Mitochondrial dynamics impair nervous system development in Wolfram syndrome

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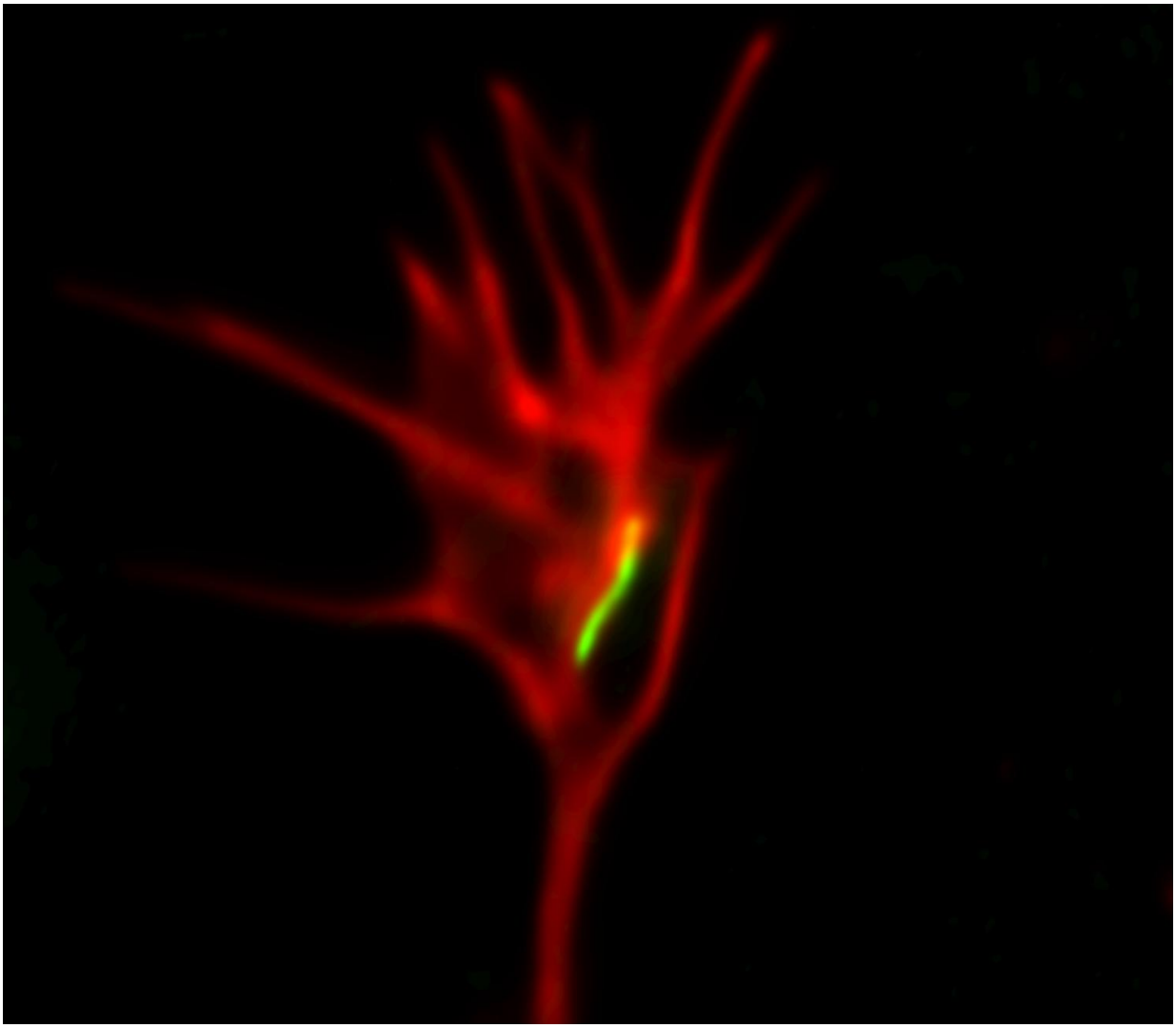

Mitochondrion in green is being enclosed to axonal growth cone in red in cultured rat cortical neuron. Credit: Michal Cagalinec, Annika Vaarmann and Allen Kaasik

Although mitochondria, the tiny capsules that produce energy for the cell, are known to play some role in neurodevelopmental and psychiatric disorders, the contribution of mitochondrial dynamics (mitochondrial trafficking, the regulated fusion and fission, and destruction of mitochondria) has been less clear. A new study now highlights a previously unappreciated causal role for the regulation of mitochondrial turnover in the defects of neuronal development that underlie the human genetic disease Wolfram syndrome.

Wolfram syndrome is caused by a mutation in the gene encoding a protein called wolframin, which resides in the membrane of the endoplasmic reticulum - another cellular compartment that functions as a manufacturing and packaging system and also acts as a reservoir for calcium ions. However, the clinical symptoms of Wolfram syndrome, which include deafness, optic atrophy and psychiatric disorders, resemble those of mitochondrial diseases, suggesting a strong mitochondrial involvement. The new study by Michal Cagalinec, Mailis Liiv and colleagues at the University of Tartu, published in *PLOS Biology* on July 19th, now clarifies the nature of the link between mitochondria and Wolfram syndrome.

Prof. Allen Kaasik, the leading investigator of the study, explains why it was necessary to explore the role of mitochondria in Wolfram syndrome: "The majority of previous research has focused on the endoplasmic reticulum and ignores the fact that most of the manifestations of Wolfram syndrome resemble those of mitochondrial diseases".

The study mostly makes use of cultured cortical neurons from rats, exploiting a wide array of molecular and imaging techniques to probe the mitochondrial function and well-being of neurons manipulated to model Wolfram syndrome. The findings reveal a causal chain of events

whereby the decreased levels of wolframin protein destabilize the endoplasmic reticulum (causing endoplasmic reticulum stress), thereby reducing calcium release. The resulting impairment in calcium management leads in turn to abnormal mitochondrial turnover and impaired mitochondrial energy production, which delays neuronal development.

Interestingly, these changes are related to the so-called PINK1-Parkin pathway that is responsible for the mitochondrial quality control system and implicated in Parkinson's disease. The results suggest that excessive and unwanted mitochondrial clearance would lead to bioenergetic deficits that are harmful to neurons.

This mechanism sheds new light on neuronal abnormalities during development in Wolfram syndrome and points out potential therapeutic targets. Moreover, the results unravel two rather unexpected links that have an impact beyond the relatively rare Wolfram syndrome. First, mild endoplasmic reticulum stress and impaired calcium release seriously disturbed mitochondrial dynamics, thus providing an explanation as to why alterations in the endoplasmic reticulum could lead to impaired mitochondrial dynamics. Second, impaired mitochondrial dynamics can affect neuronal development, suggesting that proper mitochondrial dynamics are crucial for neuronal development. As alterations in wolframin function appear to occur in different psychiatric disorders, this new study may also have rather broad implications for understanding the role of mitochondrial dynamics in neuropsychiatric diseases.

More information: Cagalinec M, Liiv M, Hodurova Z, Hickey MA, Vaarmann A, Mandel M, et al. (2016) Role of Mitochondrial Dynamics in Neuronal Development: Mechanism for Wolfram Syndrome. PLoS Biol 14(7): e1002511. DOI: 10.1371/journal.pbio.1002511