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Anomalies of Humoral Immunity in the NOD mouse

Contribution to the progression of Type 1 Diabetes

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Abstract
The non-obese diabetic (NOD) mouse is widely used model Type 1 diabetes (T1D), a chronic inflammatory disease characterized by destruction of the insulin producing β cells in the islets of Langerhans by immune cells. The classical symptoms include increased glucose levels in urine and blood, frequent urination and enhanced thirst. The disease has a strong genetic component and is also influenced by the environment. NOD mice develop T1D spontaneously. The disease occurs in two phases; insulitis - the infiltration of immune cells in the islets of Langerhans and overt diabetes caused by the destruction of insulin producing β cells. Several disease associated gene regions or loci [termed insulin dependent diabetes (*Idd*) loci] have been associated with T1D development. Although, T1D is recognized as a T cell mediated disease in both mouse and man, many studies have shown the importance of B cells in the pathogenesis of the disease. Autoantibodies appear prior to islet infiltration and several molecular and cellular events precede this beta-cell autoimmunity. Although the pathogenesis of T1D is well characterized, less is known about the environmental and immunological factors that trigger the disease.

In this thesis, we studied the contribution of B cell anomalies to the skewed immune response observed in the NOD mouse. In our studies covered in the thesis we observed that NOD mice display enhanced IgE in the serum already at one week of age. In addition, upon treatment of pre-diabetic NOD mice with anti-IgE antibodies, diabetes incidence was delayed. We hypothesize that the presence of IgE in the system may be explained due to enhanced class switching. Antibody feedback however, is an essential component of the immune response and can lead to either enhanced or dampened responses. Thus, increased IgE may provide positive feedback that might sustain an immune response. We also aimed to analyze the biological consequence of this feature. *In vitro* stimulation of B cells by the TACI ligand APRIL resulted in enhanced plasma cell differentiation accompanied with increased class switching and IgG production. In addition, $TACI^{+}$ cells were observed in NOD germinal centers facilitating increased BAFF uptake and subsequent escape of low affinity antibody producing clones. NOD mice elicited an enhanced and prolonged immune response towards T-dependent antigens such as hen-egg lysozyme (HEL). Serum HEL-specific IgG level was significantly increased and was predominantly of the IgG1 isotype. Immunofluorescence analysis of NOD spleen revealed the presence of spontaneous germinal centers which others have perceived to provide a ready niche for the entry of naïve B cells that encountered novel antigen. Adoptive transfer experiments of purified B and T cells from NOD into NOD.*Rag2*-/- (NOD-RAG) mice illustrated the importance of B cell intrinsic defects in the reproduction of the original phenotype as observed in NOD.

Keywords
Type 1 Diabetes, NOD mouse, B cells, IgE, TACI, BAFF

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