



PEER-REVIEW REPORT

Name of journal: *World Journal of Stem Cells*

Manuscript NO: 83533

Title: Role of the Bone Marrow Microenvironment and Mesenchymal stem cells in the progression of Multiple Myeloma.

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 02446101

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Professor, Surgeon

Reviewer's Country/Territory: China

Author's Country/Territory: Spain

Manuscript submission date: 2023-01-29

Reviewer chosen by: AI Technique

Reviewer accepted review: 2023-01-30 00:20

Reviewer performed review: 2023-01-30 01:05

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
Creativity or innovation of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair



	<input type="checkbox"/> Grade D: No creativity or innovation
Scientific significance of the conclusion in this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input type="checkbox"/> Anonymous <input checked="" type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

In this manuscript, the role of the bone marrow microenvironment and mesenchymal stem cells in the progression of multiple myeloma was discussed. It's a well-written manuscript and does give a detailed description of the major advances in this research direction, which is helpful to readers. However, there's still one issue which should be addressed. 1. A table of the key references (year, authors, conclusion, etc) should be provided. So, acceptance after minor revision should be recommended for this manuscript.

We are glad to hear that this reviewer thought that our manuscript was “well written” and that “it gives a detailed description of the major advances in this research direction”. We also thank the reviewer for his/her comment that we have addressed introducing two tables (Table 1 and Table 2) of the key references as suggested by the reviewer.



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Reviewer's code: 03079551

Position: Peer Reviewer

Academic degree:

Professional title:

Reviewer's Country/Territory: Reviewer_Country

Author's Country/Territory: Spain

Manuscript submission date: 2023-01-29

Reviewer chosen by: AI Technique

Reviewer accepted review: 2023-01-31 02:39

Reviewer performed review: 2023-02-08 13:59

Review time: 8 Days and 11 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
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Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The authors reviewed the interaction between MM cells and the bone marrow microenvironment, and specifically bone marrow mesenchymal stem cells (BM-MSCs), which has a key role in the pathophysiology of Multiple Myeloma (MM). This article expounds the therapeutic potential of two-way communication and two-way regulation between MM cells and BM-MSCs in the progression of MM from three aspects, providing new ideas for clinical treatment. The article had specific clinical research value. However, the article's content was insufficient, and many substantive problems need to be solved. My detailed comments are as follows: If the article is written according to the PRISMA 2009 Checklist, please provide the completed checklist and write the article according to the list. Abstract The abstract should summarize the full text in concise and standard language, please modify the expression. INTRODUCTION The introduction should include the epidemiological status of MM, the status of clinical medication and the limitations of existing treatment. Simplify the language in the introduction. Part of the content can be discussed in the discussion section. SOLUBLE FACTORS IN THE



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7041 Koll Center Parkway, Suite
160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

COMMUNICATION BETWEEN BM-MSCs AND MM CELLS. It is suggested to arrange the paragraphs reasonably or discuss the contents in sub-sections. Enhance the logical association between paragraphs, or use tables to assist in expression. A summary should be added at the end of this section to briefly review the contents of the previous article to lead to the following. EXTRACELLULAR VESICLES-MEDIATED COMMUNICATION BETWEEN BM-MSCs AND MM CELLS. It is suggested to increase the connection between paragraphs. It is suggested to briefly summarize the two-way communication mechanism and what kind of key role it has played. DISCUSSION The discussion is not deep enough. Figure Please provide high-definition pictures

We deeply thank the reviewer for his/her comments that, we hope, have allowed us to increase the quality of our work. We have introduced several changes in our manuscript following the reviewer's indications, trying to overall clarify the structure by introducing subsections and enhance the connection between paragraphs of each of the sections. Hopefully we have achieved more clarity and fluidity in our manuscript in particular in the sections *SOLUBLE FACTORS IN THE COMMUNICATION BETWEEN BM-MSCs AND MM CELLS* and *EXTRACELLULAR VESICLES-MEDIATED COMMUNICATION BETWEEN BM-MSCs AND MM CELLS*.

