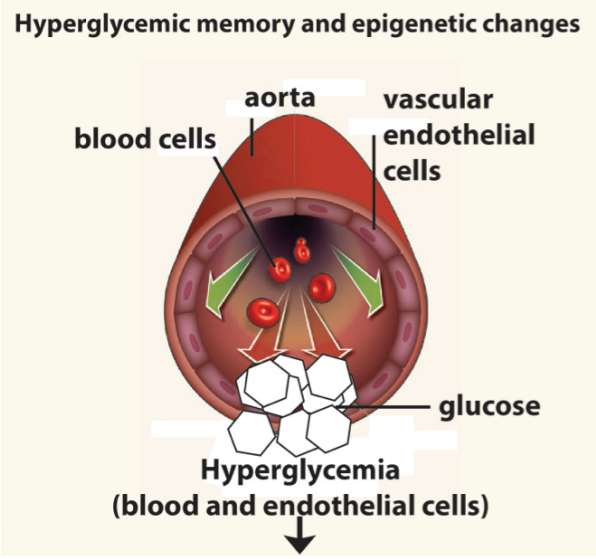
Epigenetics of diabetes, mapping the human methylome and building the epigenomic atlas of Type 1 Diabetes

Overview

Vascular complications remain the major cause of mortality and morbidity in diabetes with increasing evidence that prior glycemic exposure is a major determinant of susceptibility and progression of these disorders. Most individuals with diabetes have good health outcomes. However, many others do not. Despite the availability of effective therapies, diabetes remains the leading cause of cardiovascular disease (CVD), amputation, renal impairment and vision loss in adults. It is not simply poor metabolic or blood pressure control, as even with intensive intervention and dedicated compliance, complications still occur. Furthermore, it is not simply having the wrong genes, as GWAS studies have demonstrated that the genetic code explains only a fraction of the variability between those individuals with and without complications. The most likely explanation is that there is a complex interaction between the cellular environment and genes. In this project, we are interested in exploring non-genetic interactions which we hypothesize are an important determinant for the development and progression of vascular complications in individuals with diabetes.



Graphical representation of the hypothesis to to be tested. It is proposed that the complications of diabetes are associated with gene regulatory events that involve non-genetic (epigenetic) changes which are of direct relevance to this proposal.

We have shown in animal models of diabetes, that restoring normoglycemia per se does not reduce atherosclerosis. Furthermore we have shown that transient induction *in vivo* of hyperglycemia, either by use of a clamp or by parenteral injection were associated with persistent upregulation of genes implicated in vascular injury, as a result of epigenetic changes, namely histone modifications and DNA methylation. Among the best-characterized and most long-lasting epigenetic mark is the addition of methyl groups to the DNA, which stably modifies gene expression. DNA methylation is a key regulator of genomic imprinting and developmental disorders. However, much less is known about diabetes and its role in the development and progression of diabetic complications, including renal disease. The Finnish Diabetic Nephropathy (FinnDiane) Study, was started in 1997 with the explicit aim to study clinical, environmental and genetic risk factors for type 1 diabetes (T1D) and in particular its micro- and macro-vascular complications. Although significant progress has recently been made in elucidating the genetics of diabetes and its complications in this cohort, the non-genetic component remains poorly defined. And despite progress using GWAS approaches, it is becoming increasingly clear that genetic factors simply do not explain diabetes susceptibility and its progression.

Hypothesis and Project Aims

We hypothesize that the complications of diabetes are associated with gene regulatory events that involve non-genetic changes conferred by DNA methylation. The aims of the project involve addressing the following questions;

Is DNA methylation associated with the renal phenotype in diabetes?

Do the changes in DNA methylation drive changes in gene expression that are associated with the presence and progression of renal disease?

Overall Project Outcomes and Significance

In this project, we consider that accurately defining the molecular events that contribute to diabetic complications will lead to new strategies and specific targets for the development of therapies to prevent, retard or reverse the long term deleterious end-organ effects of chronic, intermittent and prior hyperglycemia.