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Dynamic complexomic analysis reveals a role for Von Willebrand Domain-containing Protein 8 (Vwa8) in mitochondrial morphology and substrate preference.

Link: MiP2023 Obergurgl AT

Alan Lukas (2023)

Event: MiP2023 Obergurgl AT

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Introduction: Obesity is turning into a worldwide pandemic, with most patients also affected by other comorbidities such as type 2 diabetes, hypertension, or cardiovascular disease. With mitochondria being a major site for fatty acid oxidation, they represent an important target for obesity treatment. Mitochondria are dynamic organelles, and their morphology influences both the organization of membrane protein complexes as well as mitochondrial substrate preference1.
Methods: By combining 2-dimension blue native gel electrophoresis with proteomics and bioinformatics in heart mitochondria undergoing membrane remodelling we identified a strong correlation between the key cristae biogenesis protein Opa1 and Vwa8, a putative AAA+ ATPase with a dynein conformation. In order to study the role of Vwa8 protein in mitochondrial physiology, we developed the HEK293 Vwa8 knock-out cell line and Vwa8 KO mice.
Results and discussion: Vwa8 protein localized to the mitochondrial intermembrane space where it formed discrete spots. Deletion of Vwa8 led to an increase in mitochondrial respiration on fatty acids but not on glucose or glutamine. The Vwa8 KO mice showed decreased resting energy requirements as well as higher heat production, indicating a stronger preference for lipid oxidation. Moreover, the subcutaneous adipose tissue of Vwa8 KO mice showed increased markers of browning such as an increase in mitochondria content and lipid droplet multilocularity. The Vwa8 KO mice remained more insulin sensitive and with higher lean mass proportion upon a high-fat diet. In conclusion, Vwa8 affects mitochondrial substrate preference, induces browning of subcutaneous adipose tissue and represents a new target for obesity treatment.

1. Alan L, Scorrano L. (2022) Shaping fuel utilization by mitochondria. Curr Biol. 2022 Jun 20;32(12):R618-R623. doi: 10.1016/j.cub.2022.05.006.

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Labels: **Pathology:** Obesity

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