Synopsis of Original Research Paper

Enhanced Aggregation of Ganglioside GM2 Transmit Proliferation Signals

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Sandhoff Disease is a progressive neurodegenerative disorder caused by mutations in the *HEXB* gene which encodes the β-subunit of *N*-acetyl-β-hexosaminidase A and B, resulting in the accumulation of the ganglioside GM2. Previously, we reported that astrocytes from Sandhoff Disease model mice (ASD) grew markedly more rapidly than those from wild-type mice (AWT). This was caused by c-Src and ERK activation due to accumulated GM2 in the lysosomes. These results suggested that c-Src might be directly activated by accumulated GM2. To investigate this issue, here we analyzed i) interactions between GM2 and intracellular c-Src by Western blotting of immunoprecipitation with anti-GM2 antibody; ii) localization of accumulated GM2 and c-Src, by immunofluorescence; iii) length of the fatty acids of GM2 accumulated in lysosomes, by MALDI-TOF MS. We observed that the accumulated GM2 interacted directly with c-Src and co-localized in the lysosome membrane. Analysis of the GM2 ceramide moiety revealed no difference in the fatty acid lengths in AWT and ASD, indicating that densely-packed GM2 interactions with the cytosolic kinase c-Src, and glycosphingolipid (GSL) aggregation was sufficient to result in transmission of signals for proliferation. These results indicate that excessive accumulated GSLs have direct signal transduction activity, not only at the cell surface but also at the membrane of intracellular organelles such as lysosomes.