CerS2 ko in vivo reduces pro-inflammatory ceramides and improves doxorubicin mediated cardiotoxicity

T. Kretzschmar¹, M. Bekhite¹, K. Gruen¹, T. Mueller², M. Graeler², S. Nietzsche³, M. Westermann³, P.C. Schulze¹

¹University Hospital Jena, Department of Internal Medicine I, Division of Cardiology, Jena, Germany
²University Hospital Jena, Department of Anesthesiology and Intensive Medical Care, Jena, Germany
³University Hospital Jena, Electron Microscope Center, Jena, Germany

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University Hospital Jena

Background: Ceramides and their role in various signaling pathways are believed to regulate distinct cellular effects. Accumulation of ceramides seems to be associated with an inflammatory phenotype negatively affecting cardiomyocyte vitality and mitochondrial homeostasis.

Aim: The purpose of our study is to identify underlying ceramide signaling pathways and characterize downstream effects on cell vitality of cardiomyocytes.

Methods: A CerS2 ko mouse model was generated and the animals were treated with 7 cumulative doses of 3 mg/kg BW Doxorubicin (Dox). Subsequently, hearts were extracted and analyzed, including mRNA (qPCR) and protein expression (WB) and ceramide level (mass spectrometry).

Results: The CerS2 ko was stable and Dox injection did not increase CerS2 protein expression. Mass spectrometry revealed an increase of long chain ceramides (C≥20) with the highest peak for C18:0 (5.08 ± 0.21, p<0.001) but a decrease of the pro-inflammatory very long chain ceramides C24:0 (0.65 ± 0.20, p = 0.02) and C24:1 (0.23 ± 0.22, p<0.001). qPCR showed a decrease of TNFα (0.18 ± 0.49, p<0.001), IL-1β (0.43 ± 0.27, p<0.001) and BNP (0.28 ± 0.53, p<0.001). Furthermore, mitochondrial homeostasis improved by a reduction of the mitochondria fission related gene Mitochondrial fission factor (Mff) (0.74 ± 0.23, p = 0.007).

Conclusion: CerS2 ko and subsequent ceramide reduction improves cardiomyocyte vitality on a cellular level by a reduction of inflammation and an improvement of mitochondrial function. Thus, regulation of ceramide levels through control of CerS2 activity might represent a novel therapeutic option for the control of cardiotoxicity.