Regarding the abstract, we absolutely agree with the reviewer that the abstract of our first version did not accurately reflect the contents of the manuscript as we failed to mention the different ways of cell-to-cell communication that are the main focus of our work. We have now added this information and re-write part of the abstract.

As indicated by the reviewer, we have introduced a large paragraph in the introduction that explains the current epidemiological status of MM, current treatments, and their limitations as well as the relevant references.

The comment of the reviewer about the Prisma Checklist prompted us to re-evaluate the



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characteristics of our work. In terms of the type of review we are presenting and the use of the PRISMA Checklist, we were not sure that our work would fit the category of systematic review. We have actually used a guide provided by Temple University that intends to identify what type of literature review methodology should be followed depending on the questions we want to answer (<https://guides.temple.edu/c.php?g=78618&p=4178713>). Using the tool provided by this website, we would not be able to catalog our work as a Systematic Review as we are dealing with a broad question, named the relevance of the different types of communication between Mesenchymal stem cells and multiple myeloma cells. So, we have eliminated the paragraph referring to the Prisma Checklist. We believe that introducing this paragraph in the first version of the manuscript was an honest mistake that we have corrected on reflection. .

Regarding the quality of the figure, we have increased the resolution from 300 DPI to 600 DPI. A good quality picture can be found now in figure 1. We apologize for not having done so in the first version of our manuscript.



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Reviewer's code: 05246699

Position: Peer Reviewer

Academic degree: MSc, PhD

Professional title: Academic Research, Chief Physician

Reviewer's Country/Territory: Iran

Author's Country/Territory: Spain

Manuscript submission date: 2023-01-29

Reviewer chosen by: AI Technique

Reviewer accepted review: 2023-01-29 21:49

Reviewer performed review: 2023-02-16 01:09

Review time: 17 Days and 3 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
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	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The manuscript entitled "Role of the Bone Marrow Microenvironment and Mesenchymal stem cells in the progression of Multiple Myeloma" appears to be interesting, but there are many flaws and concerns in it. Study can be greatly improved if following suggestions are incorporated. 1. Title: the title is not appropriate. I suggest making it up. 2. Some references are missing. For example, "A key characteristic of MM is the infiltration into and the colonization of the BM, one of the two primary lymphoid organs."; "The bone lesions, resulting from the stimulation of bone resorption by B-cell plasmacytomas, are associated with hypercalcemia and often, severe bone pain and bone fractures." ; "While the initiation of a tumor mainly depends on the accumulation of genetic defects, the transition from a premalignant to a malignant state highly relies on the interaction of the tumor cell with a permissive microenvironment that would support the malignant transformation and the proliferation of the tumor cells, aiding them to evade apoptosis." 3. In order to make the paper more interesting to read, I suggested that the authors could add one graphical abstract to the manuscript. 4. In order to make the paper more interesting to read,



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I suggested that the authors could also add several figures and tables to the manuscript. 5. I suggest including clear limitations of the present study in the discussion.

We thank the reviewer for his/helpful suggestions.

1. We agree with the reviewer that, in hindsight, the previous titles did not fully reflect the contents of our work. We have changed this title that, we believe, now better reflects the different sections of the manuscript.
2. We also agree that although the unreferenced sentences mentioned by the reviewer mention common features of tumor (seed and soil theory) or known characteristics of Multiple Myeloma (osteolytic lesions), it is necessary to introduce adequate references to these statements. We have added new references where these features are described in depth.
- 3-4.- Although we have found difficult to clearly summarize of the information contained in the review in a graphical abstract, following the reviewer's suggestion, we have added an additional figure (Figure 2) feature the main cell adhesion molecules involved in cell-to-cell interaction in Multiple Myeloma. This figure will also serve as a recap of the second section of the manuscript. In addition, we have also added two tables summarizing the works with the main evidence regarding multiple myeloma an Bone marrow Mesenchymal stem cells are reflected.
5. We have added a sentence about the study limitations at the end of the discussion section.