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Are cellular lipids the missing link between a faulty gene and dystonia?

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Researchers at VIB-KU Leuven have managed to get a clearer view on the roots of dystonia, a neurological disorder that causes involuntary twisting movements. Led by Rose Goodchild (VIB-KU Leuven) and supported by the Foundation for Dystonia Research, the VIB scientists unraveled the mechanism by which DYT1 dystonia – the disease's most common hereditary form – causes cellular defects. The findings shed new light on this poorly understood condition – and may, ultimately, lead to new medical approaches to overcome it.

Dystonia looks like a muscle problem, but actually originates in the brain. The patient's brain sends out too many messages that activate too many muscles, causing twisting movements. In some cases, including DYT1/TOR1A dystonia, a genetic mutation is the main culprit. In the VIB Center for the Biology of Disease at KU Leuven, Rose Goodchild and her team are conducting basic research into dystonia, the essential stepping stone for a cure.

Molecular defects unveiled

In DYT1 dystonia, a genetic error results in a defective protein called torsin. Scientists already knew that this protein disrupts the neural communication that controls the muscles, but the how has remained unclear. Until now: research in the Goodchild lab indicates that torsins regulate the levels of lipids, molecules that form cell membranes and store energy.

Prof. Rose Goodchild (VIB-KU Leuven): "For the first time, we understand that a dystonia protein is responsible for cellular lipid levels. Although we had expected a more complex picture, with various direct and indirect effects, our data clearly labeled torsin as the regulator for a particular enzyme of lipid metabolism. This now focuses attention on how the lipid substrates and products of this enzyme contribute to neuronal function, and gives us a better view on the exact molecular defects that cause dystonia."

Multidisciplinary approach

Crucial to the success of this project was the access to state-of-the-art research instruments, such as VIB's Electron Microscopy facilities, allowing deep-study of how torsin affects cellular membranes composed of lipids. Furthermore, the collaboration with the lab of professor Patrik Verstreken (VIB-KU Leuven) enabled numerous experiments on fruit flies. But although these tiny creatures have much more similarities with humans than meets the eye, research on mammals is crucial as well.

Prof. Rose Goodchild (VIB-KU Leuven): "We have already started exploring dystonia mutation in mouse neurons. This will help us understand dystonia in humans. However, much more research is still to be carried out. It is our mission to find the exact pathway between a faulty gene and the neuronal defects. And, in time, we aim to develop therapeutic approaches that intervene in this pathway."

More information: Micheline Grillet et al. Torsins Are Essential Regulators of Cellular Lipid Metabolism, *Developmental Cell* (2016). DOI: 10.1016/j.devcel.2016.06.017

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