

Response to referees

Dear editor,

We thank you and your referees for the valuable and helpful contribution to our paper. Your advices have helped us to improve the general quality of our work.

We hope to have made the necessary corrections following the advices of each reviewer and we remain open to further advice.

Below we report the point-by-point answers. All corrections realised to the manuscript have been highlighted in red.

Sincerely.

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Response to Referee 1

Aim of the present review is to evaluate the roles of the three alarmins HMGB1, IL33 and S100B in the pathogenesis of OA. These objectives of the review have been obtained through the exhaustive examination of the literature, a very useful insert of the experiments in the tables, very clear figures and language, resulting a very useful paper for the researchers on the field of OA.

Response: Thank you for your precious comments. We are glad that our work can contribute to increase knowledge in the field of OA and we hope that it could open up new insights for the future.

Response to Referee 2

Please clarify at Aim of the study that why HMGB1, S100B and IL-33 alarmins from the other alarmin proteins were chosen for this review.

Response: We agree with your suggestion. We have now specified that the considering number of papers published about the relationships between these three alarmins and osteoarthritis, and a general coherence of their results were source of inspiration of this paper.

Response to Referee 3

I have the following remarks:

L31 Please add: chondrocyte and osteocyte formation. Is angiogenesis really a characteristic? Please reconsider

Adapted

L41 Prevalence of processes is incorrect. Please adapt

Adapted

L59 Patterns instead of pattern. PAMPs is plural

Adapted

L69 the cell. please add 'the'

Adapted

L71 cell release instead of releasing

Adapted

L74 it chemoattracts

Adapted

L108 ST2V is expressed in the

Adapted

L126 The aims of the study (a) to (e) are not clearly followed in the text. Please clarify the text accordingly or adapt the definition of the aims.

Response: Thank you for your comment. We have now specified our conclusions about each aim. In particular, we have remarked that HMGB1 seems to be not only a biomarker of OA, but also a severity index of its clinical and radiological features; however further evidence is needed to clarify the possibility of a future use in clinical practise. Finally, we assume that treatment against HMGB1, like intra-articular injections of mAb, could be a future promising treatment option, partially interfering with the pathogenesis of the disease.

L130-132. Please rephrase

Rephrased

L134 performed instead of effectuated

Adapted

L137 arguments of the study meaning??? Please rephrase

Adapted

L141 Results and discussion. There is considerable overlap and redundancy between the text and tables. Please condense to improve readability

Response: We agree with the topic. In fact, we have reduced the lists of mediators within the text only indicating the category (interleukins, chemokines and degradative enzymes).

L201 it is plausible to speculate....? Recruitment of CPC into a damaged ECM with apoptic or necrotic chondrocyte is a very unlikely event. Please adapt accordingly

Adapted

L209 please include ligaments and menisci

Adapted

L218 demonstrated instead of explained

Adapted

L280 has confirmed an improvement activity? Please rephrase

Rephrased

L317 Hyperbaric oxygen (HBO) therapy. Please adapt for readability

Adapted

L336 Kellgren-Lawrence (KL)

Adapted

L366 Various instead of Diverse

Adapted

L389 starts instead of gets starts to

Adapted

L462-463 IL-33 increases mRNA levels of IL-33? Autostimulation? Please explain or adapt

Response: We appreciate your helpful advice. We have now highlighted that the scholars of the cited paper have found an auto-stimulation effect on IL-33 incubated NHAC, further confirmed by decreased synthesis of its mRNA levels in NHAC incubated with ST2 blocking antibody, an IL-33 receptor.

L474 researchers instead of scholars?

Adapted

L497 Study of Hong [92] is concerned with rheumatoid arthritis not OA. Hence the difference?

Response: We thank you for your profitable advice. In the figure 1a of the cited study, the researchers have compared IL-33 and sST2 levels in sera of healthy patients with those affected by OA and RA. The result is aligned with the topic of the paper and in contrast with the previous cited work in my paper.

L544 receptor instead of receptors

Adapted

L672-683 This section seems completely disconnected from the aims of the study and alarmins & OA data presented. Please address this to bring the conclusion section in line with your study aims

Rephrased

L690 There is HMGB1/miRNA axes. If you mean axes in plural, a proposal could be: There are severalaxes influencing OA initiation and progression

Adapted

Comments on the Quality of English Language

Please see my previous remarks

Response to Referee 4

excellent review, with details, well - presented to the reader with figures, tables and fluent use of english.

I have noticed some references that according to my opinion should be replaced in the text. For example line 365. I found very interesting this particular information, regarding the potential effect of bleeding in the cascade of inflammation in the joint. However, the paper that corresponds to reference 87, is not referring in bleeding situation but to an experiment of basic science. As written in your article, your opinion (or your conclusion, if you want) that is not incorrect of course, should not be presented as the main idea of the reference number 87. Therefore, replacement of the reference a few lines above, would be better and the reader will not be confused.

Response: We agree and thank you for the advice, so we have replaced the reference number above our opinion.