Modulating Ire1 to treat Parkinson’s Disease

https://neurodegenerationresearch.eu/survey/modulating-ire1-to-treat-parkinsons-disease/

Principal Investigators

MOLLEREAU Bertrand

Institution

LBMC Lyon

Contact information of lead PI
Country

France

Title of project or programme

Modulating Ire1 to treat Parkinson's Disease

Source of funding information

ANR

Total sum awarded (Euro)

€ 254,280

Start date of award

01/03/2014

Total duration of award in years

3

Keywords
Research Abstract

Parkinson’s Disease (PD) is a devastating neurodegenerative disease, which affects a growing number of patients in Europe. The lack of treatment for patients, who rapidly become disabled, brings high social and economic burdens for families and society. Despite numerous studies on PD, scientific research is still behind in term of strategies to halt disease progression. In our project, we will explore novel and promising protective mechanisms to reduce the pathological hallmarks in models of PD. We have recently shown that mild Endoplasmic Reticulum (ER) stress (ER preconditioning), by tunicamycin (Tm) treatment, induces the unfolded protein response (UPR), which results in neuronal protection in cellular and animal models of PD (Fouillet et al. 2012). In four specific tasks, we propose a unique approach at the whole organism (Drosophila and mice) and cellular levels (human neuroblastoma cells) to understand the underlying mechanisms of tunicamycin-mediated protection in PD. The first task will be

dedicated to the coordination of the program. In the second task, partner 1, 2 and 3 will establish the contribution of xbp-1-independent protection that is mediated by Ire1 in models of PD (Drosophila and mouse PD models as well as human cell lines). Partner 1 and Partner 2 will use the Drosophila a-Synuclein (a-Syn) model and test if the protection mediated by Tm is dependent on Ire1 and/or xbp1. Partner 3 will use the MPTP model and test if Tm treatment reduces dopaminergic (DA) death and locomotor dysfunction associated with the subchronic treatment of MPTP and if Tm mediated protection requires Ire1 independently of xbp1. Partner 1 will use SH-SY5Y cells treated with MPP+ and determine the contribution of Ire1 versus xbp1 in Tm-mediated protection. In the third task, Partner 1, 2 and 3, will determine if Tm can restore defective autophagy caused by a-Syn expression and MPTP treatment and study the role of autophagy in a-Syn aggregate clearance and DA neuron viability. In the fourth task, Partner 1, 2 and 3 will study the role of specific Regulated Ire1-dependent decay (RIDD) targets in Tm-mediated neuroprotection. This will involve monitoring by quantitative RT-PCR if the levels of specific RIDD targets, such as indy/ SLC13A3, sparc/SPARC and fatp/FAT1/4, are regulated in Drosophila and mammalian models of PD. We will also test directly the role of these RIDD targets in Tm mediated protection by doing assays in the presence of RNAi for these specific RIDD targets. This is a unique approach to precisely identify the mechanisms by which ER stress protects from neurodegeneration in PD models. The long-term objective of this project is to open therapeutic perspectives for PD patients.

Further information available at:

Types:
Investments < €500k

Member States:
France

Diseases:
N/A

Years:
2016

Database Categories:
N/A

Database Tags:
N/A