Addendum

Increased de novo ceramide synthesis and accumulation in failing myocardium

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Following the publication of our article, we became aware of a related publication by Reforgiato and coauthors that described increased de novo ceramide synthesis and inflammation adjacent to the necrotic core area in a mouse model of 30 minutes of ischemia and reperfusion injury (1). Similar to the findings of our study in a chronic model of ischemic cardiomyopathy 3 months following myocardial infarction and in a large cohort of patients with advanced heart failure, Reforgiato et al. found that ceramide accumulation was accompanied by increased levels of serine palmitoyltransferase (SPT), which could be inhibited by administration of myriocin, an inhibitor of SPT. Their study, which was performed in an animal model of acute ischemic injury, independently supports the findings of our systematic lipidomic study in patients with advanced heart failure before and after mechanical unloading and cardiomyopathy as well as *Sptlc2*-deletion mice.

We believe the detailed lipidomic analysis in our study provides an important advance to the field. This analysis allowed the differentiation of various ceramide species, and we related specific ceramide chain lengths to the biologic phenotypes described. Further, we linked ceramide metabolism and de novo ceramide synthesis using various expression plasmids (sptlc1, -2 and -3) in cell culture experiments to changes in ceramide species accumulation and dysregulation of oxidative and glycolytic metabolism as typical for the failing myocardium. Thus, we linked the lipids to changes in their metabolic pathways.

Together, these studies highlight a key role of de novo ceramide synthesis of distinct ceramide species and their accumulation following acute ischemic injury and in chronically failing myocardium.

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1. Reforgiato MR, et al. Inhibition of ceramide de novo synthesis as a postischemic strategy to reduce myocardial reperfusion injury. *Basic Res Cardiol*. 2016;111(2):12.