Author's response to reviews

Title: Causes and consequences of coagulation activation in sepsis: an evolutionary medicine perspective

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Author's response to reviews: see over
To
Drs. Martin Brüne and Ze'ev Hochberg
Guest editors
Evolutionary Medicine series
BMC Medicine

Dear Editors,

Please find attached the revised version of our manuscript entitled “Causes and consequences of coagulation activation in sepsis: an evolutionary medicine perspective” that was modified according to the reviewers and editors comments. The article was submitted for publication at BMC Medicine, in the Special Series dedicated to Evolutionary Medicine.

First, we thank the reviewers and editors for the positive comments and for the chance to improve our manuscript. All suggestions have been addressed and incorporated in the manuscript, which is much improved in our opinion These changes are detailed in our point-by-point response below, and are highlighted in red in the revised version.

Point-by-point response

Overall comments by the editors

All suggestions from reviewer 2 (M.G.) were incorporated, as detailed below. Importantly, a more balanced tone was included in the whole manuscript, highlighting the evidence that support that coagulation activation could represent a mechanism of tissue damage in sepsis. In fact, it was not our intention to refute this idea, since we believe that the level of coagulation activation is sepsis represents a continuum, in which lower levels can be beneficial, but extreme levels could be detrimental. The comment from reviewer 2 was important to show us that we needed to make this view clearer for the reader, and we believe that we have achieved this in the revised version (please see the point by point response to reviewer 1 for details).

We also included the suggested table and figure. As stated in the response to reviewer 2, Table 1 represents a comprehensive and original review of all animal model data
published so far, about the effect of coagulation factor deficiencies in pathogen clearance and sepsis severity, and we believe that it should be included in the main body of the manuscript. We would like to highlight that this table has become one of the most important pieces of information of this manuscript in our opinion, since such summary is not available anywhere in the literature to our knowledge. In regard to the figure, we tried to express the main message of the manuscript, and we hope that we have achieved this. The figure was prepared by me in Corel Draw, and I can change it if necessary.

Finally, we were asked to change our manuscript format to an “Opinion” article. We agree with the editors that this could be a more suitable format for this manuscript, and changed it accordingly: (i) the original abstract was changed for a structured version and, (ii) the main text was divided in the following sections: Background, Discussion (which was subdivided in different subsections), and Summary. On the other hand, the main strength of the manuscript in our view is the comprehensive and cross-disciplinary approach to the issue of coagulation and immune defense. This approach resulted in a very comprehensive and update review, which got even more detailed after the addition of data in Table 1, requested by one of the reviewers. With the more balanced view introduced in the revised version, the relative weight of our opinion over factual data decreased a lot, and we believe that the paper could also be presented as a narrative review. We leave this decision up to the editors, but we respectfully ask them to either reconsider it a narrative review (for the reasons mentioned above). Or else, in case they maintain the decision for an Opinion article, please waive us from the need to reduce it to 3000 words. This would require a major shift in our approach to the theme, and eliminate the main strengths of the manuscript (including Table 1, added upon request from a reviewer). We did our best to eliminate redundant parts of the manuscript, and we kindly ask the editors to allow a text with the length of a review, even if it is to be published as an opinion article. Since table 1 is quite long, we are sending two versions of the main manuscript, one with table 1 added to the main manuscript (our preferred version), and one with table 1 separated, as a supplementary file. Let us know if you need any additional change.

Reviewer #1 (M.B.):
We thank the reviewer for the positive comments. There were no specific issues to be addressed.

Reviewer #2 (M.G.):

We agree with the reviewer about the importance of balancing the content of the article, by discussing *in vivo* data demonstrating that microcirculatory changes observed in patients with sepsis can be reversed by the use of activated protein C, and by data from systematic reviews, meta-analysis and even more recent clinical trials, suggesting that anticoagulant can be beneficial to a subgroup of patients with sepsis. In fact, it was our opinion to provide this balanced view, rather than suggest that hemostasis has no detrimental effects in sepsis, and we thank the reviewer for pointing out the need to improve this aspect of our manuscript. We did our best to incorporate this balanced view, by the following changes:

1) A new paragraph was introduced in the subsection “Why coagulation is activated during sepsis”, addressing the data that contradict our main thesis, and suggest that coagulation activation can indeed be responsible for tissue damage in sepsis. In this paragraph, the paper by Donati et al, that shows that aPC can reverse microvascular perfusion deficits in sepsis was included, as well papers that contradict the results of randomized clinical trials with anticoagulants in sepsis. In the end of this paragraph, we state that these results suggest that a threshold might exist above which coagulation activation turns from a beneficial to a detrimental response in sepsis. This is in line with the suggestion of the reviewer, with which we fully agree, that “the key is perhaps the correct identification of the pathophysiological moment of the septic patient.”

