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Single-cell analysis: Illuminating the path to early diagnosis of systemic lupus erythematosus

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Abstract

Systemic Lupus Erythematosus (SLE) is a complex autoimmune disease characterized by heterogeneous clinical manifestations and the production of autoantibodies, making early diagnosis challenging. Traditional diagnostic methods lack sensitivity and specificity, leading to delayed intervention and irreversible organ damage. Single-cell technologies offer a novel opportunity to investigate the cellular landscape of SLE at the level of individual cells. By profiling the gene expression, protein expression, and functional states of thousands of individual cells simultaneously, these technologies can reveal critical findings such as the expansion of type I interferon-producing pDCs and dysregulated T/B cell subsets involved in SLE pathogenesis. This editorial highlights the transformative potential of single-cell analysis in identifying disease-relevant cell populations and their functional states, ultimately paving the way for earlier diagnosis, personalized treatment, and improved outcomes for patients with SLE.

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Editorial

Systemic Lupus Erythematosus (SLE) is a complex, chronic autoimmune disease characterized by the production of autoantibodies and immune complex deposition, leading to inflammation and damage in multiple organs (1). SLE is highly heterogeneous, presenting with a wide array of clinical manifestations, making diagnosis challenging and often delayed (2). This delay in diagnosis can contribute to the accumulation of irreversible organ damage, highlighting the urgent need for improved diagnostic strategies. Traditional diagnostic methods for SLE rely heavily on serological markers, such as antinuclear antibodies (ANA) and anti-dsDNA antibodies, alongside clinical assessment. However, these markers lack sensitivity and specificity, often failing to capture the full spectrum of disease activity and heterogeneity (3). ANA can be positive in healthy individuals or non-lupus conditions, reducing specificity. Also, anti-dsDNA titers may fluctuate and not correlate perfectly with all types of organ damage, limiting sensitivity in certain clinical contexts, which leads to missed windows for timely treatment of organ involvement. This is where the transformative potential of single-cell analysis comes into play.

Single-cell technologies, including single-cell RNA sequencing (scRNA-seq) and cytometry by time-of-flight (CyTOF), offer an unprecedented opportunity to dissect the cellular landscape of SLE at an individual cell level (4). By profiling the gene expression, protein expression, and functional states of thousands of individual cells simultaneously, these technologies can reveal the cellular dynamics underlying SLE pathogenesis. This granular view of the immune system allows researchers to identify rare cell populations, characterize distinct cell states, and uncover previously unrecognized interactions between different cell types (5).

In the context of SLE, single-cell analysis has begun to illuminate the complex interplay of immune cells contributing to disease onset and progression. Studies using scRNA-seq have identified distinct immune cell subsets within peripheral blood, including activated T cells, plasmacytoid dendritic cells (pDCs) producing type I interferons, and dysregulated B cells (6). These studies have revealed that SLE patients exhibit disease-specific T follicular helper cell (Tfh) subsets and autoantibody-secreting plasma cells, associated with disease activity and severity. Crucially, the increased frequency of interferon-stimulated genes (ISGs) in peripheral blood mononuclear cells directly correlates with disease activity in SLE patients (7). Single-cell analysis can pinpoint which specific cell types are driving this ISG signature, providing a more precise understanding of the disease process.

Beyond identifying cell subsets, single-cell analysis can also reveal critical information about the functional states of individual cells. For instance, scRNA-seq can identify T cells expressing activation markers and producing pro-inflammatory cytokines, providing insights into the immune dysregulation driving tissue damage in SLE (8). Similarly, single-cell analysis of B cells can identify those cells actively producing pathogenic autoantibodies, which are directly involved in the development of lupus-related organ damage (9). This level of functional information is not accessible with traditional bulk RNA sequencing or flow cytometry.

The ability to identify and characterize these disease-relevant cell populations and their functional states holds immense promise for improving the early diagnosis of SLE. By identifying unique cellular signatures associated with early stages of disease, single-cell analysis could enable earlier intervention and potentially prevent the development of severe complications. Furthermore, the detailed cellular profiles obtained through single-cell analysis can help stratify patients into different subgroups based on their unique disease characteristics. This personalized approach to diagnosis could lead to more targeted and effective treatment strategies (10).

While single-cell analysis holds immense potential to revolutionize SLE management, several challenges, including high cost, specialized expertise, and the need for standardized protocols, must be addressed before wide clinical implementation. The field is rapidly overcoming these barriers through technological advancements like targeted sequencing to reduce costs, the development of user-friendly

computational pipelines to aid analysis, and international efforts to establish standardized protocols for reproducibility (10). However, several challenges remain to be addressed before single-cell analysis can be widely implemented in the clinic. These include the high cost of single-cell technologies, the need for specialized expertise to analyze single-cell data, and the lack of standardized protocols for single-cell analysis (11). Despite these challenges, the future of single-cell analysis in SLE diagnosis and treatment is bright. Achieving these goals will solidify single-cell analysis as the cornerstone for earlier, personalized diagnosis and improved patient outcomes in SLE.

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Conflicts of interest

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Author contributions

Milad Ahmad-Aghdami contributed to the conceptualization and performed the literature review. Saeed Mohammadi drafted the manuscript, provided critical revision of the manuscript, and finalized the submission. Both authors have reviewed and approved the final version of the manuscript and consent to its publication in Jorjani Biomedicine Journal.

Data availability statement

N/A.

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