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

COMMENTARY

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

The concept of 'leader cells'—specialised cells orchestrating collective cell behaviours during development, tissue repair, and cancer progression—offers a compelling, yet relatively unexplored lens for examining the pathogenesis of autoimmune diseases [1]. These cells are crucial for maintaining tissue homeostasis and integrity, coordinating complex processes through mechanical force generation, signaling molecule secretion, and intercellular communication [1, 2]. Dysfunction within these critical leader cells, potentially arising from genetic predispositions, environmental insults, or pathogen interactions, can profoundly disrupt tissue equilibrium [2]. We hypothesise that such leader cell dysfunction represents a significant factor in the breakdown of self-tolerance and the subsequent development of autoimmune pathology, potentially linking tissue-level dysregulation to immune system activation, a concept often explored through mechanisms like molecular mimicry [3].

The precise mechanisms by which dysfunctional leader cells could trigger or perpetuate autoimmunity are likely multifaceted. Aberrant tissue repair responses represent a key pathway; failure of leader cells to properly orchestrate repair can lead to chronic inflammation, excessive release of damage-associated molecular patterns (DAMPs), and inappropriate exposure of self-antigens, providing triggers for autoreactive immune responses [4, 5]. Furthermore, dysfunctional leader cells might alter the local immune microenvironment through dysregulated production of cytokines, chemokines, or extracellular vesicles, shifting the balance towards a pro-inflammatory state and impairing regulatory immune cell function [6, 7]. Specific leader cell populations have been implicated in tissues prone to autoimmune attack. For instance, in the pancreas, specialized 'hub' or 'leader' beta cells that normally coordinate islet responses could, if dysfunctional, contribute to the inflammatory milieu and beta cell destruction seen in Type 1 Diabetes [8, 9]. Similarly, compromised leader cell function during repair in epithelial tissues like the gut or skin could impair barrier integrity, potentially driving conditions like inflammatory bowel diseases or psoriasis [7, 10].

This leader cell perspective complements established autoimmune mechanisms like genetic susceptibility and environmental triggers [3]. However, significant challenges remain. Distinguishing whether leader cell dysfunction is a primary cause or a secondary consequence of the autoimmune process (cause or effect) is crucial. Experimental hurdles include the precise identification and specific manipulation of leader cells in vivo within complex tissue environments. Furthermore, the potential overlap in mechanisms between leader cells in repair and cancer necessitates caution when considering therapeutic interventions [1].

Future research employing advanced techniques like single-cell multi-omics and lineage tracing in relevant animal models is needed to dissect the role of leader

Key messages

Leader cell dysfunction, disrupting tissue repair and immune communication, presents a novel and potentially crucial mechanism contributing to autoimmune disease pathogenesis. Elucidating the specific roles and dysfunctions of leader cells in various autoimmune conditions could unveil new therapeutic targets, although significant challenges in research and therapeutic implementation remain.

cells [10]. Investigating whether enhancing leader cell function or restoring their communication with immune cells can mitigate autoimmune responses may offer novel therapeutic strategies, despite the inherent challenges [7]. Targeting strategies must be highly specific to avoid unintended consequences like promoting malignancy. In conclusion, leader cell dysfunction, disrupting tissue repair and immune communication, presents a novel and potentially crucial mechanism contributing to autoimmune disease pathogenesis. Elucidating their specific roles could unveil new therapeutic targets, although significant research and implementation challenges remain.

Acknowledgements

None

Conflict of interest

I do not have any conflict of interest.

Data availability statement

Not applicable

Supplementary file

None

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