be up to 70% effective, but this figure is also to be considered because this article is a micro-mini synthesis, so there is no experimental study. There should be a problem with my expression here, so I have revised the paragraph accordingly.

4,Regarding the editor-in-chief's question about how I define new methods and new ideas, because this micro-mini review is a summary of previous researchers' relevant links between stem cells and intervertebral disc degeneration, I have roughly divided my new methods and new ideas for stem cell treatment of intervertebral discs into the following two points: 1) At present, we need to achieve a stable efficacy of existing stem cell treatment of intervertebral discs.2) On the basis of the existing foundation, we need to start from the stem cell's stability, source, carrier delivery of stem cells, and delivery method of stem cells to further enhance the therapeutic effect. Regarding the issues raised by the editor-in-chief, I have revised the article accordingly.

4): **Neither logical nor scientific: "Intervertebral discs (IDs) have a complex structure with a unique internal environment. They contain nucleus pulposus cells, fibrous rings, and extracellular matrix (ECM)[1-4], which are in a dynamic balance of self-renewal." How did such elements in a dynamic balance of self-renewal? [Introduction].**

My answer: Thanks to the editor-in-chief for pointing out the error, the disc structure

should not be in a state of dynamic self-equilibrium. I think the point I need to make is that intervertebral discs have nucleus pulposus cells, annulus fibrosus and ECM, but as the nucleus pulposus cells age and the ECM is lost, it is very difficult to regenerate these substances, and mesenchymal stem cell therapies are needed to improve the symptoms of intervertebral disc degeneration. This is why we insist on researching the purpose and significance of stem cell therapy for disc degeneration. I have revised the text accordingly.

5): **The authors did not give any transition and jumped into "this balance of secreting exosomes and vesicles, mixing other substances to promote their differentiation into nucleus pulposus cells." If IDs can be in a dynamic balance of self-renewal, why bother doing these?**

My answer: In the previous question, I incorrectly described the disc structure as being in a state of dynamic self-equilibrium (I have made the appropriate changes in the text), and thus misled the editor-in-chief. As for why I talked about "metabolites and MSCs, gel-loaded MSCs, cyclic RNA and exosomes", I have already mentioned in the abstract the general idea of what this article is going to be about. Therefore, in the subsequent introduction, there is no specific link between paragraphs and the content is described according to the sections in the abstract.

6) **Again, the authors jumped starting "METABOLITES AND MSCS, " " gel-loaded MSCS," or "GEL-LOADED MSCS" or "CIRCULAR RNA AND EXOSOMES" or "MSC MIXTURE" or "STIMULATION INDUCTION WITH MSCS" – backtracked to "HARSH ENVIRONMENT OF THE ID." None of these sections came with setting up, unfolding, and conclusion, but randomly crawling around different concepts.**

My answer: Thank you to the editor-in-chief for raising the issue that I didn't do too much articulation between paragraphs because I presented a few sections in the abstract that this article is mainly about. I have revised it accordingly in the INTRODUCTION. There are various ways for MSCs to treat disc degeneration, for example, the metabolites of stem cells are inextricably linked to the disc structure, the vesicles of MSCs can play a corresponding role to repair the degenerated disc, the ability of MSCs to treat disc degeneration can be enhanced by the corresponding gel carriers, and the directional differentiation of MSCs can be induced by certain stimuli. It can also enhance the therapeutic effect of MSCs by improving or resisting the adverse environment in which the intervertebral discs are located, thereby achieving the therapeutic effect of intervertebral disc degeneration.

7):**"FUTURE DIRECTIONS FOR STEM-CELL-BASED THERAPY" did not envision anything novel but regurgitating what was said before. So, in its conclusion.**

My answer:In this review, the main thing I want to express is to summarize the research progress of my predecessors about MSC and IDD, and summarize the experience of my predecessors. After I synthesize the content of my and article, I think in detail about the new thinking about MSC and IDD. I've revised the conclusion of my mini-review in accordingly.

8), **Neither Figure 1 nor Figure 2 offer any specific information concerning the topic, as it was too superficial and generic, not as expected from the expert's review.**
My answer:I sincerely thank the editor-in-chief for his valuable comments. I have revised my two Figures appropriately.

