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Posttranslational Modifications of Collagen type II – Effects on Antigen specific T-cell Tolerance and Autoreactivity in Collagen-Induced Arthritis

AKADEMISK AVHANDLING

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av

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ABSTRACT

Rheumatoid arthritis (RA) is a common chronic inflammatory disease affecting peripheral joints in approximately 1% of the world population. Immunization of susceptible strains with CII, leads to development of collagen-induced arthritis (CIA), an animal model for RA. The aim of this thesis was to investigate mechanisms involved in regulation of immunological T-cell tolerance in CIA by studying availability of joint-specific CII for presentation to autoreactive T cells in healthy as well as pathological settings.

This work shows that transgenic expression of heterologous CII can inhibit expansion and Th1/Th17-skewing of antigen-specific T cells upon immunization with heterologous CII. The strength of tolerance induction was found to be dependent on the abundance of the self-antigen, the genetic background of the mice, as well as the presence or absence of posttranslational modifications on CII. Data indicate that joint-specific antigens are readily available for presentation in draining lymph nodes to induce immunological tolerance. Furthermore, a defect in thymic tolerance induction suggests that certain CII modifications are presented differentially depending on the location in the organism (Paper IV).

To obtain these results, established mouse systems were refined by generating a T-cell receptor specific antibody (Paper I) or by breeding diverse mouse and human transgenes on genetic backgrounds with different susceptibilities (Paper II & III).

Even though it is accepted that T cells play an important role in arthritis development, it remains controversial where and how they contribute to pathogenic mechanisms after loss of tolerance. In summary, this thesis describes a series of new mouse models that will aid to further elucidate the arthritogenic action of T cells in disease relevant sites. This will hopefully enlarge the mechanistic framework for further investigation of human disease pathogenesis, which might lead to new therapeutic strategies to promote self-tolerance in diseased individuals.