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Gaucher-related synucleinopathies: The examination of sporadic neurodegeneration from a rare (*disease*) angle

S. Pablo Sardi [1,*], Seng H. Cheng [1], Lamya S. Shihabuddin [1]

Genzyme, a Sanofi Company, 49 New York Avenue, Framingham, MA 01701, USA

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ABSTRACT

Gaucher disease, the most common lysosomal storage disease, is caused by a recessively inherited deficiency in glucocerebrosidase and subsequent accumulation of toxic lipid substrates. Heterozygous mutations in the lysosomal glucocerebrosidase gene (*GBA1*) have recently been recognized as the highest genetic risk factor for the development of α-synuclein aggregation disorders ("synucleinopathies"), including Parkinson's disease (PD) and dementia with Lewy bodies (DLB). Despite the wealth of experimental, clinical and genetic evidence that supports the association between mutant genotypes and synucleinopathy risk, the precise mechanisms by which *GBA1* mutations lead to PD and DLB remain unclear. Decreased glucocerebrosidase activity has been demonstrated to promote α-synuclein misprocessing. Furthermore, aberrant α-synuclein species have been reported to downregulate glucocerebrosidase activity, which further contributes to disease progression. In this review, we summarize the recent findings that highlight the complexity of this pathogenetic link and how several pathways that connect glucocerebrosidase insufficiency with α-synuclein misprocessing have emerged as potential therapeutic targets. From a translational perspective, we discuss how various therapeutic approaches to lysosomal dysfunction have been explored for the treatment of *GBA1*-related synucleinopathies, and potentially, for non-*GBA1*-associated neurodegenerative diseases. In summary, the link between *GBA1* and synucleinopathies has become the paradigm of how the study of a rare lysosomal disease can transform the understanding of the etiopathology, and hopefully the treatment, of a more prevalent and multifactorial disorder.

Contents

Abbreviations: AAV, adeno-associated virus; CNS, central nervous system; DLB, dementia with Lewy bodies; ERAD, endoplasmic reticulum associated-degradation; ERT, enzyme replacement therapy; FDA, Food and Drug Administration; *GBA1*, lysosomal glucocerebrosidase gene; *GBA2*, cytosolic glucocerebrosidase gene; HDAC, histone deacetylase; iPSC, induced pluripotent stem cells; Lamp-2a, lysosomal-associated membrane protein 2a; LRRK2, leucine-rich repeat kinase 2; PCT, pharmacological chaperone therapy; PD, Parkinson's disease; RIPK3, receptor-interacting serine–threonine kinase 3; *SNCA*, α-synuclein gene; SRT, substrate reduction therapy; TFEB, transcription factor EB; VPS35, vacuolar protein sorting 35.

* Corresponding author. Tel.: +1 508 270 2089; fax: +1 508 271 4776.
E-mail address: pablo.sardi@genzyme.com (S.P. Sardi).
[1] These authors are employees of Genzyme, a Sanofi Company.

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1. Gaucher disease: a rare lysosomal storage disorder

Gaucher disease is the most common lysosomal storage disease and affects approximately 6000 individuals in the U.S. This disease was first described by Phillipe Gaucher in his doctoral thesis in 1882 (Gaucher, 1882). Dr. Gaucher described a patient who presented with splenomegaly as a result of an increased size of the splenic cells. The enlarged cells (now called "Gaucher cells") and an enlarged spleen have become signs of the disease. A succession of scientific breakthroughs occurred over the following century to ultimately achieve a Food and Drug Administration (FDA)-approved therapy for Gaucher disease in 1991 (Grabowski, 2008).

