Studies on Understanding the Pathogenic Mechanisms in Arthritis

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Rheumatoid Arthritis (RA) is a systemic, auto-immune and complex disease affecting synovial membrane and joints. It is a chronic and long lasting disease which has an effect on the quality of life. Etiology of disease is unknown and auto-antibodies against Rheumatoid Factor (RF) and anti cyclic citrullinated peptide antibodies (ACPA) are present in diagnosed patients. Smoking and Major Histocompatibility Complex genes (HLA types) are attributed as environmental and genetic risk factors respectively. In the current project preventive and therapeutic vaccination strategies against Collagen Induced Arthritis (CIA) were validated using Joining chain deficient mice (J-/-). In another project effect of *Ncf1* gene mutation to decrease the threshold for arthritis induction in less susceptible B6N mice was investigated.

Joining chain is a protein expressed in polymeric immunoglobulins (pIgs) plasma cells which aids in polymerization of dimeric IgA and pentameric IgM antibodies. Its main function is to transport the pIgs via polymeric immunoglobulin receptor (pIgR) from the lamina propria into the gut lumen to neutralize the invading pathogens. The idea of the project was to investigate whether lack of joining chain and hence no pIgs can result in more retention time of the applied antigen intranasally to induce tolerance against auto-reactive cells. Collagen induced arthritis (CIA) is an animal model used to discover new pathogenic mechanisms and to evaluate therapies as it closely resembles the human RA. J-/- mice developed arthritis induced with collagen type II emulsified in an adjuvant despite the lack of polymeric antibodies, implying negligible role of polymeric antibodies in arthritis induction. Preventive but not therapeutic vaccination with collagen type II was found to be effective in J chain deficient mice.

In mice arthritis susceptibility mainly depends on the MHC (Histocompatibility 2, H2) genes. Mice with MHC haplotypes $H2^q$, $H2^r$ are highly susceptible for CIA. B6N mice have $H2^b$ MHC haplotype which makes them less susceptible for arthritis induction. Arthritis susceptibility also depends on the ability of the mice to develop anti- CII antibody responses. Earlier studies demonstrated that the presence of a splice site mutation in gene coding Neutrophil Cytosolic Factor protein (p47phox) resulted in lower reactive oxygen species (ROS) production and increased arthritis development. We studied the effect of *Ncf1* gene mutation in B6N genetic background.

Our results demonstrated that presence of the *Ncf1* gene mutation has negligible role in B6N genetic background both in priming (CIA) and effector phase (CAIA) of arthritis. This can be due to the overall genetic influence of the B6N genetic background and also possible presence of modifier genes. In a complex disease it is possible for the interactions between genes and some genes might compensate for the functional loss of other genes. Finally in this project, heterozygosity effect of MHC haplotypes ($H2^q$ and $H2^b$) on arthritis in B6N genetic background has been demonstrated.