УДК: 616.72-002.77-092:616.71-003.93

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MECHANISMS OF OSTEODESTRUCTION IN RHEUMATOID ARTHRITIS

Abstract

The purpose of this research was to compile the most recent findings about the immunopathogenesis of RA and report them in a literature review. All of the publications included in this review were found by a comprehensive search of the following databases: PubMed, EBSCO, Web of Science, and Science Direct. Understanding the causes of illness genesis and progression can be greatly enhanced by examining the immunological alterations identified in RA. Inflammation and joint destruction are hallmarks of rheumatoid arthritis (RA), which is largely caused by autoantibodies such those against cyclic citrullinated peptide and rheumatoid factor (RF). One of the reasons the immune response is off in RA is because of T cell dysregulation, particularly in pro-inflammatory subpopulations.

Keywords: *Rheumatoid arthritis, autoantibodies, pathogenesis, cytokines*.

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МЕХАНИЗМЫ ОСТЕОДЕСТРУКЦИИ РЕВМАТОИНОГО АРТРИТА

Целью данного исследования было собрать новейшие данные об иммунопатогенезе РА и представить их в обзоре литературы. Все публикации, включенные в данный обзор, были найдены в результате комплексного поиска в следующих базах данных: PubMed, EBSCO, Web of Science и Science Direct. Понимание причин возникновения и прогрессирования заболевания может быть значительно улучшено путем

изучения иммунологических изменений, выявляемых при РА. Воспаление и деструкция суставов являются отличительными признаками ревматоидного артрита (РА), который в значительной степени вызван аутоантителами, такими как антитела к циклическому цитруллинированному пептиду и ревматоидному фактору (РФ). Одной из причин нарушения иммунного ответа при РА является нарушение регуляции Т-клеток, особенно в провоспалительных субпопуляциях.

Ключевые слова: *Ревматоидный артрит, аутоантитела, цитокины.*

Introduction. Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized not only by persistent inflammation of the joints but also by progressive osteodestruction, which ultimately leads to functional disability and systemic complications. According to the Global Burden of Disease study, the United States has the highest age-standardized prevalence of RA (0.38%, 95% CI: 0.36–0.40), followed by Western Europe (0.35%, 95% CI: 0.31–0.38) [6]. These data emphasize that RA continues to attract significant attention in human health sciences, as its social and economic impact remains particularly alarming [1,3].

The osteodestructive mechanisms of RA are largely driven by dysregulated immune responses, including abnormal T-cell activation and excessive cytokine production. This creates a pro-inflammatory microenvironment that stimulates synovial hyperplasia and promotes bone erosion. Key molecular mediators such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and receptor activator of nuclear factor kappa-B ligand (RANKL) play central roles in osteoclast differentiation and activation, resulting in accelerated bone resorption. In parallel, impaired osteoblast function reduces bone repair and regeneration, further enhancing skeletal damage. In this work, special emphasis is placed on the immunological and molecular mechanisms that underpin the osteodestructive processes in RA, highlighting the interplay between chronic inflammation, immune dysregulation, and bone metabolism.

Materials and methods. In this study, a comprehensive and systematic search strategy was employed to identify relevant published works for inclusion in the review. To ensure rigor and reliability in the data collection process, we conducted searches across several well-recognized scientific databases, including PubMed, EBSCO, Web of Science, and ScienceDirect. The selection of these databases was determined by their extensive coverage of peer-reviewed scientific literature across multiple disciplines, which allowed us to obtain a complete and representative sample of relevant scientific articles.

Results. Although the exact etiology of rheumatoid arthritis (RA) remains unknown, it is widely accepted that a combination of genetic, environmental, and immunological factors contributes to its development. Certain human leukocyte antigen (HLA) alleles, particularly those carrying the shared epitope of HLA-DRB1, are strongly associated with an increased risk of RA, highlighting the importance of genetic predisposition [7]. Environmental factors such as smoking and specific infections are also linked to RA onset in genetically susceptible individuals [1,2,6].

The rheumatoid factor (RF) autoantibody has been the subject of numerous studies. RF represents an IgM antibody, and less commonly an IgG, directed against the Fc portion of IgG [1,3]. While not disease-specific, RF is widely used for RA diagnosis. Higher RF titers correlate with increased disease severity and joint damage. Another characteristic autoantibody in RA is the anti-citrullinated protein antibody (ACPA). RF is typically identified by serological techniques such as ELISA or latex agglutination assays. RF positivity varies across populations but is more common in patients with more severe symptoms. Importantly, the presence of both RF and ACPA is not only useful for diagnostic purposes but also provides prognostic value for disease progression. RF is detected in approximately 70–80% of RA patients, though it may also occur in other autoimmune and infectious diseases [1,2].

RA is further characterized by abnormalities in T-cell subsets that lead to impaired regulation of immune responses. CD4+ T helper (Th) cells, in particular, play a central role in orchestrating immune activity and contribute significantly to RA pathogenesis [7]. An imbalance in Th subpopulations has been demonstrated, with an increase in Th17 cells and a reduction in regulatory T cells (Tregs) [6]. Th17 cells exert pro-inflammatory effects through cytokines such as interleukin-17 (IL-17), which promotes synovial inflammation and joint destruction in RA.

B cells, an essential component of adaptive immunity, also play a central role in RA pathogenesis. Autoreactive B cells recognize host antigens and drive tissue damage [3,5,7]. Normally, two checkpoints — signaling through the B-cell receptor (BCR) and a co-stimulatory signal — eliminate autoreactive B cells. In RA, both checkpoints are defective, resulting in the survival of a large pool of autoreactive naïve B cells [3,5].

Cells of the innate immune system, especially macrophages and dendritic cells (DCs), are also pivotal in RA pathogenesis. Synovial macrophages release pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6, amplifying inflammation, recruiting immune cells, promoting angiogenesis, and accelerating joint destruction. DCs, with their potent antigen-presenting capacity, activate autoreactive T cells and sustain chronic inflammation. Innate immune cells additionally produce a wide spectrum of inflammatory mediators, including IL-12, IL-23, and chemokines (CCL2, CCL3, CCL5, CXCL8), all of which exacerbate synovial inflammation. Therapeutic strategies targeting TNF-α (e.g., adalimumab, etanercept), IL-1, IL-6, as well as monoclonal antibodies against IL-12/23 or co-stimulatory molecules (CD80/86) on DCs, have demonstrated clinical efficacy by reducing inflammation and slowing joint destruction.

Taken together, these findings indicate that the innate immune response is a key driver of RA pathogenesis and an important therapeutic target.

Conclusions. The osteodestructive potential of rheumatoid arthritis results from a convergence of genetic predisposition, environmental triggers, and dysregulated immune responses. Aberrant T- and B-cell activity, together with pro-inflammatory cytokines from macrophages and dendritic cells, stimulate the RANK/RANKL pathway, leading to osteoclast activation and bone resorption. This sustained imbalance between bone destruction and repair explains the progressive joint damage characteristic of RA and highlights key targets for modern biologic therapies.

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