NTSAD - Alessandra d'Azzo, PhD

Role of ER-PM Contact Sites in GM1-mediated Neurodegeneration

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GM1-gangliosidosis, caused by deficiency of lysosomal β-Galactosidase (β-Gal), is a catastrophic, neurodegenerative lysosomal storage disease in children and adolescents, associated with massive accumulation of the β-Gal substrate GM1 ganglioside (GM1) in the nervous system. With funding from the NTSAD we have conducted a study focused on dissecting the role of GM1 in synaptic plasticity in a faithful mouse model of the disease. The primary objective was to investigate how altered GM1 concentration at membrane contact sites (MCS) formed between the endoplasmic reticulum (ER) and the plasma membrane (PM) (called ER-PM junctions) of *β-Gal*$^{-/-}$ neurons, elicits a pathogenic cascade that ultimately disturbs synaptic connectivity and leads to neuronal loss. By using ultrastructural and morphological analyses, as well as quantitative proteomics, we succeeded to identify a plethora of membrane proteins and protein complexes that are dysregulated in response to accumulation of GM1 at the ER-PM junctions. Most importantly, we have demonstrated a direct structure-function relationship between increased concentration of GM1 at the ER-PM junctions and specific synaptic abnormalities. Overall, these findings provide novel insights into the neuropathological effects of GM1 accumulation at target MCS, microdomains that are emerging as key signaling hubs in the control of neuronal homeostasis and function. (NTSAD grant: 2018-2020)