Abstract: 31O

Loss of Acyl-CoA dehydrogenase family member (ACAD10) does not alter whole-body metabolism or metformin action

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Background: Acyl-CoA dehydrogenase family member 10 (ACAD10) is a mitochondrial protein, purported to be involved in the fatty acid beta-oxidation pathway. Variants in *acad10* are associated with type 2 diabetes, insulin resistance and lipid oxidation in Pima Indians (Bian *et al.* 2010), while ACAD10-deficient mice exhibit abnormal glucose tolerance and elevated insulin levels (Bloom *et al.* 2018). Metformin is the most commonly prescribed therapy for type 2 diabetes; however, its precise mechanisms of action are still being uncovered. Interestingly, upregulation of ACAD10 is a requirement for metformin's ability to inhibit growth in cancer cells and extend lifespan in *C. elegan* (Wu et al. 2016). However, it is unknown if ACAD10 plays a role in metformin's anti-diabetic/metabolic actions.

Methods: We generated ACAD10KO mice via CRISPR and investigated the effect of whole-body ACAD10 deletion on whole-body metabolism and metformin action. At endpoint, mice were anaesthetised with Lethobarb (120mg/kg) via intraperitoneal injection and organs removed and frozen. To compliment the loss of function animal model, we investigated the overexpression of ACAD10 via adenovirus in cell culture using HepG2 liver cells.

Results: Compared to littermate wildtype (WT) control mice, we detected no difference in body composition, energy expenditure or glucose tolerance in male or female ACAD10KO mice, on a normal chow diet or a high caloric diet (high fat-high sucrose). Hepatic mitochondrial function and glucose production from isolated primary hepatocytes was also unaltered. Glucose excursions following acute administration of metformin prior to a glucose tolerance test were not different between genotypes nor was body composition or energy expenditure altered after 4 weeks of daily oral metformin treatment. Overexpression of ACAD10 in HepG2 cells, did not alter mitochondrial function but did alter components related to the insulin signalling pathways such as increasing the phosphorylation of AKT at serine 473 and the mRNA and protein expression of Serpine1 (PAI-1) and c-FOS.

Conclusion: Deletion of ACAD10 does not alter whole-body metabolism or impact the metabolic actions of metformin. However, ACAD10 up-regulation alters the mRNA and protein expression of components related to the insulin signalling pathway, a finding warranting further investigation *in vivo*.

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