PARKINSON DISEASE

Can pharmacological activation of 4E-BP suppress PD?

Administration of rapamycin suppresses PD-like phenotypes in *Drosophila* mutants, Tain and colleagues have shown. The drug upregulates the activity of 4E-BP, a protein that is crucial to cellular survival responses and which genetically interacts with PD-related genes.

PD is characterized by neurodegeneration in the striatum, leading to progressive loss of motor functions. Mutations in two genes—*PARK2* and *PINK1*—acting via a common pathway can cause the disorder, and *Drosophila* mutants display PD-like symptoms when these genes are disrupted. Using these flies as a simple animal model, Tain *et al.* used genetic manipulations to explore PD-related gene function and identify potential therapeutic targets.

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A previous genetic screen identified *Thor*, which encodes the translation inhibitor 4E-BP, as a potential *park* (the *Drosophila* equivalent of *PARK2*) modifier. First, the investigators inhibited *Thor* in *park* and *Pink1* mutants, which substantially reduced their viability. Second, they induced overexpression of 4E-BP (Figure 1), which suppressed motor and neuronal symptoms of PD. These findings suggest "4E-BP acts to mediate or promote a survival response implemented on the loss of Parkin or PINK1," according to the researchers. Under normal conditions the Akt1–TOR signalling pathway represses 4E-BP activity. In the mutants, however, this pathway was downregulated, suggesting a mechanism by which the mutant genes might influence PD progression.

From their genetic manipulations, the investigators identified the Akt1–TOR signaling pathway as a target for pharmacological intervention. Rapamycin is a known chemical modulator of this pathway, and the researchers postulated that this agent would upregulate 4E-BP activity. The researchers supplemented the food of *park* and *Pink1* mutants with rapamycin and found that this suppressed all pathological phenotypes and dopaminergic neurodegeneration in the flies.

Pharmacological stimulation of 4E-BP might warrant further investigation as a potential therapeutic approach in PD according to the authors. Interestingly, previous work has also linked 4E-BP to the most common cause of PD in humans, *LRRK2* mutations. Further research into PD-related gene function from *Drosophila* models should identify additional targets for pharmacological manipulation in this disorder.

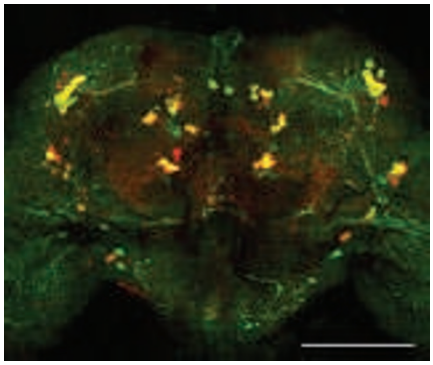

Figure 1 | Overexpression of 4E-BP in the *Drosophila* brain. Confocal micrograph of a wild-type adult *Drosophila* brain stained with antibodies against tyrosine hydroxylase (green) to highlight dopaminergic neurons, and a marker (red) for targeted expression of transgenes such as 4E-BP to these neuronal populations. Bar 0.1 mm. Image provided by Dr Alexander Whitworth.

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