aluminum, silicon and silicon dioxide. They also suggest that, beyond making a single nanostructure, improvements in ion-beam technology will allow highly parallel fabrication of nanostructures. If these ideas work out in practice, the method could find many applications in scientific studies and, ultimately, in new technologies. ■

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1. Li, J. *et al. Nature* **412,** 166–169 (2001).
2. Bezrukov, S. M., Vodyanoy, I. & Parsegian, V. A. *Nature* **370,** 279–281 (1994).
3. Ball, P. *Nature* **379,** 25 (1996).
4. Li, A. P., Müller, F., Birner, A., Nielsch, K. & Gösele, U. *J. Appl. Phys.* **84,** 6023–6026 (1998).
5. Schmidt, T., Martel, R., Sandstrom, R. L. & Avouris, P. *Appl. Phys. Lett.* **73,** 2173–2175 (1998).

Developmental biology

Vesicles and the spinal cord

Juhee Jeong and Andrew P. McMahon

The distinction between cell biology and developmental biology is becoming increasingly blurred. The latest example involves a signalling pathway switched on in the developing spinal cord.

Membrane-clad containers known as vesicles are used to distribute proteins and other molecules to appropriate locations within a cell, and so are essential for cells (and organisms) to function normally. On page 194 of this issue[1], Eggenschwiler and colleagues propose an intriguing new function for vesicle trafficking. They reveal a previously unsuspected link between a protein implicated in vesicle transport and a signalling pathway with a key role in the formation of different types of neuron in the developing spinal cord.

Proteins of the Hedgehog family are secreted signalling molecules that are involved in intercellular communication. They are essential for several processes in the development of invertebrate and vertebrate embryos[2]. For example, Sonic hedgehog (Shh) is required for patterning the mammalian spinal cord, inducing distinct ventral neurons at specific positions in the developing neural tube in a concentration-dependent mechanism[3]. So, for instance, floor-plate cells develop closest to the source of Shh in response to the highest concentration of Shh, and V3 interneurons at a more distant position in response to a lower concentration. The incorrect regulation of the Hedgehog signalling pathway has also been implicated in several cancers[2]. Yet, despite their obvious importance, the mechanisms that regulate Hedgehog signalling are only just being uncovered.

In the fruitfly *Drosophila*, the activation of Hedgehog-responsive pathways depends on interactions between two integral membrane proteins: Patched, which contains a region that might sense sterols (components of cell membranes), and Smoothened, a protein with similarity to G-protein-coupled receptors[4] (a broad class of signalling molecules). In the absence of Hedgehog, the task of Patched is to inhibit Smoothened, thereby blocking the whole Hedgehog-responsive pathway. When bound to Hedgehog, Patched can no longer block Smoothened, so the pathway is activated (one of the outcomes of this is the increased expression of Patched itself). This basic mechanism appears to be conserved from flies to humans. What remains unclear is exactly how Patched inhibits Smoothened, and how this inhibition is eliminated when Hedgehog binds to Patched.

Early studies suggested a direct interaction between Patched and Smoothened[5]. Although this may indeed be the case for a small amount of each protein, there is little overlap in the intracellular distributions of these proteins in cells that detect the Hedgehog signal[6,7]. So an indirect mechanism is now invoked, based on the observation that the binding of Hedgehog to Patched results in Smoothened becoming more highly phosphorylated and more stable[6,8]. These changes correlate with the accumulation of Smoothened at the cell surface, and with the internalization and destabilization of

Evolutionary biology

Autumn colour code

Most of us are happy simply to marvel at the autumn colours of deciduous trees, as shown here. But the late William Hamilton, one of the most influential thinkers on evolution in the twentieth century, and Sam Brown felt compelled to ask what such a show is in aid of. They hypothesize that trees are sending the message 'pick on someone else' to their insect enemies.

Most researchers, when they have considered autumn displays at all, have assumed them to be a side effect of senescence. But Hamilton and Brown felt that trees would not, without good reason, make large amounts of potentially costly compounds in their leaves just before shedding them.

In autumn, many insects are looking for plants on which to overwinter and to feed and reproduce the next year. Hamilton and Brown concentrated on aphids, because aphid species tend to be choosy about what they eat and use colour cues to find their hosts. The amount of damage aphids can inflict also gives trees a strong incentive to deter them.

