Vicious Cycles: Dysfunctional GCase and Parkinson's Disease

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Mutations in the GBA gene are one of the most common genetic factors associated with Parkinson's disease, yet it is still unknown how the enzyme coded by the gene, glucocerebrosidase (GCase), directly influences pathogenesis. However, recent systematic investigation offers answers regarding the important role GCase may play in the risk factor of developing the disease.

Imagine a disease that could strike at any time, where prevention is futile and nearly all cases have an unknown origin or cause. Parkinson's disease (PD) has a nearly identical epidemiology to this hypothetical disease, and though many breakthroughs in its pathology have occurred over the last 200 years, many of the risk factors and contributors to the development of Parkinson's disease are still shrouded in mystery. Using a combination of methods, Henderson et al. (2020) explores the complex interactions between the activity of a lysosomal enzyme, GCase, and the accumulation of dangerous forms of α-synuclein, the hallmark indicator of Parkinson's disease. This proverbial unveiling of the role of GCase activity, and by extension mutations in the GBA1 gene which codes for it, profoundly improve both our understanding of the pathology of parkinsonian diseases and opens the door to future therapeutic targets for treatment. Though many cases of PD are idiopathic, the prevalence of a relationship between GCase dysfunction and PD is apparent, with around 8-12% of sporadic cases involving a single mutation in the GBA gene (Avenali et al., 2020, p. 1). Although the majority with this mutation may not go on to develop Parkinson's disease, the likelihood of developing the disease increases five-fold for those who have it (Michel et al., 2016, p. 678). Individuals with mutations have also been shown to develop non-motor symptoms such as dysfunctional smell and psychiatric symptoms more than controls before developing any parkinsonian symptoms (Migdalska-Richards & Schapira, 2016, p. 80). Additionally, patients with GBA mutations often have much more aggressive disease development, slightly earlier onset, and more often develop dementia compared to non-GBA sporadic PD patients (Del Rey et al. 2018, p. 4), illustrating the importance of decoding these cellular interactions.

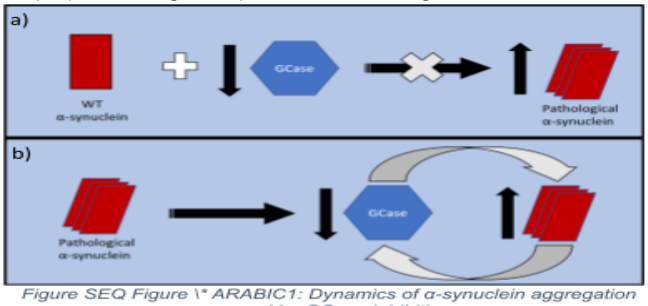

*Figure SEQ Figure * ARABIC1: Dynamics of α-synuclein aggregation caused by GCase inhibition*

- Wildtype (WT), properly folded α-synuclein found within the cell, when combined with decreased GCase activity, was not shown to cause new pathological α-synuclein aggregation. Rather,
- When pathological α-synuclein was already present within the cell, a positive feedback loop was shown to occur, where decreased or dysfunctional GCase activity instigated an increase in aggregation, which in turn further inhibits GCase activity, leading to a reinforcement to aggregation.

