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Research Roundup

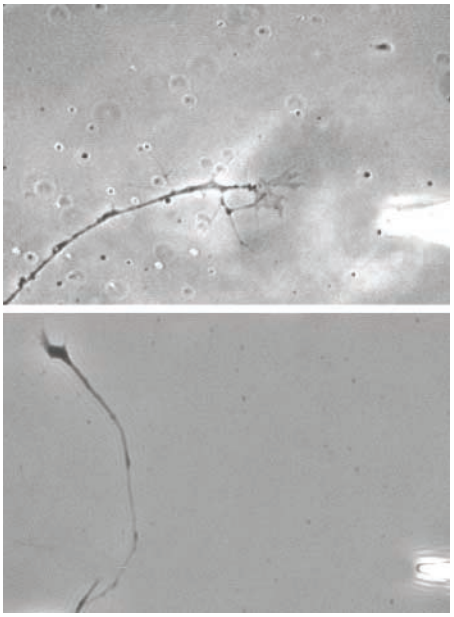
Old and unattracted

With a limited number of guidance molecules in the nervous system, the same molecules get used in multiple places. Now Derryck Shewan, Christine Holt, and colleagues (University of Cambridge, Cambridge, UK) have shown that an intrinsic timing mechanism allows netrin to be used as both an attractant and repellant for the same set of growth cones during different periods of their outgrowth.

Holt had already shown that, at the beginning of the pathway traversed by frog retinal axons, netrin leads the axons out of the eye. To study the rest of the pathway, Shewan achieved the finicky feat of culturing the entire pathway. He confirmed that netrin could later act as a repellent that probably helps to prevent overshoot of the axons' final target.

That was a nice result. But the surprise was yet to come. When the team cultured a chunk of retina, which lacked the rest of the optic pathway and had not yet initiated axon outgrowth, they saw that after two days there was the same switch from netrin attraction to netrin repulsion. Thus, the switch appears to be intrinsic.

"It was when we did the control experiment that we realized [that the switch to repulsion] was happening even without the pathway experience," says Holt. "It was one of those strange twists."



Holt/Macmillan

Young neurons turn toward netrin (top), but old neurons turn away (bottom).

The initial, acute switch during outgrowth may still be influenced by pathway cues—possibly a combination of laminin, which Holt's group has shown can flip the netrin switch, and another guidance molecule called Robo, whose receptor in the spinal cord can silence the netrin receptor. But the more long-lasting switch in netrin responsiveness may be a result of dropping levels of cyclic AMP (cAMP), which Holt's group shows is correlated with the aging of the retinal neurons. Boosting cAMP can restore the youthful attraction to netrin, but the ultimate cause of the age-dependent dip in cAMP is not yet known. ■

Reference: Shewan, D., et al. 2002. *Nat. Neurosci.* 10.1038/nn919.

Electrical healing

Electrical fields (EFs) present at wound sites can orient and promote cell divisions, according to work by Bing Song, Colin McCaig, and colleagues (University of Aberdeen, Aberdeen, Scotland).

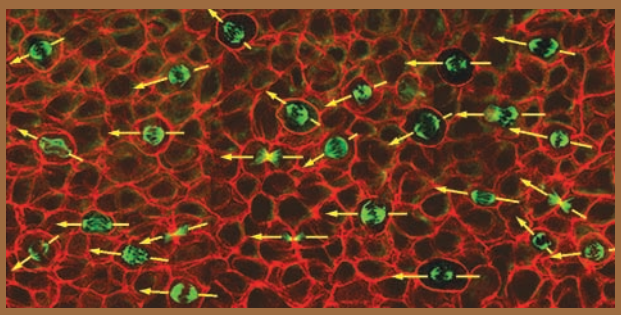
The EFs arise because channels shuttle ions between the tear fluid on the outside of the eye and the extracellular fluid bathing the underlying tissue layers. Before the surface of an eye is damaged, channels actively pump out Cl^- ions and pump in Na^+ and K^+ ions. That gradient is destroyed by wounding, leaving an EF in the extracellular fluid that runs from positive (far from the wound) to neutral or less positive (at the wound site). The authors directly measured the decline of this EF near wound sites. Various drugs changed the EF by activating or inhibiting the ion pumps.

The authors then provided the first in vivo correlation of EF magnitude with cellular behavior. Proximity to the wound and some of the drugs led to both higher EFs and greater orientation of mitotic spindles parallel to the EF. This orientation may help cells feed into the wound area—a process that is also promoted by EF-directed cell migration. McCaig and others have shown in earlier work that EGF receptors, which have charged extracellular domains, redistribute in an EF and are necessary for directed cell migration.

The high level of migration may suppress cell division nearest the wound, but further from the wound the authors again found a correlation: this time between a higher EF and increased cell division. This may also be driven by the clustering of EGF receptors on the cell surface nearest the wound.

Similar EFs may operate during neural development, so should prospective mothers be worried about the effects of high voltage power lines? McCaig says that the high electrical resistance of skin would render such voltages "vanishingly small" for an embryo, and that the power lines generate AC rather than DC electrical fields. But individuals recovering from laser eye surgery might think twice before basking in the sun under a major electrical supply. ■

Reference: Song, B., et al. 2002. *Proc. Natl. Acad. Sci. USA.* 10.1073/pnas.202235299.



McCaig/NAS

Spindles line up in response to a strong electrical field.

