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Promotionsverfahren von **Frau M.Sc. Melissa Lubeck**
Auslage der Dissertation und Gutachten sowie Termin der mündlichen Prüfung
Anlage: Einseitige Zusammenfassung der Dissertation

Sehr geehrte Damen und Herren,

in dem oben genannten Promotionsverfahren wird die Annahme der Dissertation

Role of apolipoprotein MIC26 in mitochondrial and metabolic disorders

von den Berichterstattenden Prof. Dr. A. Reichert und Prof. Dr. H. Al-Hasani beantragt. Sie kann zusammen mit den Gutachten in der Zeit

vom 01.05.2024 bis 12.05.2024

eingesehen werden. Bitte wenden Sie sich zur Einsicht an das Promotionsbüro (promotionmnf@hhu.de).

Einsprüche gegen diese Dissertation können nur zwei Tage nach der vorgenannten Frist geltend gemacht werden. Erfolgt kein Einspruch, so gilt die Dissertation als angenommen (§ 7 Ziffer (5) PO).

Sofern die Dissertation angenommen wird, findet die mündliche Prüfung am

15.05.2024 um 10:00 Uhr

im **Raum 22.02.00.35A** statt. Als Prüferinnen bzw. Prüfer sind vorgesehen:
Prof. Dr. S. Prömel, Prof. Dr. W. Martin und Prof. Dr. M. Zurbriggen.

Die Öffentlichkeit ist bei der Befragung zugelassen.

Mit freundlichen Grüßen
im Auftrag

Silke Krispin

Role of apolipoprotein MIC26 in mitochondrial and metabolic disorders

Dissertation Melissa Lubeck, March 2024

Abnormal functioning and regulation of the human metabolism is implicated in the onset of severe life hampering diseases including type 2 diabetes or non-alcoholic fatty liver disease. Mitochondria are pivotal for essential metabolic functions including cellular lipid metabolism, energy generation and fuel utilization. Malfunctioning mitochondria result in disease development and progression. As the primary metabolic hub mitochondria utilize the majority of cellular nutrients and orchestrate their conversion or storage in form of energy. Moreover, mitochondrial dysfunction has a prominent role in obesity and insulin resistance. Mitochondrial ultrastructure and intra- as well as intermitochondrial dynamics are essential features for proper mitochondrial functionality. Mitochondrial ultrastructure, especially in terms of cristae formation, maintenance, and dynamics, are dependent on the MICOS complex, comprising seven mammalian subunits: MIC60, MIC10, MIC13, MIC19, MIC25, MIC27 and MIC26. MIC26, hypothesized to have a dual cellular localization within the mitochondrial MICOS complex and the cellular secretory pathway, has been implicated to play a role in diabetes and lipid metabolism.

This dissertation aimed to elucidate the cellular localization, function of MIC26 and its contribution to metabolic diseases. Using multiple biochemical assays, cell and tissue models, including *MIC26* KO cell lines, MIC26 overexpression, along with immunoblot analysis and mass spectrometry, we demonstrate that MIC26 is exclusively present as a 22 kDa protein in the mitochondria. Additionally, we showed that MIC26 plays an essential physiological role. Patients, harboring a MIC26^{E178X} mutation, inducing protein truncation, developed progeria-like phenotypes, resulting in lethality. Biological evaluation unveiled mitochondrial ultrastructure defects, abnormalities in intermitochondrial dynamics and protein instability. To elucidate the functional role of MIC26 regulating cellular metabolism under nutritional overload conditions, a multi-omics study supported by validation using various assays in wildtype and *MIC26* KO cells under normo- and hyperglycemia, was conducted. We identified MIC26 to be a crucial cellular regulator of mitochondrial metabolite usage. MIC26 exerts a suppressive influence on glycolysis, cholesterol, and lipid metabolism under normoglycemic conditions, with opposing effects under hyperglycemia. Deleting *MIC26* resulted in nutritional independent rewiring of cellular glutamine usage and oxidative phosphorylation. Overall, we identified MIC26 as a metabolic rheostat, maintaining mitochondrial ultrastructure, leading to stability of several mitochondrial metabolite transporters while it directly impacts lipid and cholesterol metabolism by harboring a lipid binding domain, resulting in alterations of lipid metabolism. We hypothesize that balanced MIC26 levels and functionality are required to prevent excess fat accumulation under normal nutrient conditions and to mediate energy storage under nutrient overload. Thus, we propose MIC26 to be essential to prevent obesity and the development of metabolic diseases.