Gene Therapy for Rheumatoid Arthritis
Theoretical Considerations

Yuti Chernajovsky,1 Alex Annenkov,1 Charlotte Herman,1 Kostas Triantaphyllopoulos,1 David Gould,1 Hanna Dreja,1 Sasha P. Moyes,2 J. Ludovic Croxford,3 Rizgar A. Mageed,2 Osvaldo L. Podhajcer4 and David Baker3

1 Molecular Biology Laboratory, Kennedy Institute of Rheumatology, London, England
2 Clinical Immunology Division, Kennedy Institute of Rheumatology, London, England
3 Institute of Ophthalmology, University College London, London, England
4 Fundación Campomar, Facultad de Ciencias Exactas y Naturales (FCEYN), University of Buenos Aires, Buenos Aires, Argentina

Contents

Summary .................................... 29
1. Immunological Mechanisms ................................................................. 30
2. Therapeutic Target Genes ................................................................. 31
   2.1 Antibodies and Single-Chain Fv Fragments ................................... 31
   2.2 Cytokines and Soluble Cytokine Receptors .................................. 32
3. Delivery Systems .................................................................................. 35
   3.1 Viral Vectors .................................................................................. 35
   3.2 Non-Viral Vectors .......................................................................... 36
   3.3 Target Cells Ex Vivo and In Vivo ..................................................... 36
4. Conclusions ......................................................................................... 37

Summary

Current understanding of the pathogenesis of rheumatoid arthritis has provided evidence that therapeutic benefit can be achieved by using antagonists targeted to the inflammatory cytokines involved, mainly tumour necrosis factor-α and interleukin-1. Gene delivery of antagonists, which can inhibit the production or action of these cytokines and other mediators, has been achieved in experimental animal models. This new method of delivery can produce therapeutic effects at lower concentrations and in a local environment, overcoming the adverse effects that often accompany protein therapy. However, several technological and biological restraints preclude the immediate adaptation of this method to human treatment. Based on the experimental evidence, possible target therapeutic genes, cell types and vector systems that could be used are discussed in this article.
Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease with autoimmune features. Currently, there is no specific effective therapy for this condition.\[1,2\] The incidence of RA increases with age and two-thirds of those affected are women.\[3\] An association has been found between RA and the major histocompatibility complex (MHC) class II gene DR4;\[4,5\] this association is known to indicate the risk of acquiring the disease, but may also predict severity once the disease has begun. Despite the strong association between RA and certain MHC class II alleles, it is recognised that the disease is polygenic and involves unknown environmental factors.

1. Immunological Mechanisms

There are several lines of evidence to indicate that RA is an autoimmune disease. First, the presence of autoantibodies, especially rheumatoid factors and their association with human leucocyte antigen (HLA) DR4, suggests immune recognition of a specific epitope. The isolation of type II collagen–specific T cell clones has provided additional evidence for autoimmune-mediated mechanisms.\[6\] This finding was followed by experiments to assess whether specific T cell receptor and immunoglobulin variable region genes\[7,8\] are preferentially expanded to indicate the presence of a specific antigen or super-antigen that drives the autoimmune response.\[9,10\] Evidence for both polyclonal and oligoclonal mechanisms of lymphocyte expansion have been provided.

At the Kennedy Institute of Rheumatology, London, England, measurement of cytokines in synovial explants from patients with RA or osteoarthritis was an important foundation for research; this technique demonstrated that cytokine networks or cascades could be driven by a single cytokine, namely tumour necrosis factor-α (TNFα).\[11\] Inhibition of TNFα using anti-TNFα antibody reduced the level of expression of inflammatory cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin (IL)-8, together with IL-1 and IL-6, which induce catabolism of cartilage.\[2,11,12\] Recently, it has been proposed that IL-15, which activates T cells, may act upstream of TNFα in the cytokine cascade.\[13\]

Animal models of RA, such as collagen-induced arthritis (CIA) in the DBA/1 strain of mice,\[14-16\] have been essential in understanding the possible pathogenic mechanisms of this disease. They have also served as basic models for the development of biological therapies, with clinical benefits such as anti-TNF immunotherapy.\[17,18\]

In murine CIA, both humoral and cell-mediated immunity are important for the development of arthritis.\[19\] Transgenic and gene–knock-out (KO) mice, including different types of MHC,\[20,21\] T cell receptor,\[22,23\] complement\[22,24\] and cytokine genes,\[25\] have provided a wealth of information regarding the genes involved in the inflammatory process in CIA. For example, transgenic mice carrying the human TNFα gene with replacement of its 3′ terminal by a β-globin polyadenylation signal spontaneously developed arthritis,\[25\] whereas mice that were transgenic for the MHC class II Eb\(\d\) gene were protected from collagen-induced arthritis.\[21\] Furthermore, KO mice lacking the p40 IL-12 subunit gene had a reduced incidence and severity of arthritis.\[26\] Surprisingly, high doses of IL-12 are also suppressive in CIA.\[27\] Transgenic mice that express the T cell receptor V\(\beta\)12-chain gene and are deficient in the complement component C5 do not develop CIA, even though they produce high levels of anticollagen antibodies.\[22\]

Experimental strategies using antibodies against CD4,\[28\] TNFα,\[29\] the chemokines macrophage inflammatory protein (MIP)-1α and MIP-2,\[30\] CD40L,\[31\] the co-stimulatory molecules B7.1 and B7.2,\[32\] adhesion molecules such as CD44,\[33\] intercellular adhesion molecule 1\[34,35\] and CD23,\[36\] complement component C5,\[37\] IL-12\[38\] and CTLA4-Ig,\[32\] as well as complement C3–depletion by cobra venom,\[39\] have all proved beneficial for prophylactic therapy of arthritis and, occasionally, for established disease.

All of these molecules, which can be therapeutically targeted, are involved in basic immune pro-