

In This Issue

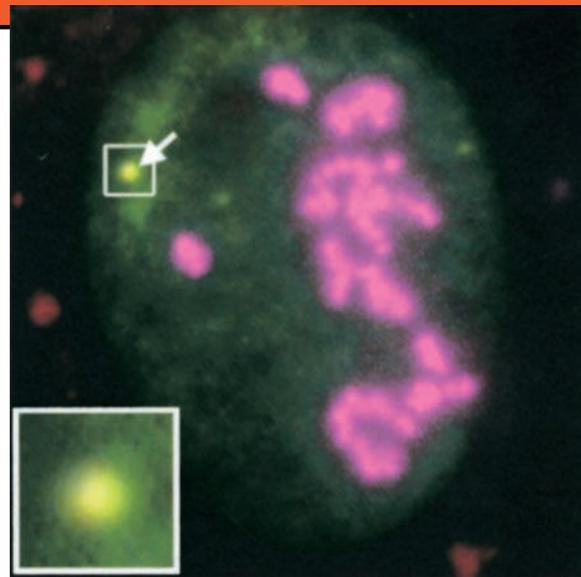
Of coilin and Cajal bodies

Cajal bodies (CBs), until recently known as coiled bodies, are revealed by silver staining as prominent spots in nuclei. Their purpose has been mostly a mystery since their discovery 98 years ago. They look similar to nucleoli, the cell's ribosome factories, and often lie close to them. Small nuclear ribonucleoproteins (snRNPs), components of the pre-mRNA splicing machinery, are known to be concentrated in the bodies. Although the presence of CBs is not required for splicing, cells that are particularly active in transcription have CBs.

For the last decade, cell biologists have used the protein coilin as a marker for CBs. It is the only molecule known to be uniquely concentrated in the bodies, although it is also expressed diffusely throughout the nucleus, in all tissues. Tucker et al. (page 293) knocked out coilin in mice, and

were surprised to find that at least some of the mutants are viable and appear normal.

When they studied cells derived from the mutant mice, they found what they term "residual CBs." These foci contain some of the typical proteins found in CBs, but they fail to stain brightly when treated with silver, and lack two complexes that are normally prominent components of CBs: snRNPs and the SMN (survival motor neuron) protein complex. The authors conclude that coilin is necessary for recruiting these



Addition of coilin (green) recruits SMN (red) to Cajal bodies. A nuclear protein is labeled in magenta.

factors to CBs. Indeed, when they transiently expressed wild-type coilin in the mutant cells, bodies formed that contain both the previously missing factors. ■

A dystroglycan ligand in the brain

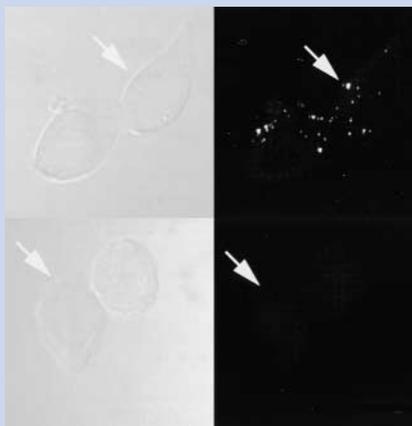
Dystroglycans are present on the surfaces of cells throughout the body, anchoring cells in the matrix that surrounds them. This function is conspicuously important for muscle cells. Defects in the protein dystrophin, which is connected to dystroglycan, destabilize the connection of muscle cells to their matrix and cause muscular dystrophy. Dystroglycans are abundant in the brain as well, even though neurons are not embedded in a classical extracellular-matrix mesh of proteins, so the role of dystroglycans on neurons and on supporting glia cells has not been clear. Sugita et al. (page 435) find that instead of anchoring cells to the outside matrix, dystroglycans in the nervous system bind to the membrane proteins neurexins, and therefore may help connect cells to each other.

Neurexins are a family of cell-surface proteins specific to neurons. Three genes encode neurexins, but rampant alternative splicing creates hundreds, if not thousands, of forms of the proteins. In a sample of 100 neurons, each neuron could have a different set of neurexins. The authors speculated that these diverse

cell-surface proteins may regulate the formation of connections within the brain.

The study describes the search for the natural binding partners of neurexins. The black widow spider toxin is one known ligand for neurexins. The authors showed that the toxin competes with dystroglycan for binding to neurexins. Multiple other lines of evidence imply that in the brain dystroglycan and neurexin are connected. The connection may be regulated by alternative splicing, which can change the surfaces of repeated domains in neurexin, thereby affecting dystroglycan binding.

The asymmetric bond between these two types of cell-surface proteins could play an important part in the organization of synapses. The study also has implications for muscular dystrophy, which is often associated with cognitive defects. Although the relevant proteins have not yet been localized to synapses, it is possible that a dystrophin deficiency could destabilize dystroglycan–neurexin links and thus disturb connections between neurons in the brain. ■



Neurexin binds cells with (top), but not without (bottom), dystroglycans.

