Examensarbete / Master thesis

Epigenetic impact on type 2 diabetes

Background: The prevalence of type 2 diabetes is rapidly increasing worldwide. Despite great efforts to prevent and cure the disease, the diabetes epidemic persists. Type 2 diabetes is a polygenic disease characterized by hyperglycemia due to impaired insulin secretion from pancreatic beta-cells and insulin resistance in peripheral target tissues such as skeletal muscle, adipose tissue and the liver. It is well established that combinations of environmental and genetic factors affect the susceptibility of type 2 diabetes. While obesity, physical inactivity and ageing represent non-genetic risk factors for type 2 diabetes, recent genome-wide association studies have identified a number of novel genetic variants associated with the disease. However, the interaction between genes and environment may also involve epigenetic factors, such as DNA methylation and histone modifications, to promote type 2 diabetes. Indeed, recent studies from our group and others propose that epigenetic factors may play an important role in the growing incidence of type 2 diabetes. Although there is no uniform definition of epigenetics, it has been described as heritable changes in gene function that occur without a change in the nucleotide sequence. In differentiated mammalian cells, DNA methylation occurs primarily on cytosines in CpG-dinucleotides. DNA methylation is associated with transcriptional silencing. This silencing can be achieved by either repressing the binding of transcription factors or by recruiting proteins that specifically bind to methylated CGs (methyl-CG binding proteins, e.g. MeCP2), which can further recruit histone deacetyltransferases (HDACs) and co-repressors, resulting in a condense inactive chromatin structure. Although we have studied the impact of DNA methylation on the pathogenesis of type 2 diabetes for some time, our knowledge about the epigenetic mechanisms linking environmental factors and type 2 diabetes remains limited.

Aim: To identify novel epigenetic mechanisms influencing the pathogenesis of type 2 diabetes.

Project plan: DNA methylation of 450 000 CpG sites will be analyzed in pancreatic islets from 90 human donors using Illumina Methylation BeadChip. Eleven of these donors had type 2 diabetes. Gene expression and genetic variation (SNPs) have been analyzed genome-wide in the same samples. The degree of DNA methylation will be correlated to gene expression, of respective gene in the genome. Moreover, an mQTL analysis will be performed where genetic variation is associated to DNA methylation of the 450 000 analyzed CpG-sites. The majority of the experimental analysis will be performed in a core facility at Lund University. To interpret and analyze all this data, this project will require bioinformatic/statistical capability and computer programming, using e.g. Perl.

This study will; **i)** identify CpG sites with important impact on gene expression in human pancreatic islets and **ii)** identify genetic variants associated with DNA methylation in human pancreatic islets.

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