Gaucher disease is caused by biallelic (homozygous or compound heterozygous) mutations in the glucocerebrosidase (*GBA1*, OMIM 606463) gene (Brady et al., 1966). The *GBA1* gene is located in a gene-rich region on chromosome 1q21 spanning 7.6 kb and including 11 exons. A highly homologous pseudogene is located 16 kb downstream and presents challenges for the molecular analysis of *GBA1* (Winfield et al., 1997). Two in-frame ATG translational initiation sites are found in the *GBA1* gene open reading frame and both give rise to active lysosomal protein (Sorge et al., 1987). Glucocerebrosidase (EC 3.2.1.45) is a 497 amino acid protein of approximately 62 kDa that hydrolyses the β-glucosyl linkage of glucosylceramide and other glycolipids in lysosomes. Glucocerebrosidase requires the coordinated action of saposin C and negatively-charged lipids for maximal activity (Grabowski, 2008). Lysosomal trafficking of glucocerebrosidase involves a specific binding partner, lysosomal integral membrane protein-2 (Limp-2) for ER maturation and correct sorting to the lysosomes (Reczek et al., 2007) through a highly regulated mechanism (Jovic et al., 2012). To date, approximately 300 different mutations have been identified in *GBA1*, including point mutations, frameshift mutations, splice-site alterations, and recombinant alleles that encompass segments of a neighboring pseudogene sequence. The glucocerebrosidase deficiency in Gaucher patients promotes widespread accumulation of substrate glycosphingolipids in various organs, including the brain. Although *GBA1* mutations are typically associated with glucocerebrosidase activity reduction, the exact pathogenic mechanism of Gaucher disease remains unknown. Experimental evidence indicates that reduced glucocerebrosidase activity plays a major role in the pathogenic mechanism. Nevertheless, various alternative mechanisms appear to contribute to the disease presentation, including the misprocessing of the enzyme into the lysosome and an increase in endoplasmic reticulum associated-degradation (ERAD) stress. Furthermore, differing clinical presentations in patients and even siblings who share the same genotype suggest a role for disease modifiers (Cox, 2001; Grabowski, 2008).

Gaucher disease displays a wide spectrum of clinical and pathological features in humans; thus, it has been subclassified according to the involvement of the central nervous system (CNS) structures. The excess accumulation of glucosylceramide in macrophages is the main manifestation in the visceral organs of affected individuals. The lipid accumulation can subsequently lead to hepatosplenomegaly, anemia and thrombocytopenia, bone involvement, and, other less frequent unpredictable clinical manifestations (Grabowski, 2008). These visceral manifestations are common to all variants of Gaucher's disease, but categorical differentiation into neuronopathic (type-2 and type-3) and non-neuronopathic (type-1) variants serves useful clinical purposes. Because of the primary visceral macrophage involvement in type-1 Gaucher disease and the intrinsic difficulties traversing the blood–brain barrier to access the CNS, this variant was the initial focus for the development of enzyme replacement therapies. Although, class 1 Gaucher disease was historically classified by the lack of neurological manifestations, a significant number of patients with type-1 Gaucher disease experience parkinsonism contesting the current classification of Gaucher disease, and suggesting that the three forms of Gaucher disease each involve a different profile of neurological manifestations (Beavan and Schapira, 2013; Grabowski, 2008; Neudorfer et al., 1996; Sidransky and Lopez, 2012).

Two types of therapies are approved for the treatment of the visceral manifestations of Gaucher disease. Enzyme replacement therapy, through the systemic administration of glycan-modified recombinant glucocerebrosidase, can effectively treat the visceral and hematological manifestations of Gaucher disease (variant 1) (Barton et al., 1991). However, this form of enzyme replacement therapy has no effect on CNS pathology in variants 2 and 3 because the recombinant enzyme is unable to traverse the blood brain barrier. An alternative therapeutic approach for Gaucher disease that is less widely used is substrate reduction therapy. This approach inhibits glucosylceramide synthase, thereby reducing the synthesis of its substrate, glucosylceramide, to balance production with the impaired rate of degradation (Cox et al., 2000). To date, treatment with the approved therapies for Gaucher disease (i.e., Imiglucerase, Velaglucerase or Miglustat) has not demonstrated effects on the progression of parkinsonism in patients who present with Gaucher and Parkinson's disease (PD) (Bembi et al., 2003; Kraoua et al., 2011; Rosenbloom et al., 2011).

Twenty years ago, the first successful enzyme replacement therapy was developed for treating Gaucher disease, a monogenic mechanistically "simple" disorder. The recent and unanticipated discovery of a genetic link between Gaucher disease and PD has opened new avenues to study this devastating neurodegenerative disease. The basic and clinical expertise accumulated for the rare disease is helping shed light on the development of therapeutics for more common and complex sporadic forms of disease. The focus of this review is to provide an update on the current understanding of the clinical and mechanistic aspects of this genetic interaction and the various therapeutic approaches under consideration.