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Hugo Bellen is a Professor at the Duncan Neurological Research Institute (NRI) in the Departments of Molecular and Human Genetics and Neuroscience of Baylor College of Medicine (BCM). His current research focuses on the discovery of new rare neurological disease genes and the elucidation of the pathogenic mechanisms of neurodevelopmental and neurodegenerative diseases using fruit flies and mice in collaboration with human geneticists. His laboratory, together with those of Drs. Shinya Yamamoto and Michael Wangler, house the fly Model Organism Screening Center for the Undiagnosed Diseases Network of the NIH. They played a key role in the discovery of 35 new rare human neurological diseases in the past 4 years. His group has also made major strides in solving key problems related to common neurodegenerative diseases such as Alzheimer’s disease and Parkinson’s disease. This research has revealed that different aspects of lipid metabolism are severely affected in these diseases and has provided inroads towards therapeutic approaches. Originally from Belgium, Bellen earned a degree in Business Engineering (University of Brussels) and a Doctor in Veterinary Medicine (University of Ghent). He obtained his Ph.D. in Genetics (University of California Davis) and completed postdoctoral research in the laboratory of Dr. Walter Gehring (University of Basel). He started his independent career at Baylor College of Medicine, where he rose through the ranks and now is the March of Dimes Professor in Developmental Biology and the Charles Darwin Professor in Genetics at BCM. In recognition of his work he received the George Beadle Award from the Genetics Society of America; the Linda & Jack Gill Distinguished Neuroscience Investigator Award from Indiana University; the Michael E. DeBakey, MD, Excellence in Research Award from BCM. He is an elected member of the National Academy of Sciences, the American Academy of Arts & Sciences, and the European Molecular Biology Organization. He is currently the President of the Genetics Society of America.

Abstract: GlucosylCeramide in the Pathogenesis of Rare Lysosomal Disease and Parkinson’s Disease

It is well documented that carriers of variants that cause Lysosomal Storage Diseases (LSD) have an increased risk of developing Parkinson’s disease (PD). Gaucher disease (GD), the most prevalent LSD, is caused by recessive mutations in GBA. GBA hydrolyzes glucosylceramide (GlcCer) into glucose and ceramide. Loss of GBA causes the accumulation of GlcCer, severe neurological symptoms and early death (Type 2-GD). GBA carriers are five times more likely to develop PD than non-carriers, suggesting a strong link between GlcCer and PD.

We have shown that loss of Phospholipase-A2-Group6 (PLA2G6), shares early onset neurodegeneration with GD patients, effects the function of lysosomes and causes an elevation of GlcCer. PLA2G6 has also been associated with Parkinsonism and is named PARK14. Interestingly, overexpression of α-Synuclein, a protein that is typically associated with PD, in neurons, also leads to an expansion of lysosomes and an elevated level of GlcCer. Moreover, PD and GD patients often exhibit elevated levels of ceramides and GlcCer in their serum, but how the elevated levels of GlcCer contribute to the neurological symptoms is unknown.

We turned to Drosophila to address this question and discovered that loss of the fly ortholog of GBA, Gba1b, causes lysosomal expansion and neurodegenerative phenotypes. To our surprise, Gba1b is only expressed in glia in flies. We found that 1) GlcCer is synthesized in the neurons upon activity; 2) loss of Gba1b causes GlcCer accumulation in glia and to a lesser extent in neurons; 3) loss of Gba1b leads to vacuolized glia and a progressive loss of neuronal function; 4) all these defects are rescued by glial expression of human GBA1; and 5), human neurons transfer GlcCer to astrocytes without direct contact in a cell culture system. Collectively, our data shows that GlcCer is produced in neurons and transported to glia for degradation, but upon loss of GBA function, GlcCer accumulates in the cytoplasm of neurons and glia where it is toxic and affects mitochondrial function. These findings provide insight into the pathogenesis of PD and a mechanism by which GBA haploinsufficiency contributes to increased PD risk.