Identification and characterisation of microglia-specific suppressors of mutant huntingtin toxicity

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A number of studies have suggested a role for microglia in the onset and progression of Huntington's disease (HD). We have characterised the enzyme kyneurenine-3-monoxygenase (KMO), which is expressed predominantly in microglia in the CNS, as a candidate therapeutic target for HD by genetic approaches in yeast and pharmacologically in mammalian cells and in the R6/2 mouse model of HD. These studies suggest a role for microglia in the pathology of HD and also imply that cell autonomous effects of mutant huntingtin (htt) expression in microglia may contribute to HD pathology. Excitingly, recent studies in humans have shown a correlation between microglial activation and HD progression. We are therefore working to identify further microglia-specific therapeutic targets.

We are currently using a yeast model of mutant htt toxicity to screen cDNA libraries from unactivated, activated, and primary microglia to identify cDNAs capable of suppressing mutant htt toxicity when overexpressed in yeast. We have identified 31 unique mouse cDNAs capable of suppressing the toxicity associated with the expression of mutant htt in yeast. Many of these suppressors are associated with processes known to be affected in HD including autophagy, protein folding, iron metabolism, actin cytoskeleton organisation, and energy metabolism. The overexpression of a number of the suppressors has also previously been shown to be beneficial in a number of neurodegenerative disease models. Promising hits are being validated in a microglia-neuron co-culture system. We are also examining the expression patterns of these genes in microglia and other CNS cell types. Using these approaches we hope to gain insights into the microglia-specific cellular pathways that contribute to the pathology of HD. The screen may also aid in the identification of processes and specific proteins for therapeutic targeting in microglia and other cell types.