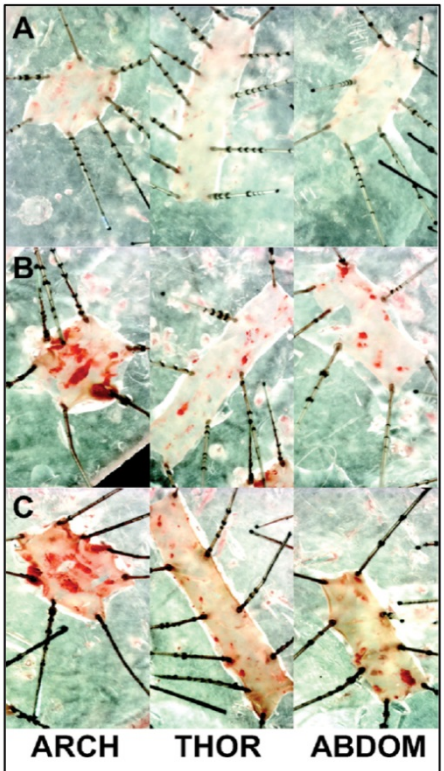
Set7 methyltransferase as a target to reduce the burden of diabetic vascular and renal complications

Overview

Diabetic complications remain the major cause of morbidity and mortality and this is primarily attributed to the damaging effects of hyperglycaemia. The complications often persist and may progress despite improved glucose control, probably as a result of prior episodes of hyperglycemia. Results from *The Diabetes Control Complications Trial* (DCCT) and the subsequent *Epidemiology of Diabetes Interventions and Complications* (EDIC) study have revealed that the deleterious end-organ effects that occurred in both conventional and intensified glycaemic control groups continued to operate more than 10 years after the patients had returned to normoglycemia. This phenomenon has now been confirmed in type 2 diabetes in a follow up report from the United Kingdom Prospective Diabetes Study –UKPDS indicating that glucose is an important factor not only for microvascular, but also, diabetes related macro-vascular disease. These studies suggest that the injurious effects of exposure to high glucose levels persist for years after better treatment, a phenomenon typically referred to as "hyperglycaemic memory". A molecular explanation for this phenomenon has remained elusive although it has recently been postulated that certain epigenetic pathways whereby glucose has sustained effects on key molecular processes to promote gene activation may explain, at least in part, metabolic memory. Since then, studies by our group have emphasized the role of histone modifications in hyperglycaemic memory and diabetic complications. In particular, *in vitro* and subsequent *in vivo* studies have identified that glucose induced activation of a particular histone methyl transferase, Set 7, appears to be critical in modulating gene-activating events implicated in vascular inflammation and renal fibrosis. This is relevant to diabetic complications since these pathological processes play a major role in diabetes associated atherosclerosis and nephropathy.



Plaque area remained increased in the previously hyperglycemic mice. Atherosclerotic plaques in aorta staining in red with picro sirus red solution in control apoE KO (A), diabetic apoE KO (B), and previously hyperglycemic apoE KO mice (C). ABDOM, abdominal; THOR, thoracic.

In this project, we plan to further build on our teams findings suggesting that Set7 is a target to develop new reno- and vaso-protective therapies in diabetes. It is planned to firstly further define the role of Set7 in diabetic renal disease and in particular to determine if this enzyme is also playing a key role in profibrotic pathways. Secondly, it remains unknown as to how glucose activates Set7. Putative mediators of end-organ injury in diabetes such as reactive oxygen species (ROS), primarily of mitochondrial origin and intermediates of the advanced glycation pathway such as the α-carbonyl, methylglyoxal (MGO) appear to play a role and we the project is designed to investigate this in appropriate preclinical models. Finally, to determine if Set7 is playing a key role in diabetic complications it will be necessary to inhibit this enzyme, initially using a conditional Set7 KO mouse that has been generated for us and subsequently using a new generation of Set7 inhibitors that are currently being characterized in the laboratory for clinical development.