Using published data, Hamilton and Brown surveyed 262 tree species and found that the yellowness or redness of a tree's autumn leaves correlates with the number of aphid species that attack it (*Proc. R. Soc. Lond. B* **268,** 1489–1493; 2001). Maples, for example, which put on some of the most spectacular displays, are some of the most heavily aphid-infested species, fitting in with the idea that tree species suffering greater insect damage should invest more in colour signalling. Costly autumn pigments would be an 'honest signal' — only trees that were truly committed to defence would make them.

RICHARD CUMMINS/CORBIS

The connection between colours and herbivores raises questions for exploring the hypothesis further. For instance, does the link hold good within species, as well as between them — that is, are brighter individuals left alone? And can the idea be broadened beyond aphids? **John Whitfield**

Patched. One model put forward to explain these data is that the phosphorylation of Smoothened is crucial to the signalling process, and that, in the absence of Hedgehog, Patched inhibits Smoothened by regulating — directly or indirectly — a dephosphorylating enzyme (phosphatase)[6].

More recently, mutations have been detected in the sterol-sensing domain of Patched that render it unable to repress Smoothened, but do not affect its binding to Hedgehog[7,9]. Together with the fact that other proteins with sterol-sensing domains, such as SCAP and NPC1, are thought to control vesicle transport, this hints that Patched might also regulate vesicle movement.

The idea that vesicle transport is in some way involved in Hedgehog signalling now receives support from Eggenschwiler *et al.*'s studies[1] of mice with mutations in the *open-brain* (*opb*) gene. Such mutations lead to the neural tube forming improperly, being open in both the brain and spinal cord. Two independently arising mutations have been isolated in *opb*[10,11], and embryos with these mutations have defects that are characteristic of overactive Shh signalling — for example, suppression of dorsal and overproduction of ventral neuronal precursors[10,12].

Eggenschwiler *et al.*[1] show that mice with mutations in both *opb* and *Shh* have similar defects to animals with mutations in *opb* alone. Remarkably, despite the absence of a localized source of Shh, the double mutants have a reasonably normal positioning of floor-plate cells and V3 interneurons in the ventral neural tube. The data suggest that a gradient of Shh is not absolutely essential either for establishing the polarity of ventral cells or for the correct gradated expression of the mouse *Patched1* gene. This is interesting because the expression of *Patched1* directly reflects the strength of signalling through the Shh pathway. Shh is clearly not present in these mice, so what could be going on here?

Part of the answer is probably that the protein product of the *opb* gene somehow inhibits signalling through the Shh pathway. Mutation of *opb* results in Shh-independent activation of the pathway. As the authors point out, bone morphogenetic proteins (which cause cells to take on dorsal identities[3]) and their antagonist Noggin[13] may provide another way to establish ventral patterning.

What, then, is the protein encoded by the *opb* gene? Positional cloning provided Eggenschwiler *et al.* with the answer[1]: *opb* encodes Rab23, a member of a large family of GTP-hydrolysing enzymes (GTPases). Although the functions of Rab23 in particular have not been investigated, Rab proteins in general are master regulators of vesicle trafficking. By serving as a scaffold for other molecules, Rab proteins coordinate the budding of vesicles from one cellular compartment, their transport, and their docking and fusion with the target compartments[14].

The implication is that vesicle trafficking is important in the Hedgehog signalling pathways. Moreover, as the detection of the Hedgehog signal by *Drosophila* cells leads to an alteration in the localization of Smoothened and Patched, it is tempting to speculate that Rab23 participates in a vesicle-transport process that promotes the inhibition of Smoothened by Patched1 in mice. For example, if the phosphorylation of Smoothened is indeed important for its activity, then Patched1 might, in a Rab23-dependent way, direct vesicles containing Smoothened (or a phosphatase that acts on Smoothened) to a cellular compartment in which Smoothened is dephosphorylated or destabilized.

