Effect of sphingomyelin synthase related protein on non-alcoholic steatohepatitis and liver fibrosis

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Sphingomyelin synthase related protein (SMSr) belongs to SMS family but it has no SM synthase activity. Recently, we found that SMSr is a phosphatidylethanolamine-specific phospholipase C (PE-PLC), however, its biological function is still unknown. In current study, we found that SMSr deficiency attenuated glucosylceramide accumulation-induced non-alcoholic steatohepatitis (NASH) and then, liver fibrosis, although the deficiency could not prevent high fat diet induced fatty liver. Further, we found that SMSr deficiency significantly reduced the production of liver inflammatory cytokines, including TNFα, IL-1, IL-6, and TGFβ1, and, consequently, reduced the production of certain fibrosis related factors, including collagen 1α1, platelet-derived growth factor receptors (PDGFRs), in hepatic stellate cells. Importantly, we further found that PE supplementation, *in vitro* or *in vivo*, could mimic the situation of SMSr deficiency, at least partially, resulting in less expression of TGFβ1, collagen 1α1, and PDGFRs. This study was the first to disclose a biological function of SMSr, as a PE-PLC, and indicated that PE is one of the key factors which prevent the development of fatty liver into NASH and fibrosis. These results implicated that the inhibition of SMSr/PE-PLC is a new approach for the treatment of NASH and fibrosis.

Sphingolipids are important lipid components in the brain and they should be deeply involved in brain health. Although our research focus is on sphingolipid in cardiovascular diseases, we would like to collaborate with our colleagues at Downstate, given the fact that we have many mouse models related with sphingolipid metabolism.