Role of Plasma membrane-ER Contact Sites in GM1-mediated Neuronal Cell Death

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Lay summary

GM1-gangliosidosis, caused by deficiency of lysosomal β-Galactosidase (β-Gal), is a catastrophic neurodegenerative lysosomal disease in children and adolescents. With the funding provided by the NTSAD we have initiated a series of studies aimed to elucidate how the primary substrate of β-Gal, GM1 ganglioside, a resident glycosphingolipid of neuronal plasma membranes, affects molecular pathways at specific membrane contact sites formed between the endoplasmic reticulum (ER) membranes and the plasma membrane of neurons, named PAMs. Using ultrastructural and morphological analyses, and quantitative proteomics, we have identified several proteins and protein complexes that are differentially expressed in response to accumulation of GM1 at these membrane contact sites. Furthermore, we have begun to connect the structural/functional changes in *β-Gal*$^{-/-}$ PAMs to the synaptic abnormalities that we have identified in the GM1-gangliosidosis model. We believe that these novel studies will set the stage for a better understanding of the neuropathological implications of GM1 accumulation at specific membrane contact sites, like the PAMs, that function as signaling hubs and play a role in the control of neuronal membrane homeostasis. Ultimately, these studies may also reveal novel or alternative therapeutic avenues for patients affected by GM1 gangliosidosis.