

TWO GENES, ONE TARGET: GBA1 AND LRRK2 CONVERGENCE ON MITOPHAGY IN PARKINSON'S DISEASE

Nikhil Rahul | Grade 10 | Singapore American School | Mentor: Dr. Hafithe AlGhosain

Parkinsons Disease (PD)

A progressive neurodegenerative disorder characterized by loss of dopaminergic neurons in the Substantia Nigra pars compacta (SNpc) and associated with α -synuclein pathology, eventually leading to a wide range of motor and non-motor symptoms

Why Mitochondrial Quality Control?

When mitophagy, the process that selectively removes dysfunctional mitochondria, is impaired damaged mitochondria can accumulate. This traps dopaminergic neurons in a destructive loop of defective mitochondria, oxidative stress and energy collapse that fuels PD pathogenesis

Why GBA1 and LRRK2?

GBA1 and LRRK2 are the two major genetic risk factors for PD, affecting different cellular processes, but eventually converging on disruption of mitochondrial quality control

Research Question

Through what distinct yet convergent molecular mechanisms do GBA1 and LRRK2 mutations disrupt PINK1/Parkin-mediated mitophagy, and how does this shared impairment of mitochondrial quality control suggest potential therapeutic targets?

Central Idea

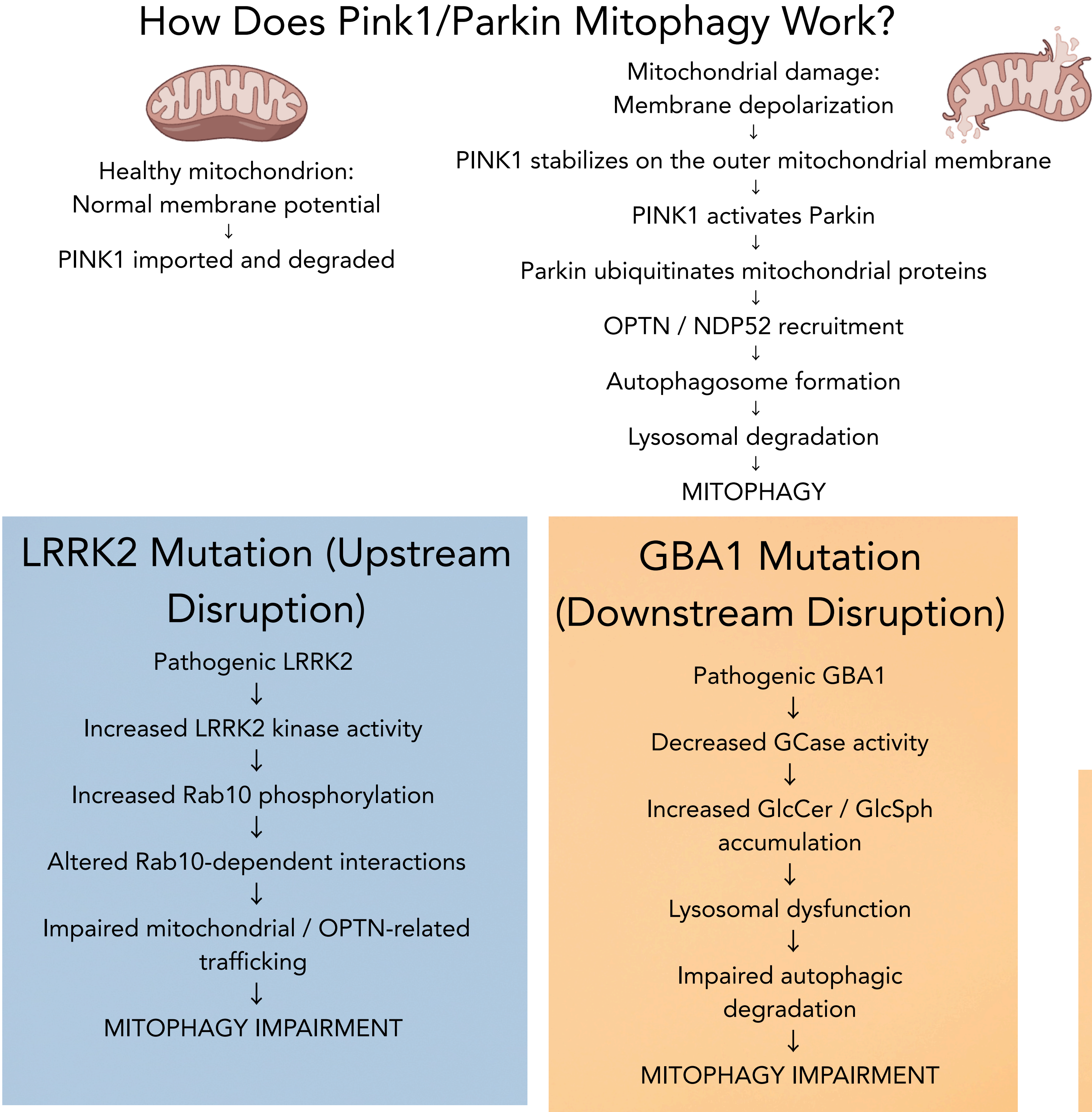
Different molecular defects → impaired mitophagy → mitochondrial quality-control failure → dopaminergic neuron vulnerability

