Self-tolerance in collagen induced arthritis

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av

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Gene therapy mediated antigen presentation by B cells establishes tolerance in collagen induced arthritis
Submitted

II. Tove Eneljung, Sara Tengvall, Pernilla Jirholt, Louise Henningsson, Rikard Holmdahl, Kenth Gustafsson, Inger Gjertsson.

Antigen specific gene therapy post immunisation reduces the severity of collagen induced arthritis.
Submitted

III. Louise Henningsson*, Tove Eneljung*, Pernilla Jirholt, Sara Tengvall, Ulf Lidberg, Wim B. van den Berg, Fons A. van de Loo, Inger Gjertsson.

Disease-dependent local IL-10 production ameliorates collagen induced arthritis in mice.
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ABSTRACT

Rheumatoid arthritis (RA) is an autoimmune chronic disease that results in damage to tissues throughout the body due to the inability of the immune system in these patients to discriminate between self-tissues and foreign invaders. Currently available treatment strategies consist of immunosuppressive drugs, which are efficacious but are associated with side-effects, such as increased risk for infections. Re-establishment of the ability of the immune system to discriminate between self and non-self through the induction of self-tolerance is an attractive treatment strategy that might lead to a cure for RA. Another interesting treatment option for RA is the design of a disease-regulated therapy, which would only be activated during a flare of the disease.

The aims of this thesis are to: 1) investigate the induction of antigen-specific tolerance in an animal model of RA (i.e., collagen induced arthritis; CIA); and 2) investigate whether disease-regulated production of an anti-inflammatory cytokine can ameliorate CIA.

We used gene therapy to express collagen type II peptide (CII) on antigen-presenting cells, so as to induce antigen-specific tolerance in animals with CIA. Our results show that gene therapy that targets haematopoietic stem cells induces strong resistance to the development of arthritis, and that B cells play a major role in the induction of tolerance. This effect is accompanied by increases in the suppressive capacities of T-regulatory cells and decreased levels of autoantibodies. We also show that gene therapy administered after immunisation with CII reduces the severity of CIA by decreasing the levels of autoantibodies and enhancing the suppression caused by T-regulatory cells.

Disease-regulated therapy was investigated using lentiviral-mediated transcription of IL-10 regulated by an IL-1 enhancer and IL-6 promoter. Our results show that gene therapy with an inflammation-dependent IL-10 gene construct generates increased levels of IL-10 in the lymph nodes, decreased levels of IL-6 in the serum, decreased levels of CII antibodies, and decreased severity of CIA.

In conclusion, we have developed gene therapy modalities and model systems that are well suited to investigations of the immunological mechanisms of antigen-specific tolerance and disease-regulated therapies in animal models of RA.

Keywords: tolerance, autoimmune, antigen-specific, collagen type II, gene therapy, disease-regulated therapy, collagen induced arthritis, mice, rheumatoid arthritis

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