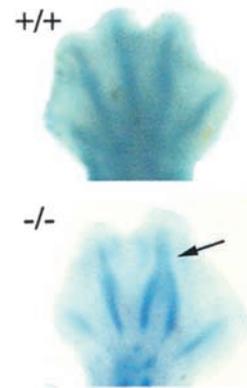
Matrix patterning of digits

Late in the formation of limbs, rays of condensing tissue appear at the tips of the developing limbs, and then grow and differentiate into digits, while the tissue in between undergoes programmed cell death. Gradients of bone morphogenetic proteins (BMPs) regulate this process, but now Artega-Solis et al. (page 275) show that an organized extracellular matrix, generally thought to be restricted to a structural, supportive role, is also necessary for proper limb patterning. In the study, the authors report what happens when mice lack fibrillin 2 (Fbn2), one of the

major constituents of the extracellular microfibrils.

Without Fbn2, the three middle digits of the limbs tend to fuse. Thus, the insoluble matrix surrounding cells appears to be necessary for the proper activity of morphogens. The authors speculate that the microfibrillar network may control the distribution of signals in the developing limb or otherwise direct signaling.

The authors also observe a genetic interaction between Fbn2 and BMP7, supporting the idea that fibrillins and morphogens work together. Mice with reduced levels of both proteins show a

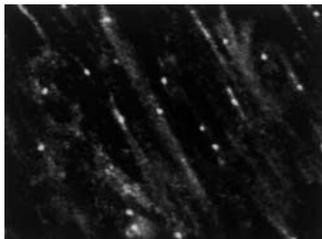


Matrix disruption causes digit fusion (arrow at bottom).

phenotype that is the sum of the phenotypes in mice that lack either protein entirely. ■

Bringing channels into the node

Nodes of Ranvier, the unmyelinated segments of myelinated axons, bear high concentrations of sodium channels to propagate action potentials from node to node. Ratcliffe et al. (page 427) suggest that the sodium channels are recruited to the nodes by interacting through their β subunits with neurofascin, one of the first molecules found in developing nodes of Ranvier.



Sodium channels (white) cluster at nodes of Ranvier.

The interaction of the β subunits with neurofascin, long known to be a cell adhesion molecule in neurons, did not come entirely as a surprise, since β subunits show sequence homology to cell adhesion molecules. This paper provides new evidence that the β subunits of sodium channels perform a dual role: anchoring the sodium

channel through lateral interactions in the plasma membrane, as well as their known function of speeding up the opening and closing of sodium channels.

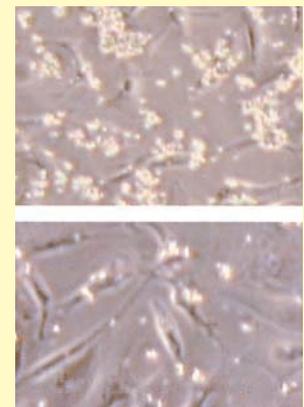
The authors transfected cells in tissue culture to show that neurofascin interacts with the $\beta 1$ and $\beta 3$ subunits of sodium channels, but not the $\beta 2$ subunit, and that the interaction between neurofascin and $\beta 1$ occurs within the same cell, rather than between adjacent cells. The $\beta 1$ subunit and neurofascin are both concentrated at nodes of Ranvier in the developing rat brain, as well as in the adult brain. The authors propose that this interaction helps concentrate sodium channels at the nodes of Ranvier. Interestingly, both the $\beta 1$ subunit and neurofascin bind to ankyrin-G, a protein in the cytoplasm, suggesting that proteins inside the cell guide the assembly of proteins at the node. ■

Tenascin turns on the EGFR

Continuing to stretch the bounds of what the extracellular matrix is known to do, Swindle et al. (page 459) show that tenascin-C, a matrix protein, can signal through the epidermal growth factor receptor (EGFR). The authors suggest that the distinction between receptor interactions that lead to signaling and those that anchor the cell in the environment may be far more tenuous than commonly thought.

Tenascin-C is found in the surrounding matrix when cells are actively dividing and moving; for example, during embryonic development, wound healing, and in invasive cancers. These are also occasions when EGFR is known to be activated. Its previously known ligands are soluble proteins. The study used cells that lack endogenous EGFR ligands to show that tenascin-C, and specifically its EGF-like repeats, activate EGFR in a dose-dependent way. Further, the study shows that EGFR and tenascin-C bind to each other directly.

Although the affinity between tenascin-C and EGFR is relatively low, the fact that tenascin-C is tethered increases its effective concentration, and because it is not internalized and degraded like soluble ligands, signaling is not attenuated. The authors conjecture that cells use soluble ligands for shorter, finely timed responses and tethered ligands for persistent signaling in defined regions. ■



Tenascin-covered beads bind cells (top) unless an antibody to EGFR is present (bottom).