The learning matrix

The old dog now has an excuse for failing to learn new tricks. Research from Karen Christopherson, Erik Ullian, Ben Barres (Stanford University, Stanford, CA), and colleagues may help to explain why the young make better learners. The work identifies a youth-related factor that is needed for synapse formation.

Learning depends in part on new synapse formation. But neurons make few synapses in the absence of astrocytes, which seem to secrete a synaptogenic factor. Christopherson et al. now show that this synaptogenic activity is thrombospondin (TSP)-1 and -2.

To find the synaptic helpers, the authors fractionated astrocyte-conditioned medium. From this soup, TSPs were both necessary and sufficient for neurons to form synapses in vitro. TSPs are extracellular matrix proteins that alter cell adhesions by binding to other matrix proteins or to membrane receptors. It is not clear how TSPs build synapses, but they boost synaptic protein localization. TSPs may activate signaling pathways via receptors on the neuronal cell body, or they may act more locally to reorganize synaptic proteins. There are many known TSP receptors; identification of the relevant ones should help to resolve this question.

The TSP-induced synapses looked normal, but they lacked functional AMPA receptors on the postsynaptic side. As functional synapses are made in the presence of live astrocytes, the findings suggest that the missing effect is due to a second, unidentified, astrocyte-derived factor.

TSP is around at the right time and place to regulate synaptogenesis in the developing brain. The authors found that TSP expression was strong in the postnatal mouse brain but was turned off in adults. Mutant mice lacking TSP-1 and -2 were missing 40% of the synaptic connections of their wild-type counterparts. Humans express much more TSP than do other primates. Perhaps this difference is one reason why Earth is not the planet of the apes.

Reference: Christopherson, K.S., et al. 2005. Cell. 120:421–433.

Cells do not relive youth

A few cells in the imaginal disc of the fly larva have the exceptional ability to transdeterminate (TD)—that is, to change fate—upon injury and regeneration. For example, injured leg precursors may form a wing instead. TD cells have many stem cell–like qualities. As stem cell multipotency is thought to be characteristic of “young” cells, it has been suggested that TD is preceded by cellular rejuvenation. Now, research from Anne Sustar and Gerold Schubiger (University of Washington, Seattle, WA) shows that no such fountain of youth is necessary. Instead, cells first adopt an unusual cell cycle profile before TD.

Using injuries or ectopic expression of Wg (a Wnt mitogen that induces TD) and a wing-specific reporter, the authors isolated transdetermining cells from imaginal discs. Young cells normally cycle more rapidly than do older cells, but TD cells kept the same relatively slow doubling time that they had before the injury or Wnt induction. In this sense, at least, they were not rejuvenated.

Though division timing was unaffected, TD cells did transiently alter their cell cycle phasing; they passed quickly through G1 and lagged in S phase. This phase change preceded TD. A longer S phase might allow time for chromatin changes that are needed for the different cell fate, and the authors propose that Wg induces chromatin remodeling proteins such as Polycomb.

Cells with the unusually long S phase were also larger than non-TD cells. Bursts of biosynthetic activity may be the driving force for the phase changes and subsequent developmental plasticity, but this remains to be shown. Forcing growth and division by overexpressing insulin pathways induced some fate changes but did not induce TD to wing. Wg may also have morphogenetic properties. “We can speculate,” says Schubiger, “that Wg targets TD cells and acts as a mitogen. But we believe that only sustained Wg signaling causes a change [in cell fate].”

Reference: Sustar, A., and G. Schubiger. 2005. Cell. 120:383–393.