“While the laboratory and clinical evidence presented so far point to a beneficial role of coagulation activation during sepsis, new evidence supporting the classical paradigm that coagulation activation can contribute to tissue damage in sepsis has also been published. *In vivo* microvascular imaging studies demonstrated disturbances of tissue perfusion in patients with sepsis, which could be reverted by the use of the anticoagulant activated protein C (De Backer et al, Crit Care Med 2006; Donati et al, BMC Anesthesiology 2013). In addition, the negative results of randomized clinical trials of anticoagulant agents in sepsis have been challenged by recent systematic reviews and clinical trials (Kalil et al, Lancet Infec Dis 2012; Iba et al, Crit Care 2014) suggesting a beneficial effect of this treatment strategy in subgroups of patients with sepsis. If confirmed (in ongoing clinical trials and in larger meta-analysis (Jiang et al, BMJ 2014), these results point to the existence of
a threshold, above which coagulation activation becomes detrimental during sepsis.”

2) This more balanced view of the whole process was further highlighted in “Summary”, by addition of the following statement (in red) to the original text:

“The analysis of coagulation activation during sepsis from this evolutionary medicine perspective could also contribute to the explanation of why the use of systemic anticoagulants were not beneficial in large-scale trials in sepsis, highlighting the importance of identifying the precise moment in which coagulation activation turns from a beneficial to a detrimental process in sepsis.”

3) In the subsection “Classical view of coagulation activation in sepsis”, a new sentence (in red) was added to the original text to highlight that there is ongoing debate about the potential beneficial role of anticoagulant agents in a subset of sepsis patients. An ongoing meta-analysis based on this very fact is cited.

“Based on this model, ambitious clinical development programs of recombinant natural anticoagulants (antithrombin, TFPI and rhaPC) in patients with sepsis were launched, going all the way to phase 3 trials and, in one case, market approval. Unfortunately, the benefits of this strategy could not be confirmed in these trials, although additional clinical trials and meta-analysis are warranted before a definite conclusion on this issue can be reached (Jiang et al, BMJ 2014).”

4) A sentence supporting this more balanced view was added to the abstract:

“(…) In this article we discuss recent basic and clinical data that point to a more balanced view of the detrimental and beneficial consequences of coagulation activation in sepsis.”

5) A few isolated words were also changed in the text, for a more balanced view (highlighted in red in the revised version)

- The reviewer also suggested a table summarizing the results of animal studies supporting that coagulation activation can be beneficial during experimental sepsis or other infectious challenges. We followed this suggestion and added Table 1 to the revised manuscript. Besides describing the original description of each animal model, we also indicate the potential effect of each genetic alteration (in general, gene knockouts) in thrombin generation and/or clot strength. This allows the reader to correlate the hemostatic phenotype of each animal model with the results of pathogen clearance and sepsis severity. The result was a very comprehensive review of studies summarized in Table 1, which in our opinion represents by itself a very important piece of information of our manuscript. We did not find any such
review in the literature, and we believe that this suggestion improved a lot the manuscript. The table is referred to in the section that discusses the evidence that support the concept that coagulation activation is an important part of the host response to an infection “Why is coagulation activated during sepsis”.

See table 1 in the revised manuscript.

• Finally, the reviewer suggests that a figure illustrating the main concepts of the manuscript is added to the text. We agree with the suggestion, and included Figure 1, which summarizes the main aspects of our review. The figure is referred to in the Summary section of the manuscript.

See Figure 1 in the revised manuscript.

The manuscript has been reviewed and approved by all named authors. The corresponding author is empowered by all of the authors to act on their behalf with respect to submission of the manuscript. This article is original and does not infringe upon any copyright.

Sincerely yours,

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