Researchers reveal mechanism for neuron self-preservation

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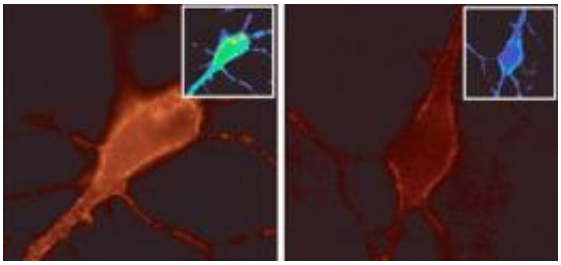

With glutamate stimulation (right), CaV1.2 channels (red) are internalized and degraded by cortical neurons under PIKfyve's direction. Credit: Tsuruta, F., et al. 2009. J. Cell Biol. doi:10.1083/jcb.200903028.

Tsuruta et al. find that a lipid kinase directs a voltage-gated calcium channel's degradation to save neurons from a lethal dose of overexcitement. The study appears in the October 19, 2009 issue of the *Journal of Cell Biology* .

An important player in cellular signaling, calcium is also terribly toxic at high levels. Neurons have evolved ways to protect themselves against the calcium influxes that come during periods of intense electrical activity. One way to limit the calcium flood is to remove the gatekeepers, calcium channels, from the cell surface. How neurons direct this is clinically important in a range of disorders, including stroke, Parkinson's disease, and Alzheimer's disease.

In a proteomic screen for binding partners of the CaV1.2 channel, Tsuruta et al. extracted what seemed a strange companion at first: PIKfyve, the lipid kinase that generates PI(3,5)P2 and promotes the maturation of endosomes into lysosomes. Other groups had recently shown that mutations affecting PI(3,5)P2 production cause degeneration of excitable cells in both mice and humans, including mutants found in ALS and Charcot-Marie-Tooth disease.

The team hypothesized that PIKfyve might be directing CaV1.2 degradation. Using glutamate excitation to simulate excitotoxic stress, the authors showed that CaV1.2 is internalized, associates with PIKfyve, and is degraded in the lysosome. When Tsuruta et al. squelched levels of PIKfyve or PI(3,5)P2, excess channels stayed at the surface and left neurons vulnerable to apoptosis.

The findings clarify how this neuroprotective mechanism unfolds and suggest that existing calcium channel-blocking drugs might aid patients with neurodegenerative disorders stemming from a PI(3,5)P2 defect.

More information: Tsuruta, F., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200903028

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