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Sphingomyelin Synthase Related Protein (SMSr) is a Regulator of Serine Palmitoyltransferase (SPT)

Sphingomyelin synthase-related protein (SMSr) is a member of the SMS family but lacks sphingomyelin (SM) synthase activity. We recently identified SMSr as a phosphatidylethanolamine-specific phospholipase C (PE-PLC) linked to metabolic dysfunction-associated fatty liver disease (MAFLD). However, its precise biological function remains unclear. Hierarchical clustering of human Genotype-Tissue Expression (GTEx) data revealed that SMSr co-expresses with SPT, the rate-limiting enzyme in sphingolipid biosynthesis, along with other sphingolipid metabolism-related genes in liver and adipose tissues. SMSr expression highly correlates with SPT expression in both tissues across genders and is associated with age and obesity. In mice, SMSr overexpression increased SPT activity, while knockout (KO) under a high-fat diet reduced it, altering levels of ceramide, SM, and glucosylceramide. Furthermore, PE treatment significantly suppressed SPT activity in vivo and in vitro in a dose-dependent manner. These findings suggest that SMSr regulates SPT and sphingolipid biosynthesis. Given the challenge of developing specific SPT inhibitors for MAFLD and cardiovascular disease treatment, targeting SMSr/PE-PLC activity may offer a novel therapeutic approach. Notably, unlike SPT KO mice, global Smsr KO mice are viable, fertile, and healthy, supporting the feasibility of this strategy.