Text By William A. Wells
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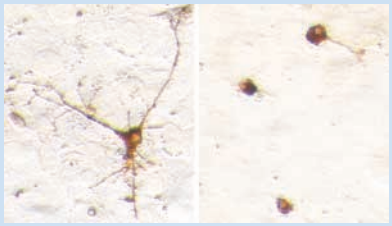
MS as a disease of immaturity

Multiple sclerosis (MS) lesions are characterized by loss of myelin, the insulating coat that surrounds axons. This is despite an abundance of the myelin-supplying glial cells called oligodendrocytes around the lesion. Gareth John, Celia Brosnan, and colleagues (Albert Einstein College of Medicine, Bronx, NY) now provide evidence that an inflammatory cascade keeps those oligodendrocytes in an immature state that does not allow for myelin production.

John started out by adding together two elements present in MS lesions: various immune molecules and glial cells called astrocytes. One change stood out: the cytokine TGFβ1 caused astrocytes to make Jagged1. This ligand for Notch (which is present on oligodendrocytes) was also made by reactive astrocytes in MS lesions. Addition of Jagged1 to cultured oligodendrocytes inhibited process outgrowth, which is one measure of maturation.

During development, Jagged1 keeps oligodendrocytes in an immature state so that they can migrate to cover entire axons before beginning the sedentary process of myelination. The induction of this pathway in brain lesions may be an attempt to generate a larger pool of oligodendrocyte precursors, or it may be an unfortunate carryover from development of the immune system.



John/Macmillan

Turning on Notch (right) inhibits oligodendrocyte maturation.

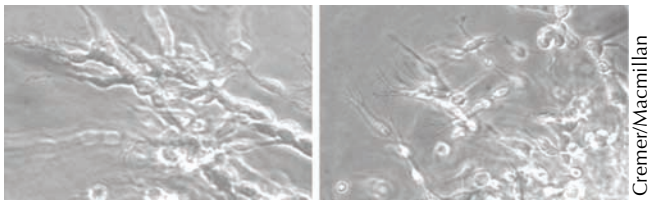
Whatever the underlying logic, the Notch pathway represents a possible target for MS treatment. The initiating immune cascades are another possible target, although here the details remain sketchy. "If we understood the actual triggers to inflammation in MS," says John, "we would be halfway to a cure." ■

Reference: John, G.R., et al. 2002. *Nat. Med.* 10.1038/nm781.

The real role of reelin

Attractants and repellents shunt neurons into their correct final location. But now Iris Hack, Harold Cremer (Université Mediterranée, Marseille, France), and colleagues have found evidence that reelin fits into neither of these categories. They propose, instead, that reelin converts cells that are migrating in association with each other into individual cells that can strike out alone to find their final position.

This conclusion comes over fifty years after the locomoter abnormality of *reeler* mice was first described. Loss of reelin, the product of the *reeler* gene, causes a failure of older neurons to migrate through the layers of younger neurons in the cortex. But, says Cremer, "the available data gave no clear idea of what reelin was doing."



Cremer/Macmillan

Cells migrating in chains (left) are dissociated by reelin (right).

Cremer studied not the cortex but the adult olfactory bulb, where he found that reelin was required for the ongoing arrival of new interneurons. Without reelin, incoming chains of migrating interneurons piled up at the entrance to the olfactory bulb, and failed to undergo their individual migrations to their final positions.

In in vitro assays, the group showed that reelin was neither a repellent nor attractant but acted to dissociate the interneurons from each other. In both the olfactory bulb and the cortex, this dissociation appears to be necessary for the final migration step. (The dissociation in the cortex displaces migrating neurons from the glial cells that are acting as their guides.) The direction of postdissociation migration is probably driven by cues other than reelin. ■

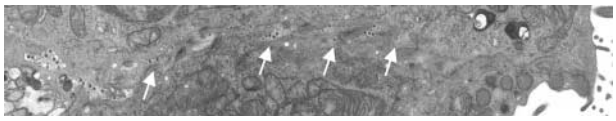
Reference: Hack, I., et al. 2002. *Nat. Neurosci.* 10.1038/nn923.

Adenovirus takes the back door

It has puzzled and frustrated gene therapists that their early workhorse, adenovirus, uses a receptor that is largely inaccessible. CAR, an adhesion protein that serves as the adenovirus receptor, is located on the basolateral surface of the lung epithelium, and is thus hidden from incoming virus. But now Robert Walters, Michael Welsh (University of Iowa, Iowa City, IA), and colleagues report that this strange arrangement helps adenovirus to spread infection by breaking up the epithelium.

Entry may remain a scattershot affair for adenovirus. "I think it's intermittent [epithelial] breaks that all of us must have that gives the initial entry," says Welsh. These hypothetical microinjuries would allow the adenovirus capsid protein called Fiber to bind CAR on the basolateral surface.

After replication, large numbers of viral particles, defective viral particles, and excess Fiber protein are all released into the basolateral solution. The authors showed that the resultant binding of CAR disrupted cell–cell adhesion, thus allowing viral escape to the apical surface. Similar disruption of endothelial CAR may allow the virus to spread into the bloodstream.



Welsh/Elsevier

Adenovirus (arrows) exits by breaking adhesions between cells.

The efficient spread of adenovirus is thus dependent on a replication step, which is not an option for most gene therapy vectors. Welsh suggests using chemicals such as calcium phosphate to induce uptake, or viruses such as adeno-associated virus type 5 that use apical receptors. Alternatively, calcium chelators such as EDTA can open the tight junctions allowing adenovirus to reach CAR. "When you open up the tight junction," says Welsh, "adenovirus works great." ■

Reference: Walters, R.W., et al. 2002. *Cell.* 110:789–799.