

VISIT TO THE PARKINSON'S UK--FUNDED LABORATORY OF PROFESSOR FLAVIANO GIORGINI AT THE UNIVERSITY OF LEICESTER.

Prof Giorgini and Dr Robert Mason and Dr Carlo Breda welcomed PEMRIG members for another visit to their laboratory to hear how the Parkinson's UK-funded work on Rab39B has progressed as the three-year grant draws to a close. We were reminded that in normal nerve cells a protein called alpha-synuclein (aSN) regulates synaptic vesicle trafficking and neurotransmitter release but that in dopaminergic neurones in the substantia nigra of brains of many people with Parkinson's aSN is present as aggregates resulting in neuronal cell death. Normally a small G protein Rab39B controls the removal of unwanted aSN to endosomes for digestion but in early-onset PD and in some cases of idiopathic PD Rab39B contains mutations that reduce its levels thereby effecting aSN aggregation. Small G proteins are molecular switches which exist in on and off states moving the unwanted aSN along a trafficking pathway to endosomes when switched on. Nerve cells contain seventy or more such small Rab proteins shuttling individual proteins and lipids around cells. The research has focussed on Rab39B because of its role in neuronal cell death in early-onset Parkinson's. The results have shown that Rab39B is involved in trafficking glutamate receptors in nerve cells while aSN itself is involved in moving vesicles full of neurotransmitters at synapses, the junctions between nerve cells where communication occurs. Prof Giorgini and colleagues have reviewed (1) the role of Rab39B in Parkinson's.

Dr Breda then described how fruit flies have been used to examine how mutations in Rab39B contribute to nerve cell death. The reasons for using fruit flies in PD research was explained in the report on the earlier visit. Nerve cells in fruit flies contain a dRab39 protein which does the same job as Rab39B in mammalian nerve cells. The team have shown that expressing human aSN in fruit flies shortens their life span and that this effect on life span is enhanced when dRab39B is reduced in nerve cells as well. Fruit fly locomotor function is also impaired when dRab39B is reduced, perhaps due to loss of or impaired function of dopaminergic neurones. Curiously, Rab39B can be detected outside dopaminergic nerve cells in the brains of fruit flies but why isn't clear. Lowering expression levels of Rab39B in a specific class of insulin-producing neurones perturbs fruit fly sleep and behaviour patterns, a common problem in PD. Such results confirm that dRab39 in fruit flies has very similar functions to Rab39B present in mammalian nerve cells in PD and that fruit flies are a good model system.

Fruit flies have also been used to examine how aSN aggregates form in PD with such devastating results on nerve cell viability. In mammalian nerve cells proteins for destruction by autophagy are marked by being ubiquitinated and bind a p62 protein as a marker. The research has revealed that Ref(2)P, the fruit fly equivalent of p62 protein in mammals, regulates protein aggregation in the adult fruit fly brain together with an autophagy-related protein Atg8. Results reveal that dRab39B has a complex function in fruit flies since mutant flies lacking the G protein have increased levels of Ref(2)P and Atg8 in nerve cells. This reveals the importance of the dRab39B in the autophagy process. In the remaining time available studies looking at the relationship

between dRab39B and mitochondrial function are in progress since in PD energy production by mitochondria is impaired as is the turnover of damaged mitochondria by a mitophagy pathway.

On being asked about whether Rab39B might be a target for treating PD, Prof Giorgini felt that this was unlikely in the short term but might have long term possibilities as a means of stimulating autophagy and decreasing the aggregation of aSN. The work is now being written up for publication and possibly for a new grant application to continue the study.

1) Dysfunction of RAB39B-Mediated Vesicular Trafficking in Lewy Body Diseases
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