

THE ROLE OF HUMAN CARTILAGE PROTEOGLYCAN AGGREGAN IN INDUCTION OF ARTHRITIS IN HLA-HUMANIZED MICE

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OBJECTIVE: To determine whether the rheumatoid arthritis (RA)-predisposing class II molecules of the major histocompatibility complex (MHC) can present cartilage proteoglycan (PG) aggrecan, and if so, to determine the epitope repertoire of the human cartilage PG in HLA-transgenic mice and determine whether HLA-transgenic mice develop arthritis in response to immunization with human cartilage PG.

METHODS: Mice transgenic for HLA-DR2.Ab(0), DR3.Ab(0), DR4.Ab(0), and DQ8.Ab(0), lacking their own (mouse) class II antigens (Ab(0)), on the original (arthritis-resistant) and the arthritis-susceptible BALB/c backgrounds, were immunized with human cartilage PG. The T cell epitope repertoire presented by these class II MHC alleles was determined using a synthetic peptide library (143 peptides of the core protein of human cartilage PG), and arthritis development was monitored and compared in wild-type and HLA-transgenic/congenic BALB/c mice.

RESULTS: Mice of the 4 HLA-transgenic lines, either on the original mixed, arthritis-resistant background or DR4.Ab(0)- and DQ8.Ab(0)-transgenic/congenic mice on the arthritis-susceptible BALB/c genetic background, responded well to PG immunization (as assessed by T cell responses and antibody and cytokine production), and a number of T cell epitopes along the core protein of human cartilage PG were identified. DR4.Ab(0)- and DQ8.Ab(0)-transgenic mice immunized with human cartilage PG developed arthritis, but only when these class II MHC molecules were present on the arthritis-susceptible (BALB/c) genetic background.

CONCLUSION: A number of human cartilage PG epitopes can be presented by HLA alleles that predispose to the development of RA, but the epitopes of the cartilage PG presented by HLA-DR4 or HLA-DQ8 can induce arthritis only in the presence of an appropriate genetic (non-MHC) background.