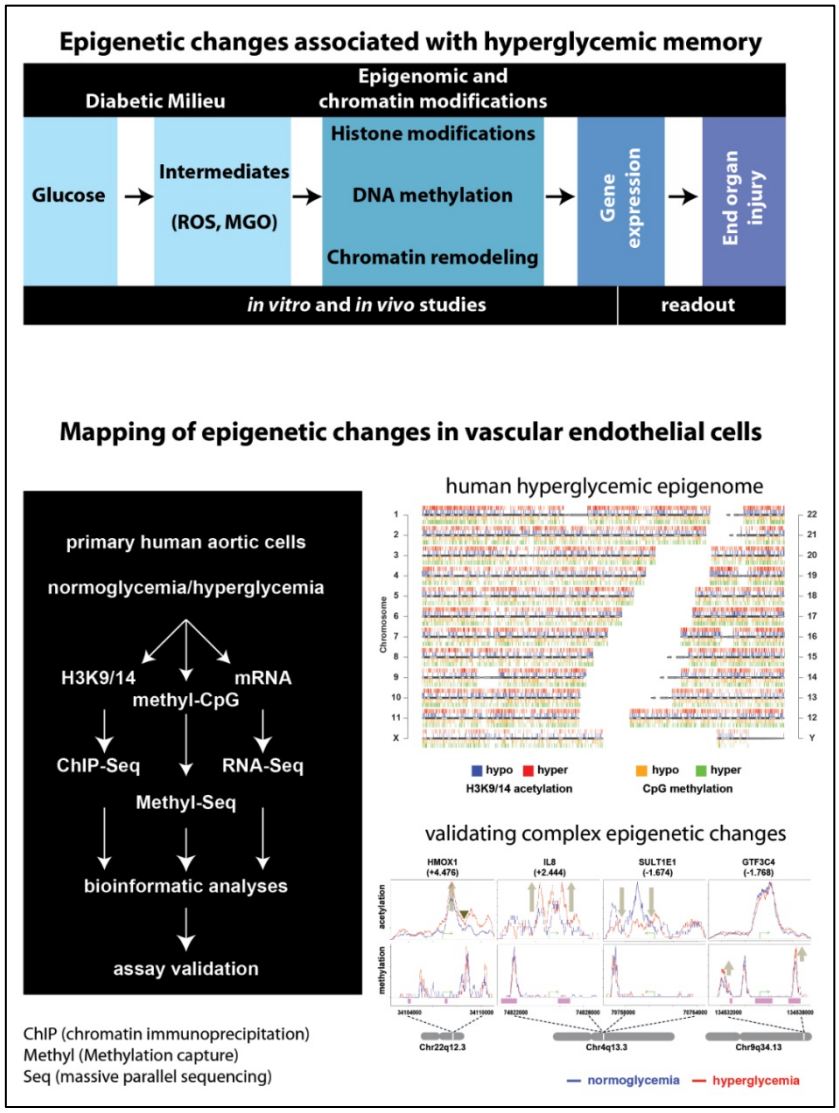
ROS mediated epigenetic changes associated with hyperglycemic memory

Overview

Metabolic memory is the name given to the phenomenon whereby previous exposure to metabolic perturbations has long-lasting patho-physiological effects, well after the event has dissipated. For example, the Diabetes Control Complications Trial (DCCT) and the subsequent Epidemiology of Diabetes Interventions and Complications (EDIC) study revealed that a period of suboptimal glycemic control in patients with type 1 diabetes, such as that experienced by those in the conventional arm, continues to be a risk factor for adverse outcomes, when compared to those who were initially intensively treated, despite the fact that glycemic control has subsequently been similar in the two cohorts for over a decade. Recent work following the UKPDS cohort of patients with type 2 diabetes also suggests that the benefits of glucose control can be sustained well beyond the period of the initial trial of intensified treatment. In addition, we have shown in animal models of diabetes, that restoring normoglycemia does not reduce atherosclerosis. Indeed, the pro-inflammatory impact of hyperglycemia persists and is similar to that seen in mice with chronic hyperglycemia. Consistent with these findings, diabetic dogs with poor glucose control and then subsequent intensive glycemic control has the same severity of retinopathy as those subjected to poor glycemic control for the entire period.



In recent studies by our group, we have determined that transient induction *in vivo* of hyperglycemia, either by use of a hyperglycemic clamp or by administration of high glucose were associated with persistent upregulation of various genes implicated in vascular injury, as a result of epigenetic events. These novel *in vitro* and *in vivo* findings have clearly identified that there is a memory at the level of the genome as a result of prior modulation of glucose levels. However, the molecular pathways involved appear to be more complex than previously appreciated and therefore need to be comprehensively evaluated.

The advent of massive parallel sequencing, access to novel *in vitro* and *in vivo* models of hyperglycemic memory and collaborations with clinical investigators with a specific interest with metabolic memory provides our team with the relevant expertise to define firstly in a integrated manner the complex series of epigenetic changes that occur as a result of prior hyperglycemia,

secondly to delineate how these changes lead to downstream effects on gene expression and finally to elucidate the relevant upstream pathways such as glucose related intermediates including methylglyoxal (MGO) and mitochondrial reactive oxygen species (ROS) generation that link hyperglycemia to genomic and epigenomic modifications, as observed in diabetes.

Hypothesis and Project Aims

We hypothesize that the damaging effects of prior hyperglycemia on the vasculature are associated with gene regulatory events that involve specific epigenetic signatures mediated by MGO, a key intermediate in the advanced glycation pathway and mitochondrial ROS generation. The aims of the project involve;

- To elucidate the underlying regulatory mechanism of gene activity as a result of transient hyperglycemia in human aortic endothelial cells
- To elucidate the underlying regulatory mechanism modulating gene activity as a result of transient hyperglycemia in animal models
- To elucidate the upstream regulators of epigenetic changes induced by transient hyperglycemia in human aortic endothelial cells

Overall Project Outcomes and Significance

Defining the molecular events that regulate the cellular effects of hyperglycemia will contribute to a better understanding of the phenomenon described as “metabolic memory”. These studies could lead to a new strategy and specific targets to develop therapies to prevent, retard or reverse the long-term deleterious effects of chronic, intermittent and prior hyperglycemia on the vasculature. Specifically, such targets would include enzymes that mediate certain histone modification events, such as methyl writing or erasing enzymes as well as enzymes that modulate genomic methylation. Other targets include the MGO/AGE/RAGE axis and antioxidants directly targeting mitochondrial and/or cytosolic generation of ROS.