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FAKULTÄT FÜR CHEMIE

Einladung zum Vortrag von

Prof. Des R. Richardson
University of Sydney, Australia

Medicinal chemistry and the design of therapeutics for the treatment of the iron overload and cardiodegeneration in Friedreich's ataxia

There is no effective treatment for the cardiomyopathy of the most common autosomal recessive ataxia, Friedreich's ataxia (FA). The identification of potentially toxic mitochondrial (MIT) iron (Fe) deposits in FA suggests that Fe plays a role in its pathogenesis. This study used the muscle creatine kinase conditional frataxin (Fxn) knockout (mutant) mouse model that reproduces the classical traits associated with cardiomyopathy in FA. We examined the mechanisms responsible for the increased cardiac MIT Fe loading in mutants. Moreover, we explored the effect of Fe chelation on the pathogenesis of the cardiomyopathy. Our investigation showed that increased MIT Fe in the myocardium of mutants was due to marked transferrin Fe uptake, which was the result of enhanced transferrin receptor 1 expression. In contrast to the mitochondrion, cytosolic ferritin expression and the proportion of cytosolic Fe were decreased in mutant mice, indicating cytosolic Fe deprivation and markedly increased MIT Fe targeting. These studies demonstrated that loss of Fxn alters cardiac Fe metabolism due to pronounced changes in Fe trafficking away from the cytosol to the mitochondrion. Further work showed that combining the MIT-permeable ligand pyridoxal isonicotinoyl hydrazone with the hydrophilic chelator desferrioxamine prevented cardiac Fe loading and limited cardiac hypertrophy in mutants but did not lead to overt cardiac Fe depletion or toxicity. Fe chelation did not prevent decreased succinate dehydrogenase expression in the mutants or loss of cardiac function. In summary, we show that loss of Fxn markedly alters cellular Fe trafficking and that Fe chelation limits myocardial hypertrophy in the mutant.

Dienstag, 2. Oktober 2018, 15:00 Uhr
Hörsaal 4 der Fakultät für Chemie
Währinger Straße 42, 1090 Wien

Bernhard Keppler
Institut für Anorganische Chemie

Veronika Somoza	Bernhard Keppler	Lothar Brecker
Vizedekanin	Dekan	Vizedekan