DR PHILLIP KANTHARIDIS

GENOMICS OF DIABETES COMPLICATIONS

Our group is focussed on identifying miRNAs and genes that contribute to development and progression of diabetic kidney disease and other complications of diabetes, and the development of novel strategies to protect against diabetic complications.

Research Brief

Diabetic nephropathy (DN) is the leading cause of chronic kidney failure in people with diabetes. It is characterized by glomerular basement membrane thickening with mesangial expansion, glomerular sclerosis and tubular interstitial fibrosis (TIF). Indeed, TIF is the strongest predictor of progression to end stage renal disease including in diabetes. Despite early clinical trials demonstrating that blockade of the renin-angiotensin system (RAS) improved renal function in advanced DN patients, recent studies indicate there is limited benefit in the early treatment of patients with RAS inhibitors to prevent progressive renal injury. These observations suggest new approaches are required to address the intrinsic causes of progressive fibrosis and to deliver better outcomes for patients with diabetes.

Our group has demonstrated a clear relationship between the pro-fibrotic factor TGF-β1 and microRNAs involved in the regulation of extracellular matrix (ECM) proteins and renal fibrosis. Based on these data which are derived from both in vitro and in vivo experiments, we hypothesize that the diabetic milieu causes a down-regulation of the certain microRNAs which have pathological consequences in the kidney and other sites of diabetic complications, leading to increased synthesis and accumulation of ECM proteins leading to fibrosis. We are exploring mechanisms by which miRNA expression can be restored to normal levels in order to prevent disease progression, leading to better outcomes in patients.

Methodologies

- Tissue culture models of various renal and vascular smooth muscle cells to explore role of microRNAs and growth factors such as TGF-β & PDGF
- Molecular manipulations of cells (transfection, miRNA, siRNA) and signal transduction pathways relevant to diabetic complications
- Lab methods include rt-QPCR, westerns, immunohistochemistry, immunofluorescence, reporter assays, miRNA assays
- Rodent models of diabetic nephropathy and diabetes-associated atherosclerosis
- Use of next generation sequencing to assess the relationship between miRNA, mRNA, DNA and histone methylation in the context of diabetes
- Viral delivery of cDNA and miRNA in vivo

Selected Publications

microRNAs In Diabetic Nephropathy

Diabetes

- SMAD7
- TGF-β
- miR-21
- CTGF
- miR-29
- miR-192
- ECM accumulation
- ZEB2
- miR-29
- miR-192
- miR-200 family
- E-cadherin

Diabetic Nephropathy

Nephropathy In The STZ-Diabetic apoE KO Mouse

Control

Diabetic (10wks)

- αSMA
- Col IV
- Fibronectin

Effect Of TGFβ On Proximal Tubular Epithelial Cells

Control TGFβ

- Light M.
- ZO-1/F-actin
- Vimentin
- Fibronectin

Control TGFβ