Project 4: Metabolic flexibility in early diabetes development.

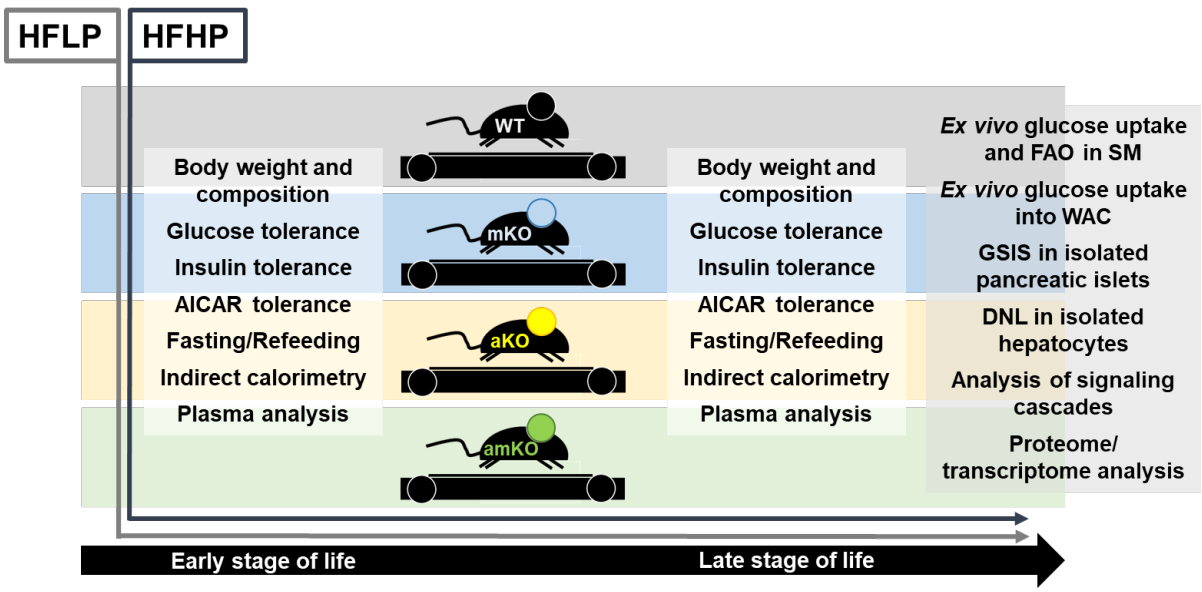
(Supervising Investigator: A. Chadt, DDZ; Co-Investigator: H. Al-Hasani, DDZ)

Background: TBC1D4 (AS160) and its close homologue TBC1D1 represent key regulators of insulin- and contraction-mediated glucose uptake and lipid metabolism in skeletal muscle and adipose tissue. RabGAP-deficient mice display a shift from glucose to lipid metabolism, indicated by impaired insulin- and AICAR-stimulated glucose uptake with concomitantly increased fatty acid oxidation (FAO) in skeletal muscle. Despite a high degree of homology, TBC1D1 and TBC1D4 play distinct roles in the diverse types of skeletal muscle and in whole-body substrate use. In contrast to their role in GLUT4-mediated glucose transport, the underlying mechanisms by which RabGAPs control lipid metabolism in skeletal muscle have not yet been elucidated. Interestingly, in arctic populations, homozygosity for a common muscle-specific *TBC1D4 p.Arg684Ter* loss-of-function variant defines a specific form of type 2 diabetes, characterized by insulin resistance and elevated postprandial plasma glucose levels. Reduced glucose clearance in *p.Arg684Ter* allele carriers may be an evolutionary adaptation to a high-protein high-fat diet.

Own previous work: We generated different RabGAP-deficient mouse models to study how lifestyle interventions like exercise and diet composition interact with genetic impairments of skeletal muscle insulin resistance. We further established protocols for *ex vivo* measurements of glucose uptake, fatty acid oxidation and contraction in isolated skeletal muscles, glucose uptake in primary adipocytes and *de novo* lipogenesis in primary hepatocytes.

Aim of the project: We will use insulin resistant mouse models and specific experimental diets to further clarify the underlying mechanisms how nutrition and exercise affect metabolic flexibility and, as a consequence, insulin sensitivity.

Work program: We will conduct time/organ-resolved metabolic characterization of mice with skeletal muscle- and adipocyte-specific deletion of RabGAPs (HSA-Cre recombinase, Adiponectin-Cre recombinase) and compromised metabolic flexibility. In these mice, longitudinal analyses of skeletal muscle, adipocyte and islet cell function and glycemic control in response to dietary and exercise interventions at different stages of life will be performed. Moreover, we will identify novel regulatory factors and mechanisms of insulin resistance using combined transcriptome and proteome analysis in different organs from RabGAP-deficient mice following dietary and exercise intervention.



References:

de Wendt C et al. Contraction-Mediated Glucose Transport in Skeletal Muscle Is Regulated by a Framework of AMPK, TBC1D1/4, and Rac1. Diabetes 2021; Schnurr TM et al. Physical activity attenuates postprandial hyperglycaemia in homozygous TBC1D4 loss-of-function mutation carriers. Diabetologia 2021; Eickelschulte S et al. AKT/AMPK-mediated phosphorylation of TBC1D4 disrupts the interaction with insulin-regulated aminopeptidase. J Biol Chem. 2021; Benninghoff T et al. The RabGAPs TBC1D1 and TBC1D4 Control Uptake of Long-

Chain Fatty Acids Into Skeletal Muscle via Fatty Acid Transporter SLC27A4/FATP4. Diabetes 2020; Espelage L et al. RabGAPs TBC1D1 and TBC1D4 in skeletal muscle function and exercise J Mol Endocrinol. 2020; Mafakheri S et al. AKT and AMP-activated protein kinase regulate TBC1D1 through phosphorylation and its interaction with the cytosolic tail of insulin-regulated aminopeptidase IRAP. J Biol Chem. 2018; Stermann T et al. Deletion of the RabGAP TBC1D1 Leads to Enhanced Insulin Secretion and Fatty Acid Oxidation in Islets From Male Mice. Endocrinology 2018; Chadt A et al. Deletion of both Rab-GTPase-activating proteins TBC1D1 and TBC1D4 in mice eliminates insulin- and AICAR-stimulated glucose transport. Diabetes 2015;64:746- 759. Diabetes 2015; Hartwig S et al. Secretome profiling of primary human skeletal muscle cells. Biochim Biophys Acta. 2014;1844(5):1011–1017; Chadt et al. Tbc1d1 mutation in lean mouse strain confers leanness and protects from diet- induced obesity. Nat.Gen. 2008