Methods

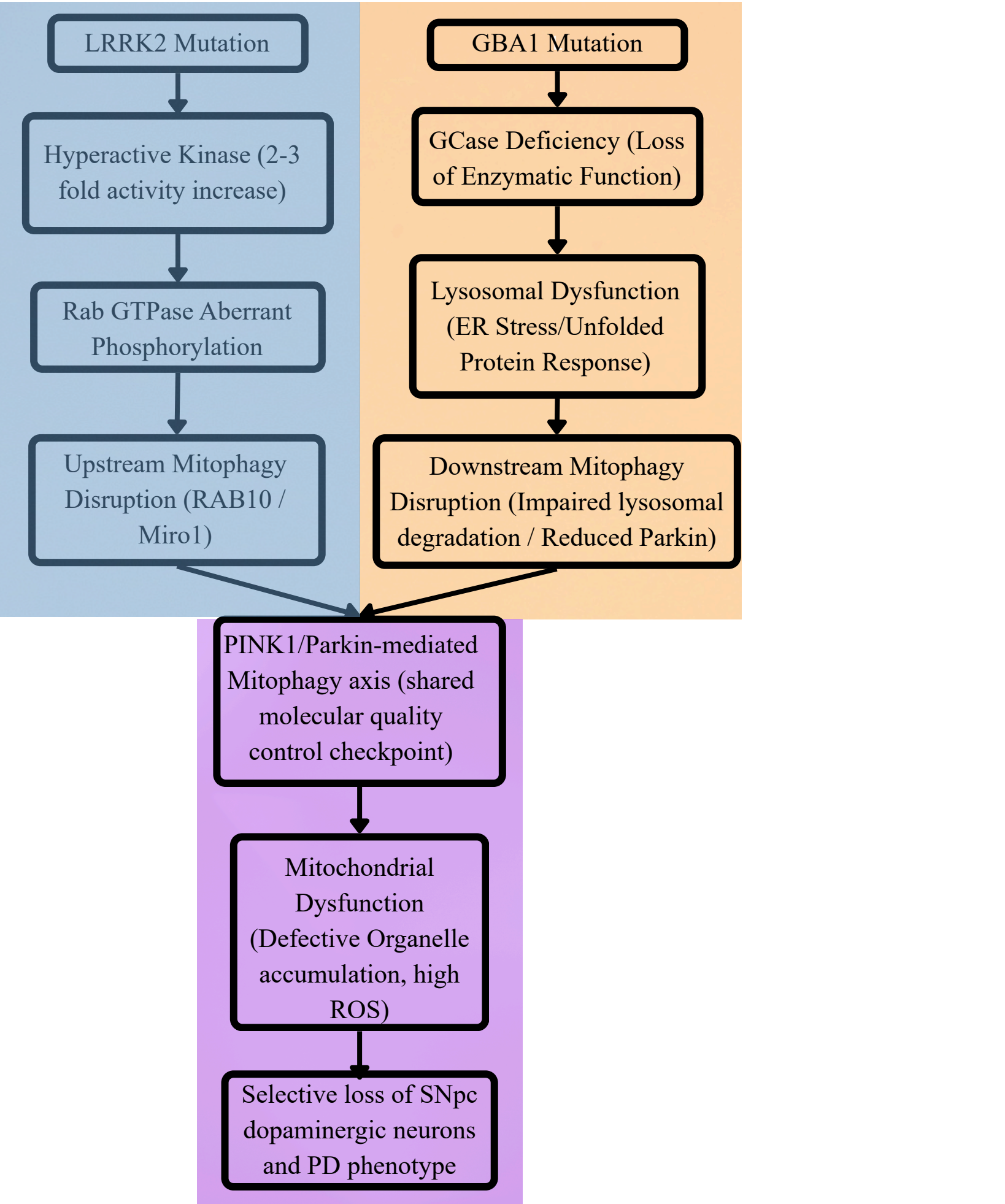
Databases: PubMed • Google Scholar
↓
Search terms: GBA1 • LRRK2 • PINK1/Parkin • Rab GTPases • mitophagy • mitochondrial quality control
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Evidence prioritized: Mechanistic studies • recent peer-reviewed research • therapeutic studies
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Synthesis: Mapped evidence onto the PINK1/Parkin mitophagy pathway

