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Complement C5a receptor 1 (C5aR1) modulates mitochondrial fatty acid oxidation and cardiolipin remodelling leading to diabetic kidney disease

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The complement C5a-C5aR1 axis plays a crucial role in mediating inflammation in several inflammatory diseases. However, its role in diabetic kidney disease (DKD) is only beginning to be unravelled. Using an orally active inhibitor of C5aR1, PMX53, we aimed to investigate whether inhibition of the C5a-C5aR1 axis attenuates renal injury in streptozotocin (STZ)-induced diabetic mice.

Diabetes was induced in C57BL/6 mice by five daily injections of STZ (55 mg/kg; $n = 6-12$ mice/group). PMX53 (2 mg/kg/day) was supplied in the drinking water for 24 weeks. Kidney function was assessed by urinary albumin and oxidative stress by urinary 8-isoprostane. Regulatory T cell (Treg, FoxP3 positive) were examined by immunohistochemistry. Plasma IL-18 was measured by ELISA. Glomerulosclerosis was assessed by glomerulosclerotic index scoring. RNA-Seq and lipidomics were performed on renal cortex.

Kidney dysfunction, assessed by albuminuria, was significantly attenuated in the diabetic mice treated with PMX53 (83 ± 18 vs $30 \pm 9 \mu\text{g}/24 \text{ h}$, $p < 0.05$), along with a reduction in oxidative stress (urinary 8-isoprostane; 12 ± 2 vs $4 \pm 1 \text{ ng}/24 \text{ h}$, $p < 0.01$), inflammatory cytokine (plasma IL-18; 624 ± 34 vs $440 \pm 60 \text{ pg}/24 \text{ h}$, $p < 0.05$) and glomerulosclerosis (GSI; 2.8 ± 0.1 vs 2.2 ± 0.2). PMX53 also rescued the loss of anti-inflammatory FoxP3 positive Tregs in the diabetic kidneys ($p < 0.05$). Transcriptomic profiling and lipidomics of the kidney in diabetes revealed downregulation of mitochondrial fatty acid metabolism (*Acad10* and acylcarnitines). Interrogation of the lipidomics signature revealed abnormal cardiolipin remodelling in the diabetic kidney, a pivotal sign of disrupted mitochondrial bioenergetics and architecture. Blockade of C5aR1 signalling in diabetic mice normalized mitochondrial fatty acid metabolism and the cardiolipin signature, restoring mitochondrial homeostasis.

This study provides evidence for a pivotal role of the C5a/C5aR1 axis in propagating renal injury in the development of DKD via metabolic reprogramming and indicates that targeting this pathway may provide a substantial therapeutic benefit for this devastating complication of diabetes.

<https://doi.org/10.1016/j.orcp.2018.11.170>

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Targeting skeletal muscle ceramides to alleviate glucose intolerance

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Skeletal muscle represents the predominant site of postprandial glucose deposition and accumulates ceramides during lipid oversupply, which contribute to the development of obesity-associated insulin resistance. Ceramides vary in acyl-chain lengths from C_{12:0}-C_{30:0} which are regulated by the (dihydro)-ceramide synthases 1–6 (CerS). Both CerS5 and 6 generate C_{16:0} ceramide whilst CerS1 produces C_{18:0} ceramide. We have previously demonstrated that C_{16:0} ceramide contribute to diet-induced obesity and glucose intolerance in the liver and brown adipose tissue, however it was not apparent if C_{16:0} ceramide also promoted insulin resistance in skeletal muscle. Therefore our aim was to determine which CerSs disrupted skeletal muscle glucose homeostasis.

Skeletal muscle ceramide profiling of high fat diet (HFD) fed animals revealed increased C_{18:0}, but not C_{16:0}, ceramide. Furthermore, experiments revealed that *CerS6* and *CerS5/6* deletion in skeletal muscle did not prevent HFD-induced glucose intolerance.

Generation of HFD fed *CerS1*^{Δ/Δ} and *CerS1*^{ΔSkM} mice selectively reduced C_{18:0} ceramide without altering skeletal muscle triacylglycerol or diacylglycerol levels. The reduction of skeletal muscle C_{18:0} ceramide resulted in significant improvements in whole body insulin and glucose tolerance. Hyperinsulinemic-euglycaemic clamps in *CerS1*^{ΔSkM} mice showed skeletal muscle C_{18:0} ceramide regulated skeletal muscle glucose uptake, which consequently improved hepatic glucose production.

Fgf21 has been demonstrated to exert glucose metabolism-regulatory functions in multiple tissues. HFD fed *CerS1*^{ΔSkM} mice show increased skeletal muscle expression of *Fgf-21* and increased circulating FGF-21 concentrations. Current experiments are assessing if Fgf21 is regulating skeletal muscle glucose uptake in HFD fed *CerS1*^{ΔSkM} mice.

These results demonstrate that targeting C_{18:0} ceramide in skeletal muscle alleviates HFD-induced insulin resistance and glucose intolerance and demonstrates a tissue-specific function of distinct ceramide species during the development of obesity-associated insulin resistance.

<https://doi.org/10.1016/j.orcp.2018.11.171>