



Targeting Immune Checkpoints in Fibroblast-Like Synoviocytes: A Systematic Review of Potential Paradigm Shift in Therapeutic Strategies for Rheumatoid Arthritis

Mahsa Kiani Bigdeli¹, Narges Basirian¹, Mohammadreza Galegirian¹, Mohammad Javad Mousavi^{2*}

¹Student Research Committee, Bushehr University Of Medical Sciences, Bushehr, Iran

²Department of Hematology, Faculty of Allied Medicine, Bushehr University of Medical Sciences, Bushehr, Iran

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*Corresponding Author:

Dept. of Hematology, Faculty of Allied Medicine, Bushehr University of Medical Sciences, Bushehr, Iran

ABSTRACT

Introduction: Rheumatoid arthritis (RA) is a chronic inflammatory and autoimmune-mediated synovial disorder affecting 0.5-2% of the world population. RA pathogenesis involves complex interactions between genetic predisposition, environmental factors, and immune cell infiltration. Fibroblast-like synoviocytes (FLSs), key players in the synovial lining, have emerged as crucial targets for therapeutic interventions. This systematic review explores the role of immune checkpoint dysregulation in FLSs in RA pathogenesis and its potential for intriguing therapeutic strategies.

Search Strategy: A systematic literature search was conducted using PubMed, Scopus, Web of Science, and Embase databases from inception to April 2024. The search strategy included keywords and MeSH related to Rheumatoid arthritis, RA FLSs, immune checkpoints, apoptosis, and targeted therapies. Studies investigating the role of FLSs in RA pathogenesis, immune checkpoint disturbances in FLSs, or potential targeted therapies for RA were included. Two independent reviewers screened titles, abstracts, and full-text articles for eligibility. Data extraction and quality assessment of observational studies were performed using a standardized form and the Newcastle-Ottawa Scale (NOS). A narrative synthesis of the findings was conducted, focusing on the role of FLSs in RA pathogenesis, immune checkpoint disturbances, and potential targeted therapies.

Results: This systematic review analyzes the current literature on immune checkpoint disturbances in RA FLSs. The adversarial behavior of FLSs in RA has been explored from various perspectives, including changes in immunophenotype, immune responses, metabolism, apoptosis, signaling, cancer-like behavior, and responsiveness to therapy. Dysregulation of specific checkpoints, including p53 mutations, PD-1/PD-L1 pathway, BCL-2/Bax ratio, NLRP3 inflammasome, and autophagy, contribute to hyperproliferation, apoptosis resistance, and inflammatory responses in RA FLSs, highlighting the key player role of immune checkpoint dysregulation in RA pathogenesis.

Conclusion and Discussion: Targeting immune checkpoints in RA FLSs presents a promising therapeutic strategy for RA. By modulating these checkpoints, we aim to restore immune homeostasis, reduce FLS hyperproliferation and apoptosis resistance, and control RA disease progression. This approach offers the potential for more targeted and effective therapies, minimizing the adverse effects of traditional immunosuppressive drugs. Further research is needed to develop novel therapeutic agents targeting these pathways and assess their efficacy in clinical trials.

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