References: Smith & Schapira, 2022, Minakaki et al., 2020, O'Callaghan et al., 2023, Williamson et al., 2023, Eshed & Alcalay, 2024, Serebryany-Piavsky et al., 2025

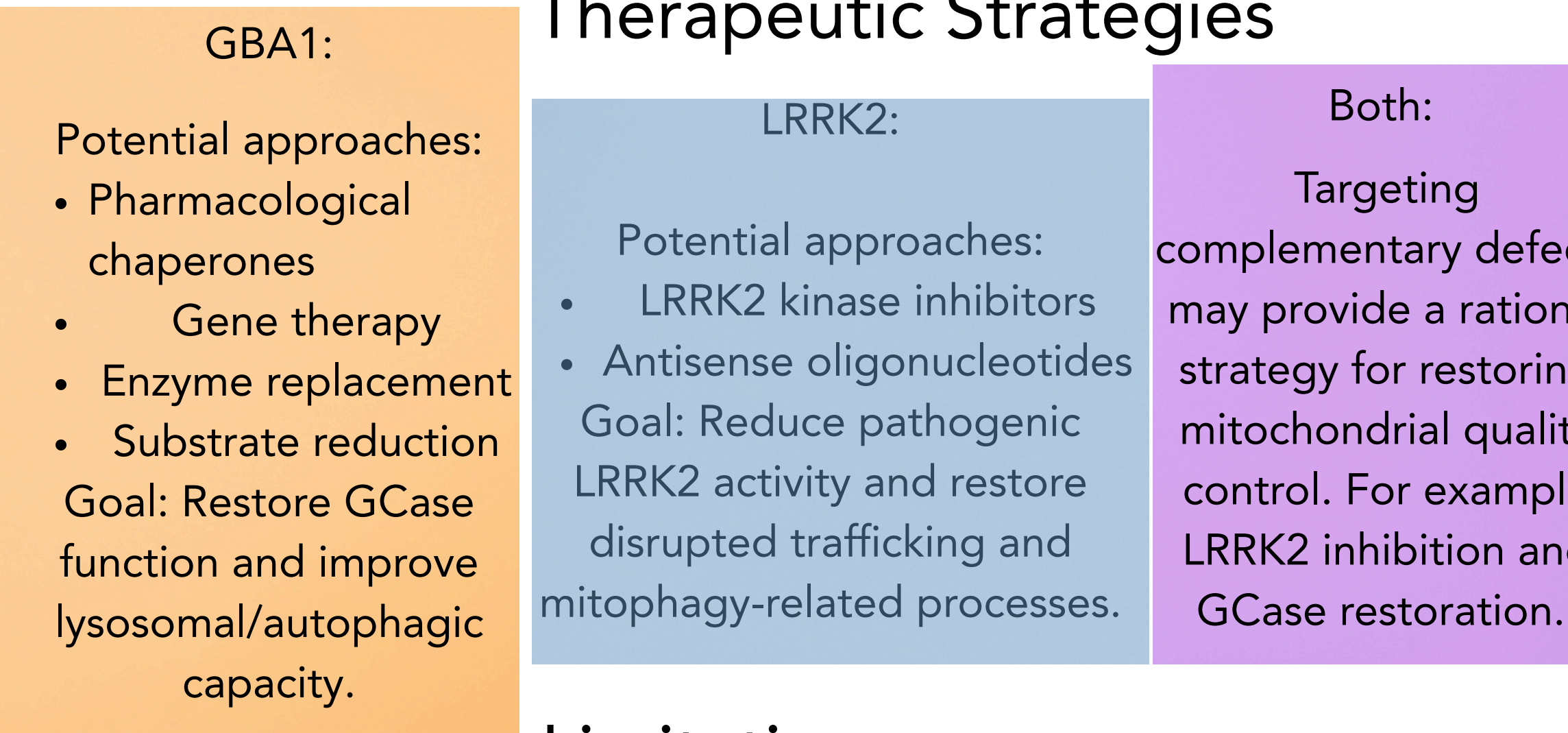
How Does Pink1/Parkin Mitophagy Work?



Convergence Model:



Therapeutic Strategies



Limitations:

01. Human vs Animal Model Translation
02. Mechanistic Gaps in Literature
03. Direct Human Confirmation and Validation

Conclusion:

GBA1 and LRRK2 mutations disrupt different molecular checkpoints but converge on impaired mitochondrial quality control.

LRRK2 primarily disrupts upstream kinase/Rab-dependent processes involved in mitophagy. GBA1 primarily compromises lysosomal GCase function and downstream autophagic degradation.

Both genes contribute to impaired mitophagy and accumulation of dysfunctional mitochondria. Mapping these pathways may help guide more precise, mechanism-based therapeutic strategies for PD patients.