Glucosylceramide : From a simple glycosphingolipid to a complex disease

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Profile

Professor Tony Futerman received his BSc degree in biochemistry at the University of Bath, England (1981), and obtained his PhD from the Weizmann Institute in 1986, where he discovered that acetylcholinesterase is attached to the cell membrane via a GPI anchor. From 1987-1990, he was a postdoctoral fellow at the Carnegie Institution (Baltimore, Maryland, USA) with Richard Pagano, and in 1990 he joined the staff of the Weizmann Institute where he is currently the Joseph Meyerhoff Professor of Biochemistry and the director of the Nella and Leon Benoziyo Center for Neurological Diseases. He is a member of the Editorial Board of the Journal of Biological Chemistry, and was the chair of the 2006 Gordon Conference on Glycolipid and Sphingolipid Biology and of the 2011 Gordon Conference on Lysosomal Diseases. He currently runs a laboratory of ~20 scientists, postdoctoral fellows and students, and has multiple international collaborations. Prof. Futerman's research focuses on the cell biology and biochemistry of sphingolipids and the roles that they play in health and disease. He works on two major issues, namely understanding the biology of ceramide and how ceramide is synthesized, and the mechanisms underlying neuronal dysfunction in sphingolipid storage diseases such as Gaucher and Tay-Sachs diseases, two genetic disorders found at high levels in Ashkenazi Jewish populations, in which glycosphingolipids accumulate. In particular, he wishes to understand how the brain is affected in these diseases, and has provided some data which may explain why nerve cells in the brain are damaged.

Lysosomal storage disorders (LSDs) are caused by the defective activity of lysosomal proteins, which results in intracellular accumulation of undegraded metabolites. Sphingolipid (SL) storage disorders are a sub-group of LSDs, in which unmetabolized SLs and glycosphingolipids accumulate. Research over the past few years has demonstrated that SL storage can result in multiple direct or indirect effects on various cellular compartments and on biochemical pathways. SL storage disorders are normally associated with devastating neurodegeneration and death at early age.

Gaucher disease (GD), the most common LSD, is caused by the defective activity of glucosylceramidase (glucocerebrosidase, GlcCerase), the lysosomal hydrolase responsible for glucosylceramide (GlcCer) degradation. As a result of this autosomal, recessive genetic defect, the glycosphingolipids, GlcCer and glucosylsphingosine accumulate intracellularly. Tissue macrophages engorged with glycolipid-laden lysosomes ('Gaucher cells') are the hallmark of the disease.

Generation of animal models that faithfully recapitulate the three clinical sub-types of GD has proved to be more of a challenge than first anticipated. The first mouse to be produced died within hours after birth due to skin permeability problems, and mice with point mutations did not display symptoms correlating to human disease and also died soon after birth. Recently, conditional knockout mice (the 'Karlsson mouse') that mimic some features of the human disease have become available, and this mouse has been of huge importance for advancing our understanding of the neurological changes that occur in neuronal forms of GD.

The rare neuronopathic forms of GD are characterized by profound neurological impairment and neuronal cell death, but little is known about the neuropathological changes that underlie these events. We systematically examined the onset and progression of various neuropathological changes (including microglial activation, astrogliosis and neuron loss), and documented the brain areas that are first affected, which may reflect vulnerability of these areas to GlcCerase deficiency. We have also identified neuropathological changes in several brain areas and pathways, such as the substantia nigra reticulata, reticulotegmental nucleus of the pons, cochlear nucleus and the somatosensory system, which could be responsible for some of the neurological manifestations of the human disease. In addition, we have established that microglial activation and astrogliosis are spatially and temporally correlated with selective neuron loss.

We have also delineated the role of neuroinflammation in the pathogenesis of neuronopathic GD and demonstrated significant changes in levels of inflammatory mediators in the brain. Levels of mRNA expression of interleukin-1β, tumor necrosis factor-α, tumor necrosis factor-α receptor, macrophage colony-stimulating factor and transforming growth factor-β were elevated by up to ~30-fold, with the time-course of the increase correlating with the progression of disease severity. The most significant elevation was detected for the chemokines CCL2, CCL3 and CCL5. Blood-brain barrier disruption was also evident in neuronopathic GD mice. Finally, extensive elevation of nitrotyrosine, a hallmark of peroxynitrite formation, was observed, consistent with oxidative damage caused by macrophage/microglia activation. Together, our results suggest a cytotoxic role of activated microglia in neuronopathic GD. We suggest that once a critical threshold of GlcCer storage is reached in neurons, a signaling cascade is triggered that activates microglia, which in turn releases inflammatory cytokines that amplify the inflammatory response, contributing to neuronal death.

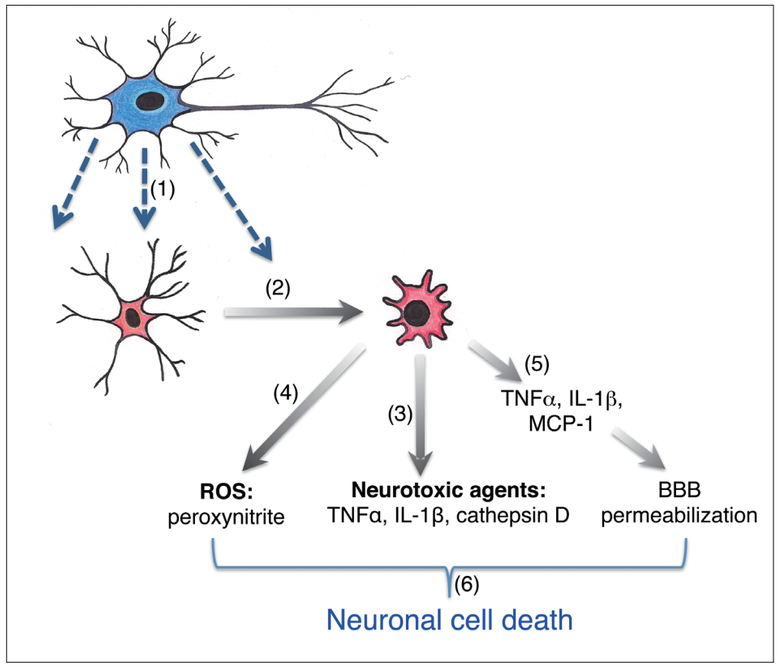

Figure 1. Proposed mechanism for the role of neuroinflammation in nGD. Upon GlcCer accumulation in neurons, neurons signal to the surrounding microglia (1) and as a result, resting microglia become activated (2). Activated microglia initiate a neuroinflammatory cascade involving elevation of cytokines, release of neurotoxic agents (3) and reactive oxygen/nitrogen species (4), and BBB permeabilization (5). The persistence of GlcCer accumulation in neurons and continuous glial activation results in chronic inflammation, which contributes to neuronal cell death (6).

Finally, Parkinson's disease is associated with mutations in the GlcCerase gene. We performed an exhaustive literature search and found that additional LSDs might be associated with Parkinson's disease, based on case reports, the appearance of pathological features such as α-synuclein deposits in the brain, and substantia nigra pathology. Our findings suggested that the search for biochemical and cellular pathways that link Parkinson's disease with LSDs should not be limited exclusively to changes that occur in GD, such as changes in GlcCerase activity or in GlcCer levels, but rather include changes that might be common to a wide variety of LSDs. Moreover, we propose that additional genetic, epidemiological and clinical studies should be performed to check the precise incidence of mutations in genes encoding lysosomal proteins in patients displaying Parkinson's symptoms.

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