New tricks for old neurons

Newborns seem to do much better than adults in healing injuries to their central nervous systems. At the cellular level, this is because inhibitory molecules in the adult central nervous system prevent neurons from extending their axons and dendrites, but the neurons in embryos and newborns are apparently insensitive to these inhibitors. Now, Tanaka et al., reporting on page 321, have uncovered the molecular mechanism underlying this change in sensitivity. The findings suggest a new approach for developing therapies for brain and spinal cord injuries.

Analyzing chick retinal neurons, the authors found that the differentiation of newborn neurons is associated with cytoplasmic expression of p21\(^{Cip1/WAF1}\), a protein best known as a nuclear-localized cell cycle inhibitor. Ectopic expression of p21\(^{Cip1/WAF1}\) lacking its nuclear localization sequence promotes neurite outgrowth, and the protein strongly inhibits Rho kinase in a dose-dependent manner.

As neurite outgrowth inhibitors like myelin-associated glycoprotein and tumor necrosis factor were previously shown to signal through Rho and Rho kinase, cytoplasmic p21\(^{Cip1/WAF1}\) appears to target the common pathway of these inhibitory signals. Inducing cytoplasmic p21\(^{Cip1/WAF1}\) expression in adult neurons might therefore make the neurons “younger,” permitting them to extend neurites to repair an injury.

Another name for autotaxin

A serendipitous discovery by Umezu-Goto et al., whose report appears on page 227, links two previously unrelated fields of study and suggests a new avenue of research for developing cancer therapies. The authors sought to study the production of lysophosphatidic acid (LPA), a lipid mediator with multiple biological functions that acts through G-protein–coupled receptors. LPA is produced in plasma from lysophosphatidylcholine (LPC) in a reaction catalyzed by the enzyme lysophospholipase D (lysoPLD), but the gene for lysoPLD had not been identified.

After biochemically purifying lysoPLD from fetal bovine serum, Umezu-Goto et al. discovered that the enzyme is identical to autotaxin, an enzyme associated with melanoma cells. Autotaxin was known to stimulate motility in tumor cells, but its mechanism of action was unclear. The new work shows that autotaxin/lysoPLD stimulates motility and proliferation in multiple cancer cell lines, apparently by producing LPA. In the microenvironment of a tumor, LPC secreted by tumor cells or available in the plasma could encounter autotaxin/lysoPLD released by the tumor cells, leading to the production of LPA and the stimulation of tumor growth and migration. Interfering with this signaling loop might be a promising strategy for cancer treatment.