UniversitätsKlinikum Heidelberg

External Seminar Speaker

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Place: **Analysezentrum 3, 2. OG, Room 02.332**
Date: **Tuesday, March 12th**
Time: **11.00 am**

Defective mitochondrial cardiolipin remodeling affects cardiac metabolism and cellular signaling

Mitochondria play a central role in the metabolism of the heart and defects in mitochondrial functions are frequently associated with cardiac disorders. Barth Syndrome (BTHS) is an X-linked cardiomyopathy caused by mutations in the TAZ gene, encoding the mitochondrial transacylase Tafazzin. Tafazzin facilitates the remodeling of cardiolipin, a hallmark phospholipid in mitochondrial membranes. The altered lipid composition affects mitochondrial morphology, the organization of the respiratory chain and causes a decrease in mitochondrial respiratory capacity. Cardiac metabolism strongly relies on the consumption of fatty acids to gain energy. Here, we show a strong defect of the mitochondrial enzymes involved in fatty acid metabolism in Barth syndrome. Structural changes in the mitochondria due to cardiolipin deficiency not only affects cardiac metabolism, but also impact cellular signaling pathways. A lack of cardiolipin remodeling in mouse embryonic fibroblasts impacts HIF-1α signaling in response to hypoxia. Human cardiomyocytes differentiated from patient-derived iPSCs recapitulate this phenotype. Tafazzin-deficient mouse hearts display impaired HIF-1α stabilization and undergo maladaptive hypertrophy with heart failure in response to pressure overload challenge. Defective cardiolipin remodeling dampens impaired HIF-1α signaling due to a lack of NF-□B activation through reduced ROS production.