Genetic Studies of the NCLs: A Window into New Therapeutic Strategies for the NCLs and Related Neurodegenerative Disorders

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The Cotman laboratory applies genetics and cell and animal biology to the study of lysosomal dysfunction in neurodegenerative disease. The neuronal ceroid lipofuscinoses (NCLs) encompass a group of single gene neurodegenerative disorders that lead to vision loss, seizures, progressive dementia and loss of motor function, and there is significant genetic and cell biological overlap between the NCLs and other neurodegenerative diseases including frontotemporal dementia and Parkinson disease. By investigating single gene NCLs, we aim to enhance a mechanistic understanding of these disorders and to drive gene, cell-based, and small molecule therapy development for the NCLs and related forms of neurodegenerative disease.

While several forms of NCL are due to lysosomal enzyme deficiencies, a significant proportion arise from loss-of-function mutations in genes encoding transmembrane proteins of the secretory pathway and the endolysosomal system. Restoring the lost function of these membrane proteins in a sufficient number of brain and retinal cells using a classical gene therapy approach is challenged by current technology. Advancements in gene therapy vectors will improve this outlook. Combination gene, cell and small molecule-based approaches are an alternative to classical gene therapy with substantial potential to advance effective therapy development for the NCLs and related disorders.

We recently identified early disease stage abnormalities in ion regulation associated with autophagy and lysosomal function in CLN3 disease, one of the most common genetic subtypes of NCL. Mechanistic studies on these pathways have identified novel targets for therapy that are now in preclinical testing in CLN3 disease models, using gene and small molecule, as well as combination therapy approaches. The role of these pathways in neuronal and glial cells and how this contributes to the CLN3 neurodegenerative disease process is also now a major focus of our research.

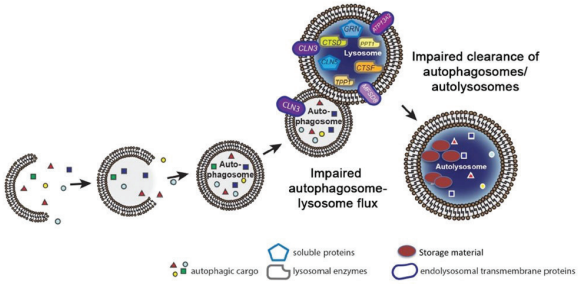

Figure 1. NCL-related proteins function in the autophagy-lysosomal pathway. The figure (adapted from Butz et al., BBA-Molecular Basis of Disease, 2020, 1866(9):165571) highlights lysosomal enzymes and soluble and transmembrane NCL lysosomal proteins in autophagosomal and lysosomal compartments and the impact of the loss of NCL protein function on the autophagolysosomal pathway. Additional NCL-related proteins localize to the endoplasmic reticulum and cis-Golgi membranes (CLN6 and CLN8, not shown) where they function to regulate the lysosomal targeting of NCL-related and other lysosomal proteins. Combination gene, cell, and small molecule-based approaches are being developed that target this pathway in the NCLs and related disorders.