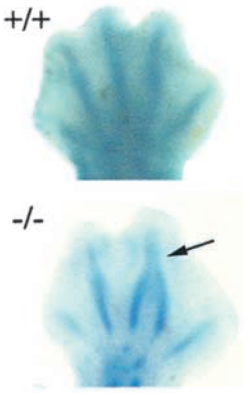
Text By Karin Jegalian
jegalian@nasw.org

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 Arteaga-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.

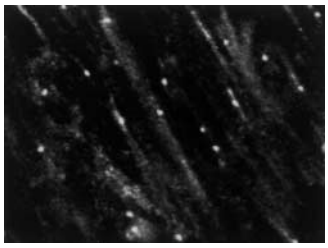
The authors also observe a genetic interaction between Fbn2 and BMP7, supporting the idea that fibrillins and morphogens work together. Mice with reduced levels of both proteins show a phenotype that is the sum of the phenotypes in mice that lack either protein entirely. ■



Matrix disruption causes digit fusion (arrow at bottom).

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.

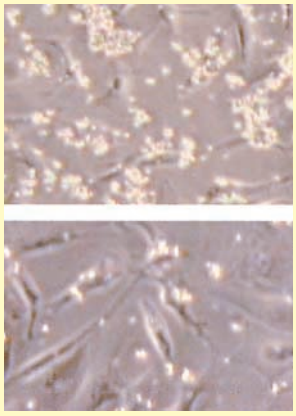
The interaction of the β subunits with neurofascin, long known to be a cell adhesion molecule in neurons, did not come entirely as a surprise, since β subunits show sequence homology to cell adhesion molecules. This paper provides new evidence that the β subunits of sodium channels perform a dual role: 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 β1 and β3 subunits of sodium channels, but not the β2 subunit, and that the interaction between neurofascin and β1 occurs within the same cell, rather than between adjacent cells. The β1 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 β1 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.



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

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. ■