MicroRNA-155 upregulation induces podocyte insulin resistance; A new Therapeutic target in Diabetic Nephropathy?

Wonnacott A; Bowen T; Coward R; Fraser DJ.
Cardiff University; University of Bristol

Background
Loss of podocyte-specific insulin-sensitivity results in histological features of diabetic nephropathy (DN) in mice, implicating this pathway in disease development. MicroRNAs (miRNAs) regulate expression of the majority of protein coding genes at the post-transcriptional level, and are critical regulators of insulin responses in "traditionally" insulin-sensitive tissues; liver, fat and muscle. The role of miRNAs in podocyte insulin-signalling is unknown. We hypothesise that miR-directed loss of podocyte insulin responses is an initiating trigger in DN development.

Methods
Podocytes were rendered insulin-resistant by culture in diabetogenic media containing high dose insulin, glucose, and inflammatory cytokines. Microarray analysis was performed to compare miRNA expression profiles of wild type and insulin-resistant podocytes. Differentially expressed miRNAs were validated using RT-qPCR. In vitro manipulation of differentially expressed miRs was achieved using lentiviral transduction and miRvana mimics, and insulin responses assessed by Western Blot.

Results
Of 442 miRNAs detected by microarray analysis, 103 were differentially expressed. 5 miRNAs were selected for further study based on fold change, statistical significance ($p<0.0002$) and bioinformatic evidence of targets in insulin-signaling pathways, 4 of which (miR-155,-146a,-222 and -204) were validated by RT-qPCR. MiR-155 overexpression in podocytes in vitro resulted in repression of mRNA target PI3KR1, and subsequent reduction in Akt/ERK phosphorylation.

Conclusion
MicroRNA-155 is upregulated in podocyte insulin-resistance in vitro. Insulin-resistance may be effected via the target PI3KR1, repression of which leads to reduced insulin-signalling via Akt signalling. Thus miR-155 may be used as a biomarker of early DN, and may represent a novel therapeutic target to prevent disease progression.