SynCAM and sidekick synchronize synapse synthesis

Learning, memory, forgetting—these are functions of synapses, the connections between nerve cells. Although studies of nerve cell differentiation, migration, and axonal pathfinding have put neurons in the right neighborhood, considerable work is needed to understand the smaller scale problems of choosing an axon partner and forming a synapse.

Synapse formation requires SynCAM, according to Thomas Biederer, Thomas Südhof, and colleagues (University of Texas Southwestern Medical Center, Dallas, TX), who found that SynCAM mediated cell adhesion and initiated synapse differentiation. Expression of SynCAM in nonneuronal cells both induced neighboring neurons to form functional presynaptic terminals and, if glutamate receptors were added to the mix, induced postsynaptic terminals and, if glutamate receptors were added to the mix, induced postsynaptic membranes capable of electrical responses to glutamate. According to Biederer, the widely expressed SynCAM is one of four closely related proteins that may initiate synapse formation throughout the central nervous system.

With SynCAM so widely expressed at many synapses, the brain needs an additional method to order neurons into an organized pattern. This process of synaptic partner choice is addressed by Masahito Yamagata, Joshua Weiner, and Joshua Sanes (Washington University, Saint Louis, MO). They chose retinal ganglion cells (RGCs) to study synaptic specificity because axons of RGCs restrict themselves to specific layers within neuronal tissue, forming easily identifiable parallel lines of synapses.

They then looked for proteins that marked one RGC subset as different from another and found two adhesion proteins, sidekick (sdk)-1 and sdk-2. Sdks were concentrated at synapses and mediated adhesion only with other cells expressing the same sdk. Each sdk was found in nonoverlapping sets of cells, and ectopic expression redirected RGC axons toward inappropriate layers. Not every synaptic layer contained a sdk isoform, indicating that other proteins also mediate specificity. Both SynCAM and sdks are transmembrane immunoglobulin domain proteins with intracellular PDZ protein-binding motifs. Determining which PDZ domain proteins interact with SynCAM or sdk will be one next step toward determining the mechanics of synapse assembly.

References: Biederer, E., et al. 2002. Science. 297:1525–1531. Yamagata, M., et al. 2002. Cell. 110:649–660.

Integrin is being examined inside and out. Olga Vinogradova, Edward Plow, Jun Qin, and colleagues (The Cleveland Clinic Foundation, Cleveland, OH) have focused on its intracellular portion, and Junichi Takagi, Timothy Springer, and colleagues (Harvard Medical School, Boston, MA) have examined extracellular domains. Their combined efforts reveal a jackknife-like opening of the stimulated protein.

Changes in integrin structure in response to cellular signals regulate its binding to extracellular matrix (ECM) proteins like fibrinogen during processes such as platelet aggregation. Integrin is composed of α and β subunits, each of which is a transmembrane protein with a short cytoplasmic tail and several large extracellular domains. The binding sites for extracellular ligands lie far from the transmembrane domain, so how an intracellular signal is transmitted through so many extracellular domains has been difficult to determine.

The Cleveland Clinic group examined how the cytoplasmic tails respond to internal signals. Their studies revealed that the α and β tails of inactive integrin interact at a region adjacent to the plasma membrane. Activation of integrin, either by known constitutive mutations or by binding of the cytoskeletal protein talin, disrupted the cytoplasmic interaction and allowed the extracellular portion to bind fibrinogen.

The extracellular structural consequences of cytoplasmic uncoupling was then examined by the Harvard group. Their electron micrographs of linked soluble extracellular α and β domains confirmed a previous crystal structure of integrin in a condensed shape, like a “V” that points back toward the cell. A cell surface version held in this bent conformation by a disulfide bond did not bind fibrinogen unless the disulfide was broken. Based on the EM of the soluble protein, disrupting a membrane-proximal link between integrins causes the integrin to extend upwards like an opening switchblade. The extended form places the ligand-binding domain atop the dimer, where it is more accessible to physiological substrates. Thus, says Takagi, “we show that extension is at least partly responsible for making integrin high affinity.” However, two extended forms were found, which differed in the angle of the ligand-binding region. Takagi is now examining how these two conformers affect ligand binding.

References: Vinogradova, O., et al. 2002. Cell. 110:587–597. Takagi, J., et al. 2002. Cell. 110:599–611.