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Tak P-P, Parnham MJ, editors. New Therapeutic Targets in Rheumatoid Arthritis

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Field of medicine: Rheumatology, immunology, clinical pharmacology.

Format: Hardcover book.

Audience: Researchers in immunology and rheumatology, rheumatologists, immunologists, internal medicine practitioners, pharmacologists.

Purpose: To provide an overview of advances in research of the novel therapeutic targets in rheumatoid arthritis.

Content: This book is a part of Birkhäuser's series "Progress in Inflammation Research," which intends to provide researchers and clinical practitioners with the most recent developments in the pathophysiology, pathology, and treatment of inflammatory diseases. This volume provides insight into targeted therapies of rheumatoid arthritis, describing the novel mechanisms of action that were identified after tumor necrosis factor (TNF) blockade and that have recently been registered or are currently under development.

The first 3 chapters of the book summarize the proven clinical effects and mechanism of action of new anti-rheumatic treatments already in clinical use, like rituximab, abatacept, and tocilizumab. B cells were proven as critical for the pathogenesis of rheumatoid arthritis by the efficacy of depletion of B cells in many patients with rheumatoid arthritis using anti-CD20 monoclonal antibodies – rituximab. Furthermore, therapies targeting co-stimulatory pathways aimed at modifying the activation of T-cells, important effectors in the immunopathogenesis of rheumatoid arthritis, may be an effective alternative to T-cell depletion. One such treatment is abatacept (CTLA4Ig), which in large controlled trials effectively reduced disease activity in patients with rheumatoid arthritis. Also, several international clinical studies confirm the efficacy and safety of tocilizumab, humanized anti-IL-6 receptor antibody, in the treatment of patients with rheumatoid arthritis. Considering the fact that almost one third of the patients do not respond to currently available treatments, which included the TNF blockers, treatments with rituximab, abatacept, or tocilizumab have made a significant advance in the efficacy of targeted therapy.

The next 6 chapters provide an overview of the new therapeutic approaches with still uncertain clinical effectiveness, which need further investigation. IL-1, besides TNF and IL-6, is considered to be a master cytokine in chronic destructive arthritis and its blockade has been shown to ameliorate joint destruction in many animal models of arthritis. However, clinical trials have shown variable responsiveness of rheumatoid arthritis patients to anti-IL-1 therapy. Within synovial tissues, IL-15 has been ascribed an inflammatory role because of its capacity to activate T cells, NK cells, macrophages, and neutrophils. In vivo model studies suggest that IL-15 neutralization leads to reduction of articular inflammation and damage. Early clinical trials have shown promise for IL-15 blockade using a monoclonal antibody in rheumatoid arthritis patients for the improvement of disease symptoms.

Moreover, IL-17, the TH17 cell derived cytokine, was found to induce bone and cartilage destruction, which has further extended the choice of possible modalities to control rheumatoid arthritis.

Several autoimmune diseases, like systemic lupus erythematosus, Crohn disease, psoriasis, graft versus host disease,

and rheumatoid arthritis, are believed to be mediated in part by IL-18. The IL-18 blocking options currently under development are inhibitors of caspase-1, human monoclonal antibodies to IL-18, soluble IL-18 receptors, and IL-18 receptor monoclonal antibodies.

Anti-chemokine and anti-chemokine receptor targeting may be therapeutically used in future biological therapy of arthritis, which is described in chapter 8. Most of data in this field are obtained from experimental models of arthritis; however, results of some human trials have also become available, making it possible that a number of specific chemokine and chemokine receptor antagonists will be administered to arthritis patients in the near future.

Chapter 9 gives an overview of signaling pathways, which regulate various cellular functions, like apoptosis, cell differentiation, and proliferation. When the same signaling cascades escape from normal controls and increase the production of cytokines, proteases, growth factors, and chemokines up to harmful levels, it leads to an autodestructive process as seen in rheumatoid arthritis. The complex signaling mechanisms involved in all rheumatic diseases converge on key pathways, including the mitogen-activated protein kinase and nuclear-factor-κB pahways. Mapping the hierarchy of these pathways identifies which specific targets can be inhibited to safely reduce the levels of inflammatory molecules.

Oncostatin M is a pleiotropic cytokine and is also a potential target in the treatment of inflammatory arthritis. This pro-inflammatory cytokine is increased in the rheumatoid arthritis but not in the osteoarthritic joint. Chapter 10 describes how the strategies to block the actions of oncostatin M for use in inflammatory arthritis are being developed, showing significant promise in murine models of disease and giving the background on which the possible future clinical trials will be based.

Targeting the epigenetic modifications of synovial cells is a fundamentally different therapeutic approach in the treatment of rheumatoid arthritis, which is still in pre-clinical phase. The advances of that approach are described in chapter 11.

The last chapter provides a more general perspective of how targeted therapeutic agents have changed the landscape of therapy in rheumatoid arthritis. It gives insight into the lessons learned from the use of targeted therapies with regard to the use of animal models of rheumatoid arthritis, clinical trial design, pharmacodynamics, immunobiology, and key pathogenic elements of disease.

Highlights: The important breakthroughs in the treatment of rheumatoid arthritis, especially anti-TNF therapy after identifying TNF as a key factor in inflammation and matrix destruction, have revolutionized the treatment of rheumatoid arthritis and provided proof of concept for the principle of targeted therapy. However, it was found that either not all of the patients responded to these drugs or the anti-drug antibodies and other drug escape mechanisms related to the disease developed. Therefore, every new approach in the targeted therapy of rheumatoid arthritis could contribute to the effectiveness in treating that chronic disease. This book is of great interest not only to those closely related to research or clinical practice in the field of rheumatoid arthritis, but also to the wider audience of medical specialists, because it offers an excellent overview of what is currently being done to find new targets and improve the treatment of rheumatoid arthritis.