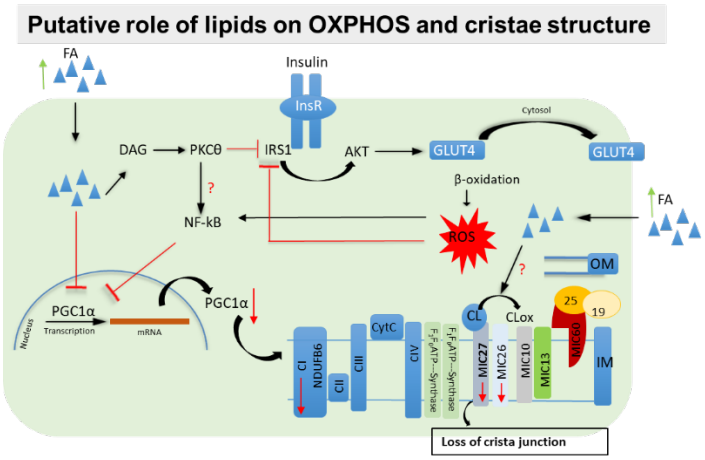
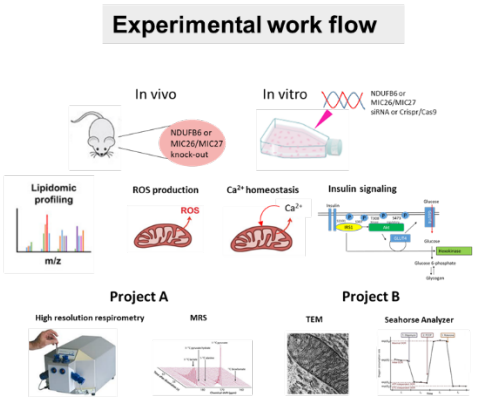
Project 3: Role of mitochondrial function in lipid-induced insulin resistance.

(Project 3a: Supervising Investigator: Prof. Michael Roden, DDZ; Co-Investigator: Prof. Andreas Reichert, UKD; Project 3b: Supervising Investigator: Prof. Andreas Reichert, UKD; Co-Investigator: Prof. Michael Roden, DDZ)

Background: Insulin resistance and type 2 diabetes (T2DM) are associated to decreased oxidative phosphorylation (OXPHOS), altered mitochondrial ultrastructure, increased reactive oxygen species (ROS) production as well as increased fat accumulation. Increasing mitochondrial functionality and biogenesis through PGC-1α leads to improved insulin sensitivity and glucose homeostasis. NDUFB6, a subunit of complex I of the electron transport chain, is a key regulator of OXPHOS and its expression in skeletal muscle is reduced upon aging as well as in T2DM patients. Cristae structure and crista junctions are essential for normal mitochondrial function and they are regulated by the MICOS (mitochondrial contact site and cristae organizing system') complex including 7 subunits. The subunit MIC26/APOO has been linked to fatty acid metabolism within the mitochondria promoting lipotoxicity in the heart. Thus, alteration of cristae morphology and MICOS complex might lead to abnormal NDUFB6 expression and altered mitochondrial function which represent a critical step for developing insulin resistance and consequently T2DM.
Own previous work: We demonstrated that lipids affect mitochondrial function and silencing of NDUFB6 lowered mitochondrial activity and insulin signaling and increased ROS production in contracted muscle cells. Furthermore, we identified the subunits MIC27 and MIC26 as essential for mitochondrial ultrastructure and OXPHOS and in particular showed that MIC27 binds to cardiolipin and that the non-glycosylated mitochondrial isoform of MIC26 is required for proper formation of crista junctions and is linked to cardiolipin metabolism. We further found a MIC26 ER/Golgi-resident form and a MIC26 secreted isoform.
Aim of projects 3a and 3b: We will use *in vitro* and mouse models to decipher the effects of lipids on mitochondrial OXPHOS (**project 3a**) and cristae structure (**project 3b**) in the pathogenesis of IR. We will evaluate the role of NDUFB6 and the MICOS subunits MIC26 and MIC27 in skeletal muscle and we will determine whether fatty acids and/or other physiological and metabolic factors can modulate NDUFB6 and/or MIC26/MIC27 expression.
Work program: We will characterize cellular metabolism and mitochondrial ultrastructure and function in siRNA-induced knock-down or Crispr/Cas9-generated knock-out C2C12 cells and then in mice with skeletal muscle-specific knock-out of NDUFB6 or MIC26/MIC27. In these mice the lipid metabolites, ROS production, Ca^{2+} homeostasis and insulin signalling pathway will be analysed. Moreover, we will determine the methylation state of NDUFB6 and whether its expression is regulated by PGC-1α. We will assess the role of MIC26 isoforms T1DM and T2DM models as well as in NDUFB6 knockout-mice.
Title PhD project 3a (Roden/Reichert):
Abnormal expression of NDUFB6 and related proteins in the pathogenesis of type 2 diabetes
Title PhD project 3b (Reichert/Roden):
Role of MICOS subunits MIC26 and MIC27 in insulin resistance and type 2 diabetes mellitus





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