Sphingomyelin synthase 1 deficiency decreases atherosclerosis in mice: reduced sphingomyelin, induced glycosphingolipids, and decreased NFκB and MAP kinase activation

Sphingomyelin synthase (SMS) catalyzes the formation of sphingomyelin (SM). SMS has two isoforms: SMS1 and SMS2. Although having same SMS activity, they are different enzymes with distinguishable subcellular localizations and cellular expression patterns. It is conceivable that these differences could yield different consequences, in terms of sphingolipid metabolism and its related atherogenesis.

We created *Sms1* gene knockout (KO) mice and found the *Sms1* deficiency significantly decreased plasma, liver, and macrophage SM (59%, 45%, and 54%, respectively), but had marginal effect on ceramide levels. Surprisingly, we found that *Sms1* deficiency dramatically increased glucosylceramide and GM3 levels in plasma, liver, and macrophages (4-12 folds), while *Sms2* deficiency had no such effect. Since the major SMS isoform in the macrophage is SMS1, we thus evaluated HDL- or apoA-I-mediated cholesterol efflux and LPS-mediated inflammatory responses in *Sms1* deficient macrophages. We found that *Sms1* deficiency had no effect on cholesterol efflux. However, the deficiency significantly attenuated Toll-like 4 receptor-mediated NF-κB and MAP kinase activation after LPS treatment. To evaluate atherogenesity, we transplanted *Sms1* KO mouse bone marrow into LDL receptor KO mice (*Sms1*+/−→*Ldlr*+/−). After 3 months on a Western diet, *Sms1*+/−→*Ldlr*+/− mice showed a significant decrease of atherosclerotic lesions in the root and the entire aorta (35% and 44%, *P*<0.01,
respectively), and macrophage content in lesions (51%, P<0.05), compared with
WT→Ldlr−/−) mice. In conclusion, Sms1 deficiency decreases SM but dramatically
increases the levels of glycosphingolipids. Atherosclerosis in Sms1−/−→Ldlr−/− mice are
significantly decreased.