Bangabandhu Sheikh Mujib Medical University Journal 2025;18(2):e79761
ISSN 2074-2908 | eISSN 2224-7750 |

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Review report

Final title: When leaders fail: Exploring the role of dysfunctional leader cells in autoimmune disease pathogenesis

Title at submission: When leaders fail: Exploring the role of dysfunctional leader cells in autoimmune disease pathogenesis

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Publication history
Received: 8 Feb 2025
Accepted: 3 June 2025
Published online: 16 June 2025

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Keywords
leader cell, autoimmune disorders, dysfunction

Funding
None

Ethical approval
Not applicable

Trial registration number
Not applicable

Declaration
Not applicable

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Published by Bangabandhu Sheikh Mujib Medical University (currently, Bangladesh Medical University).

Reviewer: Chandan Kumar Roy, ORCID: 0000-0003-1679-9454

1 Comment There may be a potential link between leader cell dysfunction and autoimmune diseases, and by elucidating the role of leader cells in immune regulation, this may help uncover new therapeutic targets and strategies for managing autoimmune disorders. Recommendation: Accept Submission.

Response We thank the reviewer for their positive assessment and agreement with the potential significance of the proposed hypothesis.

Reviewer: Sheuly Ferdoushi, ORCID: 0009-0009-4037-3833

2 Comment Provide a brief or clear pathogenesis or mechanism of leader cells inducing autoimmune disease.

Response Thank you for this suggestion. We have expanded the second paragraph (now titled "Pathogenesis Mechanisms") to elaborate on the potential mechanisms. This includes detailing how dysfunctional leader cells might lead to aberrant tissue repair, chronic inflammation, DAMP release, exposure of self-antigens, and altered immune communication (e.g., via cytokines/exosomes), thereby contributing to the breakdown of self-tolerance.

3 Comment In this commentary, the author discusses the leader cell dysfunction in type 1 DM. Instead of this writing, the author should have explained what occurs when leader cell dysfunction occurs in various autoimmune diseases.

Response We appreciate this point. While Type 1 Diabetes was used as an initial example, we have now broadened the discussion in the "Pathogenesis Mechanisms" paragraph to include potential implications in other autoimmune-prone tissues, specifically mentioning the gut (relevant to inflammatory bowel diseases) and the skin (relevant to conditions like psoriasis), citing relevant concepts and references [7, 8, 9, 10].

4 Comment Author has expressed that leader cells are a new therapeutic target for managing autoimmune diseases, but the issue of challenges of implementation of therapeutic strategies and how to overcome it has not been discussed.

Response This is a valid concern. We have added discussion on the challenges and limitations of targeting leader cells therapeutically in the third paragraph ("Context and Challenges") and the final paragraph ("Future Directions and Conclusion"). This includes the difficulty in distinguishing cause vs. effect, experimental hurdles, the need for specificity to avoid off-target effects (especially considering links to cancer), and potential strategies to overcome these challenges, such as highly specific targeting or modulating downstream effects [1, 7].

5 Comment The references presented date back to 2009 to 2018. therefore it would be better to have more recent references.

Response Thank you for pointing this out. We have reviewed the references and incorporated more recent relevant publications (e.g., references 5, 7, 8, 9, 10 from 2016-2024) while retaining foundational citations where necessary. We have also ensured the total number of references adheres to the journal's limit (10 references in the final version.

Reviewer: Afzalun Nessa, ORCID: 0000-0002-4474-9836

6 Comment (Lines 32 & 32-34): Literature citations should be more relevant to reflect the hypothesis with recent publications. The number of literature citations is not adequate to support the hypothesis. For the deeper understanding of the proposed hypothesis involves the major immune cells in the tissue repairing process as leader cells. It is necessary to illustrate this with literature citations, which will impact the logical connection between the existing knowledge of autoimmune disease pathogenesis and the present hypothesis.

Response We agree with the reviewer's suggestions. We have significantly revised the manuscript to incorporate more recent and relevant citations (References 5, 7, 8, 9, 10). We have expanded the text, particularly in the "Pathogenesis Mechanisms" paragraph, to better illustrate the proposed links between leader cell dysfunction, tissue repair processes (including DAMP release and altered immune communication), and the potential triggering of autoimmunity, citing supporting literature [e.g., 4, 5, 6, 7]. We believe the revised text and updated references provide stronger support for the hypothesis and better connect it to existing knowledge.

Reviewer: **Umme Shahera**, ORCID: 0000-0002-8811-578X

7 **Comment** The manuscript would benefit from clearer identification or characterisation of leader cells in specific autoimmune-prone tissues. Add specific examples of known leader cells in tissues commonly affected by autoimmunity (e.g., gut, pancreas, skin).

Response Thank you for this valuable suggestion. We have incorporated specific examples in the "Pathogenesis Mechanisms" paragraph, discussing potential roles of specialized beta cells ('hub'/'leader' cells) in the pancreas (Type 1 Diabetes) [8, 9], leader cells in gut epithelial repair (Inflammatory Bowel Diseases) [7, 10], and leader keratinocytes in skin inflammation/repair (Psoriasis) [7, 10].

8 **Comment** There is little mention of competing hypotheses or how this perspective fits within current models of autoimmunity.

Response We have addressed this in the third paragraph ("Context and Challenges"). We now explicitly state that the leader cell hypothesis is complementary to, rather than exclusive of, established mechanisms like genetic susceptibility, environmental triggers, and molecular mimicry [3], positioning it as a potential link between tissue-level events and immune activation.

9 **Comment** Briefly discuss potential limitations of the hypothesis or experimental challenges, such as distinguishing causation from correlation in cell dysfunction.

Response We have incorporated a discussion of limitations and challenges in the third paragraph ("Context and Challenges") and the final paragraph ("Future Directions and Conclusion"). This includes the challenge of determining causation versus correlation, experimental difficulties in identifying and manipulating leader cells in vivo, and the potential therapeutic challenges related to the overlap with cancer mechanisms [1].

Responsible Editor: **M Mostafa Zaman**, ORCID: 0000-0002-1736-1342

10 **Comment** A Research Letter does not start with a salutation to the editor. Just double-check that you have four paragraphs that correspond to IMRD.

Response We apologize for the oversight. The salutation "Dear Editor," has been removed from the revised manuscript. We have also restructured the main text into four distinct paragraphs, broadly corresponding to Introduction, Pathogenesis Mechanisms (Methods/Results implied in hypothesis), Context and Challenges (Discussion), and Future Directions and Conclusion, to better align with a structured format.

11 **Comment** Do not exceed 10 references.

Response We have carefully reviewed and reduced the number of references to exactly 10 in the revised manuscript, prioritizing the most relevant and impactful citations, including recent findings.

12 **Comment** Point-by-point responses to review comments are yet to be submitted. Please take this seriously, as it will be published along with the article. See examples on our website (each article has a review report based on the point-by-point response). We cannot accept your submission without it.

Response We understand the importance of the point-by-point response. This document provides detailed responses to all comments received from the reviewers and the editor, outlining the changes made in the manuscript accordingly. We hope this meets the journal's requirements for publication alongside the article.