A NOVEL VARIANT OF G-SUBSTRATE, A NEUROPROTECTIVE PHOSPHATASE INHIBITOR IN DOPAMINERGIC NEURONS

M.O. Vigbedor

University of Edinburgh, Edinburgh, UK

Introduction: G-substrate inhibits protein phosphatase 2A (PP2A) when phosphorylated on two threonine residues (68 and 119 in humans). This inhibition has a greater effect on hyperphosphorylation of tau protein than the activation of key tau kinases. Tau hyperphosphorylation contributes to the formation of neurofibrillary tangles in Alzheimer's disease (AD). A10 dopaminergic neurons of the substantia nigra, which have a higher level of G-substrate expression, are less vulnerable to Parkinson's disease (PD) toxins than the adjacent A9 DA neurons of the ventral tegmental area.

Aims: An mRNA has recently been described for a shorter variant (104aa) of G-substrate, which only retains one of the phosphorylatable threonine motifs. We are determining whether this variant interacts with different proteins from those observed for full-length G-substrate. This may be significant to PP2A regulation and consequently for the pathology of AD and PD.

Methods/results: Our database searches so far indicate that this new variant is expressed only in humans, and not in any other mammalian species including rodents and primates. This may have implications for the validity of the current models of PD. We have expressed this shorter variant and are comparing expression level and its function as an inhibitor of PP2A.

Conclusion: Elucidating the role of G-substrate in protecting DA neurons from PD toxins will lead to a better understanding of the disease. If the shorter variant does play an important role in the protection of DA neurons, this new knowledge will provide information for better models of the disease.