**Inhibition of complement C5a receptor C5aR2 in diabetic kidney disease**

**Background**

Diabetic kidney disease (DKD) is the primary cause of end-stage renal disease (ESRD). Conventional therapies only slow, but do not stop, the progression of DKD to ESRD. Previously, we have shown that activation of the complement system, specifically the C5a-C5aR1 pathway, plays a pathogenic role in DKD. Complement C5a signals via a second receptor, C5aR2, and its role in diabetes is yet to be determined.

**Aim**

To investigate the role of complement C5a receptor C5aR2 in the pathogenesis of diabetes.

**Methods**

Diabetes was induced in 6-week-old wild type C57BL6/J and C5aR2-/-  mice by five daily injections of low dose streptozotocin (STZ; 55mg/kg). Mice were followed for 20 weeks. 24-hour urine was collected for the assessment of albuminuria, a marker of kidney dysfunction. Mitochondrial function was analysed using the Seahorse XF Bioanalyzer. Spectral flow cytometry was employed to immunophenotype renal and splenic immune cell populations. Gene expression and kidney structure were analysed using qPCR and histological staining, respectively.

**Results**

Consistent with this experimental model, wild type diabetic mice exhibited polydipsia, polyuria, and polyphagia, however the ablation of C5aR2 did not have a significant impact on these metrics. In contrast to our previous findings in diabetic C5aR1-/-  mice, deletion of C5aR2 had no effect on albuminuria, plasma cystatin C, or renal fibrosis in diabetic  C5aR2-/- mice. Interestingly, mitochondrial functional assays revealed dysfunction in complex II-mediated respiration in C5aR2-/-  mice. Spectral flow cytometry revealed a slight increase in CD11b+ monocytes in the spleen and kidneys of C5aR2-/- mice, and moreover a significant decrease in C5aR1+ monocytes in the diabetic kidney in comparison to wild type diabetic mice. This reduction in C5aR1+ monocytes, however, did not result in an improvement in kidney function or structural damage in diabetic C5aR2-/- mice.

**Conclusion**

Inhibition of C5aR2 is not renoprotective in this preclinical model of diabetes.