

Glucocerebrosidase Biology and Its Role in Parkinsons Disease

<https://www.neurodegenerationresearch.eu/survey/glucocerebrosidase-biology-and-its-role-in-parkinsons-disease/>

Principal Investigators

KO, HANSEOK

Institution

JOHNS HOPKINS UNIVERSITY

Contact information of lead PI

Country

USA

Title of project or programme

Glucocerebrosidase Biology and Its Role in Parkinsons Disease

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,622,321.10

Start date of award

01/07/2013

Total duration of award in years

2

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

glucosylceramidase, Parkinson Disease, synuclein, synucleinopathy, Biology

Research Abstract

DESCRIPTION (provided by applicant): Mutations and activation of glucocerebrosidase (GBA) play a prominent role in the pathogenesis of the alpha- synucleinopathies, PD and LBD. GBA plays a pivotal role in the lysosomal degradation pathway by functioning as a lysosomal

enzyme. Most disease causing mutations of GBA are thought to be loss of function mutations that ultimately lead to the GBA deficiency, compromised glucosylceramide (GlcCer) metabolism and the subsequent failure of lysosomal mediated degradation of GBA substrates including alpha-synuclein. Depletion of GBA results in α -synuclein accumulation and neurodegeneration suggesting compromised GBA cascade contributes to the pathogenesis of α -synucleinopathies. We and others have found that brains of PD patients with or without mutations in GBA, as well as brains of A53T alpha-synuclein transgenic (Tg) mice, exhibit reduced GBA activity suggesting a role of the enzyme in the pathogenesis of the disease. Interestingly, the loss of catalytic activity of GBA correlated with its quantitative protein reduction, suggesting that unidentified key modulators might play an important role in GBA protein levels and activity through posttranslational modifications (PTMs). Accordingly, we investigated the mechanisms underlying the loss of GBA activity and protein levels by identifying key GBA modulators using tandem affinity purification (TAP) analysis. In preliminary data, we discovered GIP1 (GBA interacting protein 1) and show that GIP1 belongs to a new class of E3 ligases. In this project, we propose to explore the regulation of the GBA by GIP1 and their roles in regulating the pathogenesis of α -synuclein in PD and LBD. In specific aim 1 we will determine whether GIP1 interacts with and ubiquitinates GBA in vitro and in vivo. In specific aim 2 we will examine whether GIP1 targets GBA for degradation, thus regulating GBA activity and its substrates, GlcCer. Since GBA is a lysosomal enzyme that potentially regulates the expression of alpha synuclein, we will also explore whether GIP1 mediated GBA degradation ultimately regulates alpha-synuclein expression and aggregation. To accomplish these specific aims we will utilize lenti-GIP1 shRNA virus to knockdown GIP1 and a herpes simplex-GIP1 virus to overexpress GIP1. In preliminary studies we discovered that GIP1 accumulates in A53T alpha-synuclein Tg mice, PD brains and neurons treated with alpha-synuclein preformed fibrils (PFFs). Thus, in specific aim 3 we will further evaluate whether alpha-synuclein pathology is associated with accumulation of GIP1 and if its accumulation correlates with GBA deficiency and the severity of the alpha-synuclein pathology in A53T alpha-synuclein Tg mice and PD patients, as well as α -synuclein PFFs treated neurons. Moreover, preliminary data indicates that depletion of GIP1 significantly reduces alpha-synuclein PFFs induced neuronal death. Thus, in specific aim 3, we will also evaluate the role of GIP1 in alpha-synuclein PFFs induced neuronal death. Ultimately this project will determine the full implications of the GIP1-GBA-alpha-synuclein neurodegenerative pathway and will identify new targets for therapeutic intervention in PD and LBD.

Lay Summary

PUBLIC HEALTH RELEVANCE: Mutations in GBA are the most prevalent risk factor of PD, yet little is known about how this protein functions in the pathogenesis of PD and alpha-synucleinopathies. The goals for this project are to understand the function and dysfunction of GBA and identify the potential therapeutic targets to treat PD and alpha-synucleinopathies.

Further information available at:

Types:

Investments > €500k

Member States:

United States of America

Diseases:

Parkinson's disease & PD-related disorders

Years:

2016

Database Categories:

N/A

Database Tags:

N/A