Molecular and functional aspects of type 1 diabetes genetics

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This PhD dissertation was accepted by the Faculty of Health Sciences of the University of Copenhagen, and defended on June 26, 2009.

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Dan Med Bull 2009;56:175

ABSTRACT

The studies included in this dissertation were conducted at Steno Diabetes Center and Hagedorn Research Institute, Gentofte, Denmark, with the aim to further investigate molecular effects of genetic risk factors in T1D.

In study 1 and 2 we analysed SNPs covering the human leukocyte antigen (HLA) region on chromosome 6, genotyped in a large family collection provided by the Type 1 Diabetes Genetic Consortium. In a system of biology approach we combined association signals with protein-protein interaction data for the corresponding genes in the HLA region. Furthermore we stratified the diabetic probands according to their HLA genotype and were thereby able to identify functional interaction modules that differed between risk groups.

In study 3 and 4 we investigated the SNP rs13266634 in the gene *SLC30A8* originally identified to confer risk of T2D in genome wide association scans (GWAS). rs13266634 changes the amino acid at position 325 from arginine to tryptophan in ZnT8, a zinc transporter involved in the transport of zinc ions into the insulin vesicles in β-cells. In study 3 we were unable to demonstrate an association for rs13266634 to T1D in a large Danish case-control material. In study 4 the same SNP was analysed in diabetic probands and siblings and the genotypes correlated to their autoantibody response against the ZnT8 Arg325Trp epitope. We confirmed the correlation between genotypes of rs13266634 and antibodies for ZnT8 Arg325Trp. Furthermore we demonstrated differences in HLA genotypes between individuals with a ZnT8 Arg or Trp restricted antibody response.

In study 5 we conducted a full SNP × SNP analysis for epistasis, as part of a GWAS in T1D. The pair-wise SNPs with the lowest p-values for interaction were included in a follow-up study and one of the interactions was replicated. In an effort to functionally characterise the identified genetic variations we investigated the expression of the corresponding genes in human islets before and after cytokine stimulation and in leukocytes from diabetic and healthy individuals. We identified significantly different expression for one of the corresponding genes identified through epistasis.

We now know that multiple genetic variants influence the risk of T1D, but combinations of genetic as well as environmental factors may also play an important role. Understanding how genetic variants affect the function of proteins and molecular mechanisms and influence the pathogenesis of disease is vital for the future development of intervention strategies and therapeutic treatments. An integrative approach, as demonstrated by the studies in this dissertation, will help us understand the underlying mechanisms by which genetic variation affect disease pathogenesis and will hopefully eventually lead to this goal.