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Functional and Genetic Analyses of the MHC and its impact on Autoimmunity in the Rat

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FUNCTIONAL AND GENETIC ANALYSES OF THE MHC AND ITS IMPACT ON AUTOIMMUNITY IN THE RAT

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ABSTRACT

The major histocompatibility complex (MHC) is an allele-rich and exceptionally gene dense region on human chromosome 6. Over 40% of the genes in this region have immune-related functions, including genes encoding MHCI and MHCII molecules. These molecules, which are found in nearly all vertebrates, present antigenic peptides to CD4 and CD8 T cells. Alleles of MHCI and MHCII are also believed to be strong risk factors in autoimmune disorders, such as rheumatoid arthritis (RA), as well as in infectious diseases. However, the differentiation between haplotype and allele associations in the MHC is not straightforward. Strong linkage disequilibrium exists between gene segments throughout the region which impedes identification of disease associated variants. These gene segments can be isolated and studied individually in congenic mice and rats. We produced for this thesis an extensive number of intra-MHC congenic rats to study the association between MHC genes and experimental arthritis, T cell selection and MHC regulation. *Study I* describes a genome-wide approach in heterogenous stock rats to identify quantitative trait loci (QTLs) associated with variations in MHC levels and CD4 and CD8 T cell numbers. A total of 10 QTLs were identified, of which 3 mapped to the MHC. We showed by congenic mapping that two minimal haplotypes of ~0.2 Mb explained the associations to the MHC. We further identified two allelic variants of the gene Tap2 that contributed to the variation in T cell numbers. *Study II* describes the effect of these minimal haplotypes on arthritis development and positions the MHCII region for the first time in an adjuvant model. We show that genes in the MHCII regulate onset, progression and severity of arthritis but not chronicity. Comparative analyses of different congenic MHCII haplotypes showed an inverse correlation between arthritis severity and a low proportion of recent thymic emigrants. *Study III* shows an MHCII associated T cell response to the cartilage protein collagen type XI in chronic pristane-induced arthritis (PIA) and the corresponding antibody response to the same antigen in human RA. *Study IV* describes the adoptive transfer of PIA in DA rats and outlines the conditions necessary for the model.

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