Inflammatory stress on induced neurons carrying Parkinson's disease-associated LRRK2 Mutations

Jose Torrellas[1], Aravindraja Chairmandurai[1,2], Adamantios Mamais[1,2], Matthew LaVoie[1,2], Paramita Chakrabarty[1]

[1] Department of Neuroscience, University of Florida College of Medicine, Gainesville, Florida, USA
[2] Department of Neurology, University of Florida College of Medicine, Gainesville, Florida, USA

Mutations in the leucine-rich repeat kinase 2 (*LRRK2*) gene, particularly the *G2019S* and *R1441C* variants, are the most prevalent genetic determinants of Parkinson's disease (PD). *LRRK2* is increasingly recognized for its roles in immune signaling, with studies suggesting that interferon-gamma (IFNγ), a master immune regulator, may modulate its activity. Based on these findings, we hypothesize a synergistic interaction between *LRRK2* mutations and IFNγ. To explore this hypothesis, we utilized neurons derived from human induced pluripotent stem cells (iPSCs) harboring homozygous *G2019S* or *R1441C LRRK2* mutations, with isogenic wildtype (WT) controls. After differentiation into neurons, cells were treated with recombinant human IFNγ or control media on DIV-17 and harvested after 6 hours of treatment. Six experimental conditions were analyzed: (WT + IFNγ, WT + Control, G2019S + IFNγ, G2019S + Control, R1441C + IFNγ, R1441C + Control). We analyzed these experiments using immunoblotting and immunofluorescence methods to assess interferon-pathways, tau phosphorylation, and LRRK2 substrate engagement. Using a dose-dependent paradigm, we optimized the minimum IFNγ dose to achieve maximal target engagement (STAT1 and phosphorylated-STAT1, pSTAT1). We found that levels of pSer202 tau (CP13) levels were moderately increased in G2019S and R1441C neurons following IFNγ treatment, but not in wildtype neurons. IFNγ treatment phosphorylated Threonine73 on Rab10 (a LRRK2 substrate) more efficiently in G2019S-LRRK2 neurons compared to R1441C-LRRK2. This data lays the groundwork for future studies to dissect mechanisms of neuronal vulnerability in PD and the interplay between *LRRK2* mutations and disease pathways.

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Presenter Name and contact information:
Jose Torrellas, B.S, Graduate Student
Department of Neuroscience
University of Florida, College of Medicine
Gainesville, Florida, USA
Email: jtorrellas@ufl.edu