9). **Many grammar errors crawled across the pages to obscure its logic. E.g., "Here, we reviewed current treatments for disc degeneration and summarize studies on stem cell vesicles, enhancement of therapeutic effects when stem cells are mixed with related substances, and improvements in the efficacy of stem cell therapy by adjuvants under adverse conditions (abstract)."**
Thank you for raising the errors, I have revised the issues you raised accordingly, I have touched up the language of this article twice (by the journal's recommended touch-up agency), and in addition, I have sent the proof of touch-up report to the editorial board along with it.
These are my responses to the questions you posed, and again, thank you for reading my mini-roundup on your busy schedule. I would like to thank you again for reading my mini review in your busy schedule.

Yours ·

Min Cui

Dear Editor-in-Chief: Hello!

First of all, I would like to thank you for reviewing our manuscript in your busy schedule and providing valuable suggestions for revision. I have benefited greatly from your insightful comments.

The following is my response to your comments.1.For instance, at page 6, "The combination of heat-sensitive decellularized ECM hydrogels with adipocyte-derived MSC exosomes does not damage the therapeutic activity of MSCs. The heat-sensitive dECM@exo hydrogel system produces gelation in situ to help MSCs differentiate into nucleus pulposus cells and maintains the content of ECM. This hydrogel also creates a suitable environment for the proliferation and differentiation of nucleus pulposus cell [22]". The cited reference "Pretreatment of nucleus pulposus mesenchymal stem cells with appropriate concentration of H(2)O(2) enhances their ability to treat intervertebral disc degeneration. Stem Cell Res Ther 2022; 13: 340 [PMID: 35883157 DOI: 10.1186/s13287-022-03031-7]" only reports the use of hydrogels in the introduction section, but the study per se is not meant to assess the hydrogel effect on the investigated context. Nevertheless, the paper reported in the Minireview as reference [22] cites in its introduction section two papers (refs, 21 and 22: 21. Xing H, et al. Injectable exosome - functionalized extracellular matrix hydrogel for metabolism balance and pyroptosis regulation in interverte - bral disc degeneration. J Nanobiotechnol. 2021;19(1):264. https://doi.org/ 10.1186/s12951 - 021 - 00991 - 5. 22. Zeng Y, et al. Injectable microcryogels reinforced alginate encapsulation of mesenchymal stromal cells for leak - proof delivery and alleviation of canine disc degeneration. Biomaterials. 2015;59:53–65. https://doi.org/10. 1016/j.biomaterials.2015.04.029.). These references are more appropriate to be cited in this Minireview with regard to the hydrogel effect.

My answer: Thank you for pointing out the error, I have cited the appropriate literature in the corresponding places in the text.

2. Similarly, by reading ref 23 cited in the minireview (Hu Y, Tao R, Wang L, Chen L, Lin Z, Panayi AC, Xue H, Li H, Xiong L, Liu G. Exosomes Derived from Bone Mesenchymal Stem Cells Alleviate Compression-Induced Nucleus Pulposus Cell Apoptosis by Inhibiting Oxidative Stress. Oxid Med Cell Longev 2021; 2021: 2310025), I couldn't find any explicit experiment done with hyaluronic acid and platelet-rich hydrogels, nor any clear result on keratin gene expression as it is instead reported in the Minireview (page 6). Some more appropriate Reference supporting this statement should be cited in the Minireview.

My answer: Thank you for pointing out the error, I have cited the appropriate literature to support my claim where appropriate.

3. At page 8, please correct miRNA-cahama into miRNA-199a! Again at page 8,

“Similarly, the combination of MSCs with in situ bioresorbable gel (dMD-001) produced the above therapeutic effects in IDD and was used after discectomy to prevent IDD.

My answer: Thank you for pointing out the error, I have corrected the error here and I have cited the appropriate literature at " Similarly, the combination of MSCs with in situ bioresorbable gel (dMD-001) produced the above therapeutic effects in IDD and was used after discectomy to prevent IDD ".

4. Similarly, when MSCs are combined with coenzyme Q10 for the treatment of most ID lesions, it reduces oxidative stress in the ID, inhibits degradation of nucleus pulposus cells, and steadily improves the efficacy of IDD treatment”. These sentences don’t report any reference in support! (These issues are not part of the study quoted as Ref 37 in the Minireview). Please, clarify and add specific related references. At page 11, please correct methanipine cross-linked into genipin-cross-linked.

My answer:Thank you for pointing out the error, I have added the appropriate reference at " Similarly,when MSCs are combined with coenzyme Q10 for the treatment of most ID lesions, it reduces oxidative stress in the ID, inhibits degradation of nucleus pulposus cells, and steadily improves the efficacy of IDD treatment". And I have corrected methanipine cross-linked into genipin-cross-linked on page 11.

Yours ·

Min Cui