MOLECULAR NEUROSCIENCE

Fat chance of survival

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PHOTOALTO

Appreciation for the significance of lipids for neuronal function is growing; however, the low abundance of some lipids, including phosphatidylinositol-3,5-bisphosphate ($PI(3,5)P_2$), has made their functions difficult to decipher. Weisman and colleagues approach this problem by generating mice that lack VAC14, a key regulator of $PI(3,5)P_2$ synthesis, and reveal the importance of $PI(3,5)P_2$ for neuronal survival.

Although VAC14 is expressed throughout the body, the *in vivo* effects of its loss were restricted to the nervous system. The mice exhibited lesions in several brain regions, including the midbrain, the pons and the medulla. Within these lesions, neuronal cell bodies contained large vacuoles or had completely degenerated. This was accompanied by high levels of apoptosis in these regions. The cortex and hippocampus were not affected; however, when cultured, cells from these regions also became vacuolated.

The authors overexpressed either *VAC14* or the gene that encodes phosphatidylinositol-3-phosphate 5-kinase (the enzyme that synthesizes $PI(3,5)P_2$) in fibroblasts that lacked VAC14 (which also became vacuolated in culture). Both manipulations abolished the existing vacuoles and suppressed vacuole formation, confirming that the cellular degeneration resulted from the loss of VAC14 and the subsequent reduction in $PI(3,5)P_2$ levels.

To determine the origin of the vacuoles, the authors continued to examine the mutant fibroblasts. They found that the vacuoles were labelled with late-endosomal markers. Furthermore, the trafficking of the cation-independent mannose-6-phosphate receptor from late endosomes to the trans-Golgi network was abnormal, indicating that endosome function was disrupted.

This study demonstrates the importance of maintaining $PI(3,5)P_2$ levels for neuronal survival and supports similar findings obtained by the authors earlier this year in mice that lacked FIG4, another regulator of $PI(3,5)P_2$ synthesis. In addition to $PI(3,5)P_2$, VAC14 and FIG4 control the levels of phosphatidylinositol-5-phosphate, suggesting that this lipid might also be crucial for normal neuronal function. Future investigations might uncover whether the neuronal degeneration in these mice results from abnormal endosome function, as observed in fibroblasts.

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ORIGINAL RESEARCH PAPER Zhang, Y. *et al.* Loss of Vac14, a regulator of the signaling lipid phosphatidylinositol 3,5-bisphosphate, results in neurodegeneration in mice. *Proc. Natl Acad. Sci. USA* **104**, 17518–17523 (2007)
FURTHER READING Piomelli, D., Astarita, G. & Rapaka, R. A neuroscientist's guide to lipidomics. *Nature Rev. Neurosci.* **8**, 743–754 (2007) | Chow, C. Y. *et al.* Mutation of *FIG4* causes neurodegeneration in the pale tremor mouse and patients with CMT4J. *Nature* **448**, 68–72 (2007)