

AUTHORS' RESPONSES TO THE REVIEWERS' COMMENTS

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Etanercept-synthesizing adipose-derived stem cell secretome: A promising therapeutic option
for inflammatory bowel disease

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We thank the reviewers and the associate editor very much for their insightful and valuable comments. We believe that *International Journal of Molecular Sciences* is appropriate for our manuscript that we intend to be a practical paper that is helpful for future clinical applications. In this document, we quote the reviewers' comments in **bold type**; our replies follow in regular lettering. Moreover, we corrected a few minor improper expressions and grammatical errors that are not specifically mentioned here; we hope that this is acceptable.

Specific Comments to Authors: The authors have successfully demonstrated promising results with adipose-derived stem cell-derived Etanercept-secretome, in the setting of IBD, trying this on CCD-18Co colon cell line and in DSS induced mouse model. While doing this the authors have not indicated about lack of benefit with etanercept in IBD as shown in many studies. (Ref quoted 13 use TNF α inhibitors, but not etanercept). When etanercept is not beneficial in IBD, to expect benefit with Etanercept- secretome in IBD is an interesting concept.

It remains to be proven whether the secretome will really help in IBD, though the immunomodulatory effect has been well demonstrated. It is also not indicated that Etanercept can induce IBD when used to treat other autoimmune conditions like psoriasis. The role of secretome in IBD pathogenesis is not touched upon.

RESPONSE) Thank you for your insightful comments. We recognize the essential observations highlighted by the reviewer, notably the yet unvalidated therapeutic efficacy of Etanercept in IBD and its reported instances of inducing IBD in the treatment of autoimmune diseases such as psoriasis. Despite these challenges, our approach is fundamentally grounded in the distinctive properties of ASCs and their secretome. ASCs are well known for their remarkable anti-inflammatory and immunomodulatory attributes, as well as their capacity to secrete a broad spectrum of bioactive molecules. These molecules, encompassing cytokines, growth factors, and extracellular vesicles, play a crucial role in modulating immune responses and facilitating tissue regeneration. Et-Sec represents the secretome of ASCs, specifically engineered to produce etanercept, with its principal component being the augmented ASC secretome, not etanercept, hypothesizing a synergistic effect that could more effectively

tackle the intricate pathophysiology of IBD than Etanercept alone. While etanercept targets TNF α directly, the ASC secretome can modulate multiple inflammatory pathways and cellular interactions. Thus, this approach aims to provide a more comprehensive modulation of the inflammatory milieu characteristic of IBD, potentially leading to improved therapeutic outcomes. Moreover, the ASC secretome's role in tissue repair and regeneration could offer additional benefits in IBD treatment. The chronic inflammation in IBD often leads to tissue damage, and the regenerative properties of the ASC secretome could play a crucial role in healing and restoring the integrity of the intestinal mucosa.

In response to the valuable insights provided by the reviewer, we have incorporated the following paragraph into the revised manuscript; The therapeutic efficacy of Etanercept in IBD has been a subject of debate, with evidence suggesting its potential to induce IBD in the treatment of other autoimmune conditions such as psoriasis [21, 22]. However, it is important to differentiate between the effects of Etanercept alone and ASC-derived Et-Sec. ASCs are renowned for their anti-inflammatory and immunomodulatory properties, further enhanced by their secretion of a wide array of bioactive molecules, including cytokines, growth factors, and extracellular vesicles. These molecules play a crucial role in regulating immune responses and facilitating tissue regeneration. Et-Sec represents the secretome of ASCs, specifically engineered to produce etanercept, with its principal component being the augmented ASC secretome, not etanercept, hypothesizing a synergistic effect that could more effectively tackle the intricate pathophysiology of IBD than Etanercept alone (Fig. 5). While etanercept targets TNF α directly, the ASC secretome can modulate multiple inflammatory pathways and cellular interactions. This approach not only targets TNF α directly but also modulates multiple inflammatory pathways and cellular interactions, offering a

comprehensive modulation of the inflammatory environment characteristic of IBD. Furthermore, the role of the ASC secretome in tissue repair and regeneration may provide additional therapeutic benefits in IBD treatment, particularly in managing chronic inflammation-induced tissue damage and promoting the healing and restoration of intestinal mucosa integrity.

Once again, we thank you for your response and hope we have been thorough in answering your comments. Your comments have aided us immensely in improving our manuscript. We hope our revision is satisfactory to your high standards and we readily await your next feedback.

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