Analysis of Gene Interactions in Neurodegeneration

Supervisory team:
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Project description:

Background: Understanding the mechanisms of neurodegeneration is a fundamental topic in Neuroscience. How does it occur and how can it be regulated? One established paradigm is the degeneration of the medium spiny neurons (MSNs) of the striatum that occurs in Huntington's Disease (HD), with its associated severe voluntary movement impairment. The causal mutation of this condition is expansion of the "CAG repeat" of the Huntingtin (Htt) gene. Analysing the molecular mechanisms that produce MSNs in normal brain development and those by which mutant Htt (mHtt) leads to MSN degeneration are important questions to address. In the longer term, they are both critical to producing new treatments for HD (no disease modifying treatments are currently available). An established approach for progress is to use model organisms as an in vivo system for the required mechanistic analysis.

The mouse is a favoured model for MSN research. We use it to investigate the cell differentiation pathway that produces MSNs during brain development and have identified two transcription factor-encoding genes, Mef2C and FoxP1, required for normal striatal MSN development. Intriguingly, both Mef2D (closely related to Mef2C) and FoxP1 are reported to suppress mHtt-induced neurodegeneration in a Drosophila model. This implicates these transcription factors not only in the developmental pathways, but also in rescue of neurodegeneration.

Project outline and Experimental Approach: To explore these novel findings, you will use diverse techniques from genetics and neuroscience. In vivo genetic analysis in the classic model organism, Drosophila, has many advantages with its sophisticated range of techniques that give rapid insight. You will use Drosophila to complement the mouse research by efficiently testing hypotheses. Only analyses most likely to be informative will be brought to the mouse, which has closer links to human biology, but where experiments take much longer.

You will use the Drosophila eye as an in vivo "test tube" to analyse mammalian gene function in neurodegeneration. It provides a simple readout of this phenomenon. You will use genetic tools to drive expression of mHtt in the eye to induce neurodegeneration and then test genetic modifiers of this process. Initial results will guide subsequent mechanistic analysis. Your complementary experiments will use a mouse model that expresses mHtt and produces a mild neurodegenerative phenotype. You will assess this by immuno-histochemistry for MSN markers and neuronal inclusions, and by movement assays, and then will test effects of up- or down-regulation of candidate genes on the neurodegeneration phenotype.

Hear about the project from Dr Michael Taylor directly >>