Helping neurons stay on track

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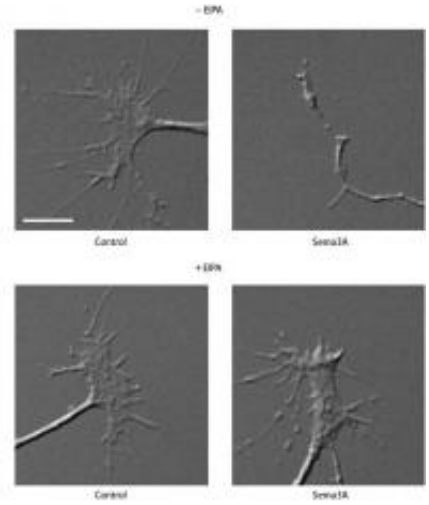

Compared to highly branched controls (left), axons of neurons treated with Sema3A tend to collapse (top right). However, this effect can be blocked by treatment with macropinocytosis inhibitor EIPA (bottom right), revealing the central importance of this mechanism in responses to repulsive signals (scale bar, 10 μm). Credit: 2011 the Society for Neuroscience

The complex inner wiring of the brain is coordinated in part by chemical guidance factors that help direct the interactions between individual neurons. As growing cells extend their axons outward, these tendrils are simultaneously drawn in the correct direction by attractive signals and steered away from 'wrong turns' by repulsive signals.

New work from a team led by Hiroyuki Kabayama and Katsuhiko Mikoshiba of the RIKEN Brain Science Institute in Wako has revealed

insights into how one of these repulsive guidance cues, semaphorin 3A (Sema3A), gives axons their marching orders. In an earlier study, the researchers found evidence that Sema3A causes large-scale internalization of the cellular membrane at the growth cone, the tip of the growing axon, and determined that this internalization occurs via a process known as macropinocytosis. “These findings suggested an important role for massive, macropinocytosis-mediated membrane retrieval during Sema3A-induced growth cone collapse,” says Kabayama.

The neurotoxin C1, a protease enzyme, induces similar effects on growth cones, and Kabayama and Mikoshiba and their colleagues were able to uncover Sema3A’s mode of action via experiments using this enzyme. Based on a series of experiments with cultured neurons isolated from chick embryos, the researchers determined that the enzyme works by breaking down syntaxin 1B (Syx1B), a protein with a prominent role in membrane trafficking, thereby releasing an inhibitory mechanism that otherwise keeps macropinocytosis in check.

Accordingly, direct inhibition of Syx1B expression in neurons led to reduced axonal growth and increased growth cone collapse. On the other hand, treatment with the macropinocytosis-inhibiting compound EIPA countered the growth cone-collapsing effects of either neurotoxin C1 or inhibition of Syx1B. The researchers also found that this drug alone was sufficient to undermine Sema3A’s axon-repulsive effects (Fig. 1).

Kabayama, Mikoshiba and colleagues obtained additional confirmation of the central role of Syx1B in experiments that revealed that the treatment of neurons with Sema3A triggers rapid degradation of this protein as a prelude to the initiation of macropinocytosis. This effect could be countered by forcing these cells to overexpress Syx1B. Kabayama also notes that another repulsive signal, ephrin A2, appears to act via the same cellular mechanism. “It is likely that repulsive axon

guidance is generally mediated by syntaxin 1B-regulated macropinocytosis," he says.

In future studies, Kabayama and Mikoshiba intend to test this hypothesis by manipulating this pathway in transgenic animals. "We are going to generate Syx1B-overexpressing mice and investigate whether inhibition of macropinocytosis by Syx1B can prevent ephrin A2- or Sema3A-dependent growth cone collapse," says Mikoshiba.

More information: Kabayama, H., et al. 1B suppresses macropinocytosis and semaphorin 3A-induced growth cone collapse. The Journal of Neuroscience 31, 7357–7364 (2011).

Kabayama, H., et al. Ca2+ induces macropinocytosis via F-actin depolymerization during growth cone collapse. Molecular and Cellular Neuroscience 40, 27–38 (2009).

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