Master de Sciences et Technologies
Mention Biologie Intégrative et Physiologie
Parcours : Neurosciences
Responsable : Professeur Régis Lambert

Internship Proposal
Academic Year 2019-2020

1. Host team :

Research Unit (e.g. Department or Institute) : Institut du Cerveau et de la Moelle épinière
Research Unit Director : Alexis Brice
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2. Internship project title:

Deciphering the contribution of long non coding RNAs in the specific vulnerability of dopaminergic neurons to mitochondrial stress in PD.

3. Internship Description :

The genetic revolution of the past twenty years has greatly broadened our understanding of the molecular mechanisms leading to neurodegeneration in Parkinson's disease (PD). The discovery of genes involved in mitochondrial maintenance, particularly PINK1 and PARK2/Parkin, has brought convincing support to the role of mitochondrial impairment, already pinpointed as potentially relevant since the description of defects in mitochondrial complex I activity in brains of PD patients. Since then, a growing number of studies from patients' brains to PD animal models have reported changes to mitochondrial biology, including morphology and dynamics, mitochondrial membrane potential and mitophagy. These alterations are thought to induce a homeostatic imbalance that enhances the vulnerability to cell death. Interestingly, degeneration occurs within several neurons subtypes in PD, but affects predominantly dopaminergic (DA) neurons from the substantia nigra pars compacta (SNpc). Their progressive but massive loss (up to 80%) is indeed responsible for the appearance of the motor symptoms that mainly include rigidity, bradykinesia and tremor. DA neurons from the SNpc appear therefore particularly vulnerable and prone to engage in cell death pathways than other neuronal subtypes in PD. Moreover, some pathogenic mitochondrial DNA mutations have been suggested to trigger neuronal loss in the SNpc. Altogether these data indicate that SNpc DA neurons display an enhanced vulnerability to mitochondrial stress, even though the molecular mechanisms underlying this susceptibility are widely unknown. **This raises the issue of the specificity associated with DA neurons: discovering the specific and intrinsic features of these neurons that render them more susceptible to mitochondrial stress compared to other neuronal subtypes would significantly contribute to the understanding of PD pathophysiology and the search for therapeutic treatments**. So far, specific molecular

signatures defining neuronal cells have been obtained using transcriptomic data only focused on protein-coding genes. However, recent developments suggest that non-coding elements of the genome, such as long non-coding RNAs (lncRNAs), constitute repertoires displaying a much greater cell specificity than protein-coding genes. LncRNAs are increasingly scrutinized for their multiple regulatory functions from the epigenetic to the post-translational levels, and for their involvement in crucial developmental and cellular processes, such as neuronal differentiation. Conversely, growing literature associate lncRNAs to human diseases, including Alzheimer disease, Parkinson's Disease, schizophrenia, drug addiction, cancer, or diabetes. In this context, we infer that lncRNAs are of particular interest regarding the issue of cell-specificity in pathological conditions and constitute candidates that could mediate the intrinsic and specific molecular mechanisms associated with DA neurons vulnerability to mitochondrial stress in PD. Therefore, our project aims at assessing the contribution of lncRNAs in the response of DA neurons to mitochondrial stress in PD. We will:

i) establish the repertoires of lncRNAs expressed in DA neurons from healthy individuals and PD patients, under basal conditions and following treatment with mitochondrial toxins;
ii) identify lncRNAs whose expression changes under basal conditions or after mitochondrial stress in a PD context and
iii) manipulate expression of a candidate lncRNA in order to repair mitochondrial function and/or improve neuronal viability under mitochondrial stress.

Since our project stems from the importance of the cell specific features of DA neurons in the context of PD, we will use induced pluripotent stem cell (iPSc) technology to differentiate DA neurons from healthy individuals and PD patients. We will focus on patients affected by mutations in the *PARK2* gene, representing the most frequent cause of recessive PD familial forms and associated with vulnerability to mitochondrial dysfunction. Overall, our project constitutes an innovative approach aiming at identifying novel mediators of the specific vulnerability of DA neurons to mitochondrial stress, particularly in a PD context, in order to develop strategies to repair, or at least significantly restore, this detrimental susceptibility.