Accumulation of sphingomyelin in Niemann-Pick disease type C cells disrupts Rab9-dependent vesicular trafficking of cholesterol

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Niemann-Pick disease type C (NPC) is a genetic disorder in which patient cells have endosomal/lysosomal accumulation of cholesterol and sphingolipids. However, the relationship between sphingolipids and cholesterol accumulation in NPC cells has not been established. Here, we investigated the role of sphingomyelin (SM) on the accumulation of cholesterol in NPC cells. Reduction of SM by inhibition of the ceramide transfer protein CERT decreased the cholesterol accumulation in NPC cells. The accumulation of SM in NPC cells inhibited the transport of cholesterol to the endoplasmic reticulum. Overexpression of Rab9 in NPC cells reduced the cholesterol accumulation, which was recovered by treatment with SM. In NPC cells that overexpressed a Rab9 constitutively active mutant, SM treatment did not lead to the cholesterol accumulation. These results indicate that SM negatively regulates the Rab9-dependent vesicular trafficking of cholesterol, and a reduction in SM levels in NPC cells recovers the Rab9-dependent vesicular trafficking defect.