Controlling genes to reverse the symptoms of Parkinson's disease

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Video Abstract

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Abstract

Researchers from the United Kingdom recently discovered several genes that protect neurons in Parkinson's disease, creating possibilities for new treatment options. Two of the genes affect how mitochondria break down amino acids to generate nucleotides – the metabolism of these molecules produces the energy that cells need to live. Dysfunctional mitochondrial metabolism has been linked to Parkinson's, and these researchers previously showed that boosting this generation of nucleotides can protect neurons. Based on these findings, they set out to identify the genes that control this process. Some forms of Parkinson's are caused by mutations in the genes _PINK1_ and _PARKIN_, which are instrumental in mitochondrial quality control. Fruit flies with mutations in these genes accumulate defective mitochondria and exhibit Parkinson's-like changes, including loss of neurons. The researchers used _PINK1_ and _PARKIN_ mutant flies to search for other critical Parkinson's genes. Using a bioinformatics approach, they discovered that the _ATF4_ gene has a key role in the disease: it acts as a switch for genes that control mitochondrial metabolism. When the expression of _ATF4_ is reduced in flies, expression of these mitochondrial genes drops. This drop results in dramatic movement defects, shortened lifespan, and dysfunctional mitochondria in the brain. Interestingly, when the researchers increased expression of these mitochondrial genes in the flies with Parkinson's, mitochondrial function was recovered, which prevented neurons from dying. These findings highlight the importance of mitochondrial metabolism for neuron health. By discovering the gene networks that orchestrate this process, the researchers have singled out new therapeutic targets that could prevent neuron loss. Studying the roles of these genes in human neurons could lead to tailored interventions that could one day prevent or delay the neuronal loss seen in Parkinson's.