Hypothesis and Project Aims

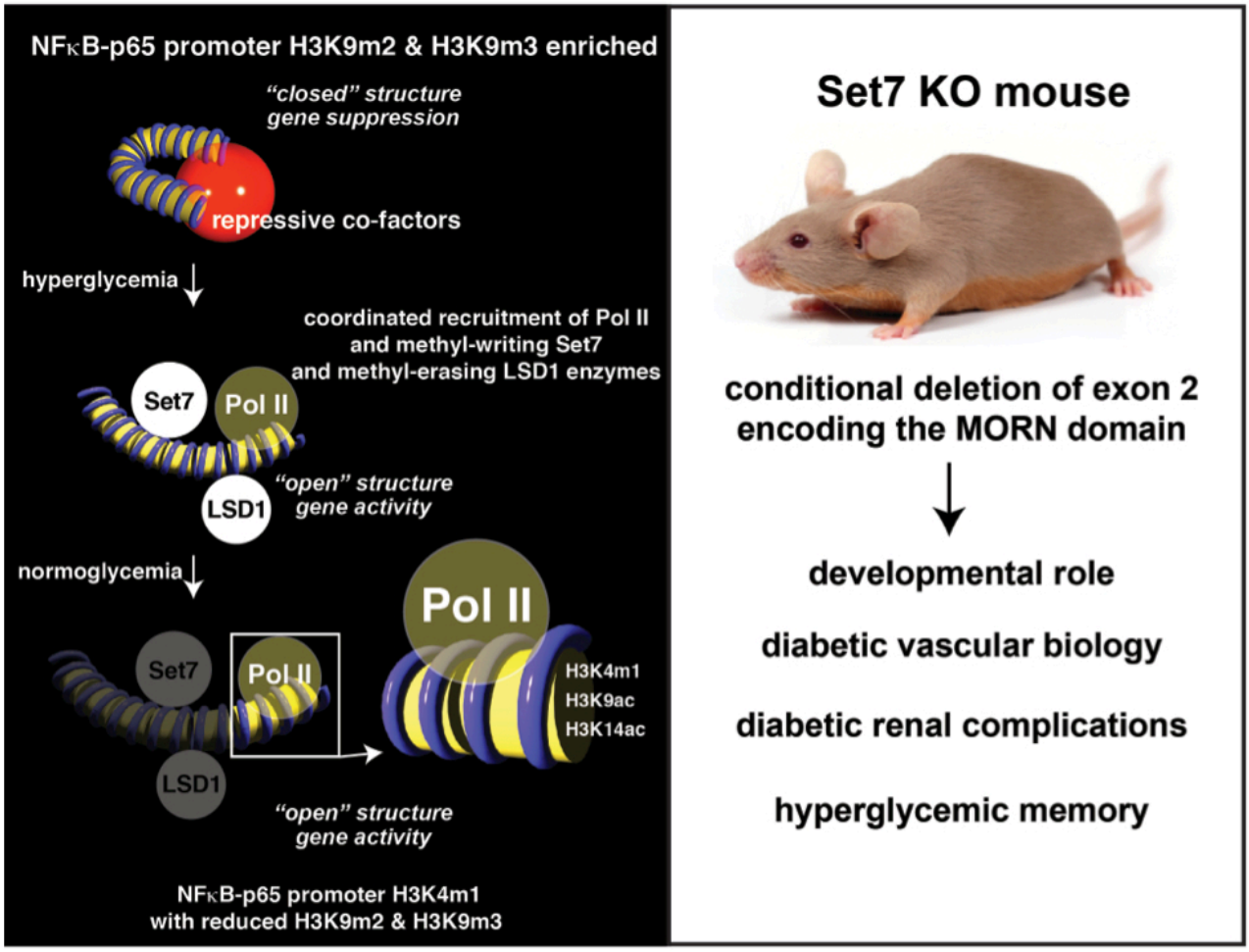
We hypothesize that the Set7 methyltransferase is a target to reduce the burden of diabetic vascular and renal complications. The specific aims of the project include;

- To further define Set7 as a key modulator of macrovascular and renal injury by identifying key genes that are modulated as a result of glucose induced Set7 mobilisation.

- To characterize the key stimuli, both metabolic and haemodynamic, in the diabetic milieu which promote Set7 mobilisation.

- To specifically target Set7, using molecular and pharmacological approaches, using *in vivo* models of diabetic complications.

Role of Set7 in diabetic renal and vascular injury in association with the expression of key proinflammatory and profibrotic molecules



Characeterizing the role of Set 7 in models of hyperglycemic memory. Using *in vitro* and *ex vivo* models of hyperglycemic memory we have identified persistent epigenetic changes include the recruitment of the methyl-writing and methyl-erasing enzymes that mediate histone modification and gene expression (left panel). Hyperglycemia associated with endothelial dysfunction and alterations in blood vessel growth, is the primary cause of vascular complications in diabetes. Furthermore, these vascular complications often persist and may progress despite improved glucose control, possibly as a result of prior episodes of hyperglycemia. In this schematic we simplify the signalling pathways mediated by hyperglycemia to show some of the key transcriptional events associated with gene activation and the concept of epigenetic persistence. Including pharmacological approaches to inhibit Set7 activity, we have developed a conditional Set7 knockout (KO) mouse model to understand the role of the methyltransferase in embryonic development, diabetic vascular and renal complications (right panel).

Overall Project Outcomes and Significance

Diabetic complications remain the major burden in diabetes. Unfortunately, despite improvements in management, complications often progress as a result of "hyperglycemic memory". If Set7 is a key mediator of this memory, by developing approaches to inhibit this enzyme in a manner without undue side effects this could represent a major strategy to optimize end-organ protection in diabetes.