It is both unknown and debated whether the mechanism for PD pathogenesis due to GCase dysfunction is a loss-of-function mechanism, where reduction of GCase activity results in pathology. Likewise, it is similarly debated whether a gain-of-function mechanism is at play, where the mutated form is the cause of pathology itself (Migdalska-Richards et al., 2016, p. 83-84). Despite these two conflicting hypotheses, the former is more widely accepted (Blumenreich et al., 2020). Additionally, research suggests there may be a positive feedback loop where accumulation of α-synuclein may act as an inhibitor of GCase activity, which in turn allows for more accumulation of α-synuclein (Michel et al., 2016, p. 678). This leads to a vicious cycle that only amplifies itself and shows that the interaction may not be a simple linear relationship. However, the actual process of how mutations of GBA1 modulate and elevate the risk of developing dangerous forms of α-synuclein still remains a mystery for neuroscientists. Using a variety of in-vitro cell cultures and in-vivo mouse models, Henderson et al. (2020) systematically set out to answer this question once and for all. The researchers hypothesized that GCase inhibition acted as a modulator, rather than a direct cause, performing more like a dimmer knob on a lamp rather than a full-blown switch itself. To test this, they first set out to define the dynamics of the interaction between α-synuclein and GCase. First, Henderson et al. (2020) investigated the role GCase inhibition played in the formation of new pathological α-synuclein aggregates. Using primary hippocampal neurons (PHN), the brain cells found within the part of the brain responsible for memory, they inhibited GCase activity by injecting conduritol-β-epoxide (CBE), which is a small molecule that acts as an inhibitor. CBE effectively acts as a stop sign, halting all GCase activity without actually reducing the amount of GCase in the cells (Henderson et al., 2020, p. 824). Additionally, the researchers injected small clumps of pre-aggregated α-synuclein protein called pre-formed fibrils (PFFs) into some of the cells to act as an additional control. It was found that aggregation of α-synuclein, both wildtype and pathological forms, were not present with only GCase inhibition. However, with the addition of PFFs, aggregation significantly increased when paired with GCase inhibition. This shows that inhibition of GCase alone is not enough to cause new aggregation in healthy cells (Figure 1a) but supports the hypothesis that the enzyme modulates pre-existing pathology. Additionally, Henderson et al. (2020) found that with the addition of PFFs, healthy hippocampal cells with normal GCase function experienced a time-dependent reduction in GCase activity prior to addition, further supporting the idea of a positive feedback loop between the two proteins (Figure 1b). Additionally, Henderson et al. (2020) investigated whether different neuronal cells were susceptible to developing synucleinopathy more than others when plagued with GCase dysfunction. Using similar methods to the ones described previously, neurons from three different regions of the brain were shown to respond to GCase inhibition differently. In addition to hippocampal neurons, cortical neurons, which constitute the outermost part of our cerebral cortex, and midbrain neurons, most often associated with the connections responsible for motor functioning, were tested. Whereas hippocampal neurons showed very little elevation in pathological α-synuclein with the addition of CBE, when pathology was initially low as seen with the cortical and midbrain neurons, pathological α-synuclein aggregation increased by 50% and 4-fold, respectively (Henderson et al., 2020, p. 825-827)! These results show a significant susceptibility of midbrain neurons to aggregation related to GCase dysfunction, which is an important confirmation as midbrain neurons are both primarily and initially affected in PD. By providing a much deeper, more concrete understanding related to one of the most common genetic factors associated with Parkinson's disease, these findings not only shed light on intracellular aggregation of α-synuclein, but may also provide additional hints for how pathology spreads throughout the brain. Lysosomal dysfunction may lead to increased exocytosis, or the dumping of intracellular molecules out of the cell. This has been hypothesized as a possible way that pathological α-synuclein spreads from one region of the brain to another, as is the case in later stages of the disease (Abeliovich and Gitler, 2016, p. 212). In addition to simply illuminating this neurobiological interaction, these findings also confirm the possibility of a brighter future as this understanding can open the door to future therapeutic targets for treatment. One such treatment could arise from the use of small-molecule chaperons, which act like big brothers, guiding misfolded GCase proteins back into alignment to allow for increased activity, which may in turn affect the degradation of pathological α-synuclein (Aflaki et al., 2017, p. 743). One such small molecule chaperone that is currently in a Phase 2 clinical trial, Ambroxol, has shown promising results through increased GCase activity and subsequent α-synuclein (Blandini et al, 2019, p. 16). Though a cure for Parkinson's disease is still quite far from the grasp of neuroscientists, as our understanding of the disease expands and the weaknesses with which we can formulate treatments are illuminated, we are brought closer to a moment where the sporadic nature of the disease no longer lurks in the shadows. With their research, Henderson and colleagues have laid a strong foundation for future investigation into the mechanisms that underlay this relationship. As our knowledge grows, understanding of how GCase inhibition may play a part in purely sporadic cases may grow as well.