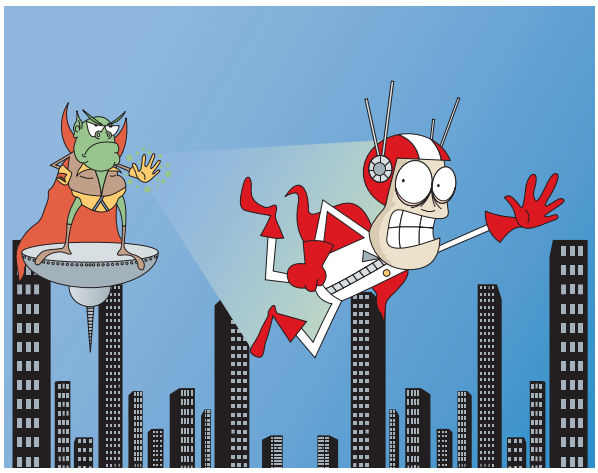
NEURODEGENERATIVE DISEASE

microRNAs under threat from LRRK2

Mutations in leucine-rich repeat kinase 2 (LRRK2) cause Parkinson's disease through an unknown molecular mechanism. Lu and colleagues now show that pathogenic forms of LRRK2 inhibit the translational repression of the transcription factors E2F1 and DP — components of a transcriptional regulator complex — through microRNAs (miRNAs), and thereby cause the death of dopaminergic neurons in *Drosophila melanogaster*.

Flies expressing the pathogenic LRRK(Ile1915Thr) or human LRRK2 (Gly2019Ser), both of which have increased kinase activity, showed reduced miRNA-mediated gene repression, whereas gene repression was normal in flies expressing the kinase-dead LRRK(3KD). This suggests that altered LRRK2 activity might deregulate miRNA pathways.



Neil Smith

The authors investigated whether LRRK2 impairs miRNA function through interaction with components of the RNA-induced silencing complex (RISC). They showed that one of the RISC components, the *Drosophila* homologue of Arabidopsis Argonaute 1 (*Ago1*), associated with LRRK in co-immunoprecipitation studies. In addition, AGO1 levels were reduced in aged flies that expressed LRRK2(Ile1915Thr) but not in young flies. Furthermore, overexpression and downregulation of DCR1, another RISC component, respectively suppressed and exacerbated the neurodegenerative effects in LRRK(Ile1915Thr) mutants. These results support a mechanistic link between LRRK2 and the miRNA pathway.

Next, the authors identified the mRNAs of which translation is upregulated by pathogenic LRRK2. From the numerous candidates, the authors investigated *E2f1*, as deregulation of this transcription factor has been implicated in the pathogenesis of Parkinson's disease. E2F1 interacts with differentiation-regulated transcription factor proteins, including DP. Levels of E2F1 and DP were upregulated in flies expressing pathogenic LRRK2, and downregulation of E2F1 or DP suppressed the death of dopaminergic neurons in these flies.

The authors identified two miRNAs, miR-184* (one mature strand of the processed RNA stem loop generated from the miR-184/miR-184* locus) and let-7, which bound to the 3′ untranslated regions of *E2f1* and *dp*, respectively. miR-184* binding to *E2f1* and let-7 binding to *dp* repressed the translation of these genes. Increasing miR-184* or let-7 levels, specifically in dopaminergic neurons, partly rescued the mutant phenotype of LRRK(Ile1915Thr)-expressing flies. Moreover, in wild-type flies inhibition of let-7 or miR-184* resulted in a phenotype similar to that of pathogenic LRRK2.

These results show that translational regulation of E2F1 and DP by miRNAs is implicated in LRRK2-mediated pathogenesis. These findings might lead to the development of new treatment strategies for Parkinson's disease.

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