Eggenschwiler *et al.*'s work[1] offers several testable predictions. First, if Rab23 is indeed required for the inhibition of Smoothened by Patched1, then ventral cell identities should be lost in mice with mutations in both *opb* and *smoothened*, much as in *Shh* mutants. Second, Smoothened or Patched1 might be localized incorrectly in *opb* mutant cells. Third, the defects in mice with mutations in *opb* alone are less severe than in mice lacking *Patched1* (ref. 15), so the inhibition of Smoothened might not be completely blocked in *opb* mutants. Reducing the levels of Patched1 in *opb* mutants might then be expected to enhance the defects. Finally, given that the sterol-sensing domain of the fruitfly Patched protein is essential for the inhibition of Smoothened, this domain might be needed in some way for the Rab23-mediated regulation of vesicle transport. If so, Rab23 might also control vesicle movement by working with other proteins that contain a sterol-sensing domain. ■

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1. Eggenschwiler, J. T., Espinoza, E. & Anderson, K. V. *Nature* **412,** 194–198 (2001).
2. Hammerschmidt, M., Brook, A. & McMahon, A. P. *Trends Genet.* **13,** 14–21 (1997).
3. Jessell, T. M. *Nature Rev. Genet.* **1,** 20–29 (2000).
4. Ingham, P. W. *EMBO J.* **17,** 3505–3511 (1998).
5. Stone, D. M. *et al. Nature* **384,** 129–134 (1996).
6. Denef, N., Neubüser, D., Perez, L. & Cohen, S. M. *Cell* **102,** 521–531 (2000).
7. Martín, V., Carrillo, G., Torroja, C. & Guerrero, I. *Curr. Biol.* **11,** 601–607 (2001).
8. Kalderon, D. *Cell* **103,** 371–374 (2000).
9. Strutt, H. *et al. Curr. Biol.* **11,** 608–613 (2001).
10. Günther, T., Struwe, M., Aguzzi, A. & Schughart, K. *Development* **120,** 3119–3130 (1994).
11. Kasarskis, A., Manova, K. & Anderson, K. V. *Proc. Natl Acad. Sci. USA* **95,** 7485–7490 (1998).
12. Eggenschwiler, J. T. & Anderson, K. V. *Dev. Biol.* **227,** 648–660 (2000).
13. McMahon, J. A. *et al. Genes Dev.* **12,** 1438–1452 (1998).
14. Rodman, J. S. & Wandinger-Ness, A. *J. Cell Sci.* **113,** 183–192 (2000).
15. Goodrich, L. V., Milenkovic, L., Higgins, K. M. & Scott, M. P. *Science* **277,** 1109–1113 (1997).

Daedalus

Bashing the bugs

Britain's National Health Service has been accused of giving patients diseases they didn't have when they entered hospital. Indeed, a recent survey claims that a third of British NHS wards fall below basic sanitary standards. And one study found that certain multiple-antibiotic-resistant bacteria, such as MRSA (methicillin-resistant *Staphylococcus aureus*) abound on specific wards. In this connection, Daedalus recalls an old American remedy.

Late nineteenth-century warehouses in the United States were often infested with rats, cockroaches and bugs of all sorts. The cure was to close all the windows, and place in every room a large pellet of sodium cyanide, together with an apparatus for covering this with hot sulphuric acid. When all was ready, the operator left the building, pulling the strings which worked the apparatus in each room. The whole warehouse became a gas chamber, killing all the infesting organisms. A little while later, the windows were opened (from the outside!). Later still, the building, now free of pests, could be safely reoccupied by its human owners.

So, says Daedalus, let us adapt this technology for the NHS. Hydrogen cyanide should be readily available in cylinders or adsorbed on vermiculite, for example; other volatile agents to kill viruses, such as formaldehyde or ethylene oxide, are also freely accessible. (Formaldehyde has already been blamed for affecting people in houses whose cavity walls have been filled with urea–formaldehyde waterproof resin.) Mixtures of ethylene oxide and carbon dioxide, just as deadly to infestations but less lethal to human beings, have also been used in pest control.

The NHS patients would have to be rehoused in a day-room or vacant ward, and external fans might have to be installed to prevent gas issuing from the treated ward from inconveniencing surrounding wards or dwellings. But what worked for early Americans should also work well for the NHS. Insects, bacteria and viruses should be neatly eliminated, and patients would be safely rehoused in completely sterile surroundings.

The only snag, says Daedalus, might be the bugs left in the patients themselves. The American solution was to disinfect the warehouses at regular intervals, so that nothing nasty could build up even by mutation. Whether NHS hospitals could build such a procedure into their routine is another matter. But if patients arrive free of these infections, the problem should not arise.

David Jones