**Division:** Diabetes and Nutritional Sciences

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**Project description (max 500 words) (497 words excluding reference list)**

The prevalence of type 2 diabetes (T2D) has increased inexorably in recent decades, with parallel increases in associated complications, and socio-economic costs(1). T2D ultimately develops as a consequence of pancreatic islet β-cell failure, resulting in markedly reduced insulin secretion and onset of hyperglycaemia. Therefore, determining the underlying mechanisms responsible for β-cell failure is essential for identification of new therapeutic targets for treatment and prevention of T2D(2).

Lipocalin 2 (LCN2) belongs to the lipocalin family of secretable small-molecule transporter proteins(3). LCN2 is well characterised as an iron-transporter protein(3) and is widely expressed and secreted from a range of tissues, including pancreatic islets(4). In year 1 the student will measure levels of LCN2 protein and mRNA in mouse islets and β-cell lines, and will correlate this with cellular levels of iron and expression of other genes and proteins controlling iron metabolism. In addition, we will investigate the effect of altered cellular iron content on LCN2 expression.

Evidence is accumulating that implicates LCN2 in the pathophysiology of insulin resistance and T2D. LCN2 levels are markedly elevated in serum and adipose tissue of obese, insulin resistant and T2D patients, and positively correlate with insulin resistance and hyperglycaemia(5). Similar findings have been observed in rodent models of insulin resistance and T2D(6).

These observations imply a pathophysiological role for LCN2 in onset insulin resistance and T2D. However, the precise function of LCN2 in mediating insulin resistance is unclear with several studies reporting conflicting results(6-8), whilst the role of LCN2 in β-cell function has not been examined.

In support of a pathophysiological role for LCN2 in mediating β-cell failure, our preliminary data shows that LCN2 gene expression is elevated in human T2D islets, whilst exposure of isolated mouse islets to recombinant LCN2 impairs insulin secretion. In year 2 the student will measure LCN2 gene and protein levels in islets isolated from rodent models of T2D, and
in isolated islets exposed to diabetogenic conditions (glucomlipotoxicity, inflammation). In addition, the effects of LCN2 exposure on islet/β-cell function will be determined using in vitro and ex vivo models.

Many of the reported consequences of iron overload and elevated LCN2 (in other disease states), such as inflammation and apoptosis(9-10), are consistent with a role in mediating β-cell failure(11-13). In year 3, using mouse islets, the mechanisms of action underlying the effects of LCN2 in islet function will be assessed, initially focussing on the roles iron metabolism/transport, inflammation and apoptosis. In addition the specific factors regulating LCN2 expression and secretion in islets will be examined. In year 4 the effects of LCN2 in islets will be examined in vivo. These studies will include administration of recombinant LCN2 to mice or treatment of diabetic models with LCN2 monoclonal antibody, with impact on islet function and glucose homeostasis examined. In addition, human islets are available to corroborate findings in mouse islets.

Through these studies we hope to identify a novel therapeutic target for treatment of T2D as well as revealing novel information regarding the role of iron in development of T2D.

References


