The role of γδ T lymphocytes in the pathogenesis and response to biological treatment of autoimmune joint diseases

Summary

Autoimmune diseases, including rheumatic disorders, constitute a major challenge in contemporary medicine due to their chronic nature, complex etiopathogenesis, and significant impact on patients' quality of life. Their development results from a disruption of immune system homeostasis, leading to the loss of immunological tolerance and the generation of immune responses directed against self-antigens. This process results in a chronic inflammatory state that gradually damages tissues and contributes to disease progression. Among the most common disorders of this type are rheumatoid arthritis (RA) and ankylosing spondylitis (AS). Although these diseases differ in clinical manifestation, they share common pathogenic mechanisms, including chronic activation of immune cells—particularly T and B lymphocytes—and overproduction of proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin (IL-) 1β, and IL-6. The introduction of biologic therapies, especially TNF-α inhibitors, represented a breakthrough in the treatment of these diseases, markedly improving therapeutic efficacy and patient prognosis. However, despite therapeutic advances, a substantial proportion of patients fail to achieve complete remission, and the clinical response to treatment varies significantly among individuals. This underlines the need to identify of prognostic biomarkers and develop more personalized therapeutic strategies.

In recent years, increasing attention has been directed toward the role of less-studied immune cell subpopulations, such as γδ T lymphocytes, which combine features of innate and adaptive immunity. These cells, which represent a small fraction of peripheral blood T lymphocytes, are characterized by a unique TCRγδ receptor that enables antigen recognition independently of major histocompatibility complex (MHC) molecules. Owing to this property, γδ T cells can respond more rapidly than conventional αβ T cells, acting as a "bridge" between the early inflammatory response and the adaptive immune response developed over time. Γδ T cells express a wide repertoire of surface receptors, similar to NK cells, which allows them to exert both cytotoxic and immunoregulatory functions. Moreover, they secrete a variety of cytokines, including IL-17, IL-5, and IL-9, which play crucial roles in modulating inflammation and disease activity. IL-5 promotes eosinophil differentiation and activation, whereas IL-9 exhibits dual activity — it may enhance protective immune mechanisms or contribute to the persistence of chronic inflammation in tissues.

The present study aimed to determine the potential significance of genetic polymorphisms in genes encoding Th2 cytokines (IL-5, IL-9) and surface receptors of γδ T cells (NCR3, FCγR3A,

and DNAM-1) in the pathogenesis and response to TNF-α inhibitor therapy in patients with RA and AS. Single nucleotide polymorphism (SNP) analysis indicated that the presence of certain genetic variants may influence disease course and the effectiveness of biologic therapy. The *A* allele of rs2069812 (*IL5*) and rs2069885 (*IL9*) polymorphisms correlated with better clinical response and lower levels of inflammatory markers such as C-reactive protein (CRP) and visual analogue scale scores (VAS) in patients treated with anti-TNF agents. These findings suggest that genetic variability within cytokine-coding genes may affect their expression and, consequently, the activity of γδ T lymphocytes and the intensity of the inflammatory process.

Further analyses focused on genetic variants of surface receptor genes: *NCR3* rs1052248, *FCγR3A* rs396991, and *DNAM-1* rs763361. These polymorphisms were associated with clinical parameters, such as disease activity and treatment response. Particularly noteworthy were the results concerning the *NCR3* rs1052248 variant, which appeared to influence the clinical course of RA and the response to anti-TNF therapy, as well as the *FCγR3A* rs396991 polymorphism, associated with CRP levels and VAS scores. Although these findings are preliminary, they provide important insights and a basis for further research into the genetic determinants of biologic treatment response.

Parallel to the genetic studies, phenotypic analysis of γδ T cells in RA patients was conducted, focusing on the expression of their surface receptors and the relationship between these parameters and disease activity. A significantly lower frequency of γδ T cells was observed in peripheral blood compared with healthy controls, which may reflect their migration to inflamed tissues or a state of functional exhaustion. γδ T cells from RA patients exhibited increased expression of inhibitory receptors such as TIM-3, TIGIT, and PD-1, and decreased expression of activating receptors including CD27, CD28, and DNAM-1. Additionally, an increased proportion of terminally differentiated cells was detected, suggesting chronic antigenic stimulation and prolonged immune activation.

Correlation analyses between surface receptor expression and clinical parameters revealed that a lower proportion of γδ T cells and higher expression of inhibitory receptors were associated with increased disease activity and more severe clinical symptoms. Furthermore, ROC analyses indicated that both γδ T cell counts and receptor expression profiles could serve as valuable parameters supporting diagnosis, disease monitoring, and therapy individualization. During TNF-α inhibitor treatment, a trend was observed in which decreases in γδ T cell numbers and TCRγδ expression correlated with a weaker clinical response, suggesting that monitoring phenotypic changes in these cells may hold prognostic significance for evaluating biologic therapy effectiveness.

The results of this study indicate that γδ T lymphocytes play a significant role in the pathogenesis of RA and in the immune response to biologic therapy. Quantitative and qualitative disturbances in these cells—including reduced frequency, increased expression of inhibitory receptors, and loss of activating receptors—may contribute to immune

dysregulation and the persistence of inflammation. In turn, genetic analyses confirm that polymorphisms in genes encoding cytokines and surface receptors of γδ T cells may modulate the response to TNF-α inhibitors. The integration of genetic and immunophenotypic data provides deeper insight into individual mechanisms of treatment response, opening new perspectives for the identification of predictive biomarkers and the advancement of personalized medicine in rheumatology.