NANYANG TECHNOLOGICAL UNIVERSITY

School of Biological Sciences

SBS Seminar Announcement

Autophagy inhibition rescues structural and functional defects caused by the loss of the Parkinson's disease-associated mitochondrial chaperone *mortalin* in *Drosophila*

Dr Tobias Rasse
Junior Research Group Synaptic Plasticity, Hertie-Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany

ABSTRACT:

Impairments in mitochondrial function, lysosomal degradation pathways and synaptic transmission are cardinal features in Parkinson's disease (PD) pathogenesis. Genetic studies have identified mutations in mitochondrial chaperone protein *Mortalin/Hsc70-5/GRP75* in PD patients. We show that knockdown of the PD-associated *Hsc70-5* in *Drosophila* causes cellular defects characterized by impairment in axonal transport, presynaptic cytoskeleton disturbances and depletion of synaptic vesicles and active zone components from synapses. While both expression of *Drosophila Hsc70-5* or wild-type human *GRP75* can rescue loss-of *mortalin* knockdown-related phenotypes, human *GRP75* bearing patient-derived mutations (A476T and P509S) does not reverse developmental, behavioral and mitochondrial defects caused by *mortalin* knockdown. Dysregulation of autophagy has been implicated in PD. Although *in vitro* and *ex vivo* studies have suggested that therapies up-regulating autophagy may be beneficial in PD this hypothesis has not been thoroughly examined *in vivo*. Remarkably, genetic screens using temperature induced paralysis as assay revealed that knockdown of genes involved in autophagy induction rather than the promotion of autophagy achieved by ATG1-overexpression, is sufficient to reverse all cellular defects observed in at the early-symptomatic stage of disease progression. Protective effects of autophagy suppression are also observed later in disease progression, both under baseline conditions and upon induction of oxidative stress. However, the beneficial effects of autophagy suppression such as improved locomotion skills, rescue of defects in wing posture and increased ATP-level are accompanied by a reduction of lifespan that might be caused by detrimental effects of limiting degradation of functionally impaired mitochondria.

Tuesday, 26 Aug 2014 2.30pm to 3.30pm SBS Classroom 2 (SBS-01n-22)

Host: A/Prof Rachel Kraut

60 Nanyang Drive, Singapore 637551
Tel: +65 6316 2800 Fax: +65 6791 3856
Email: d-sbs@ntu.edu.sg www.ntu.edu.sg/sbs