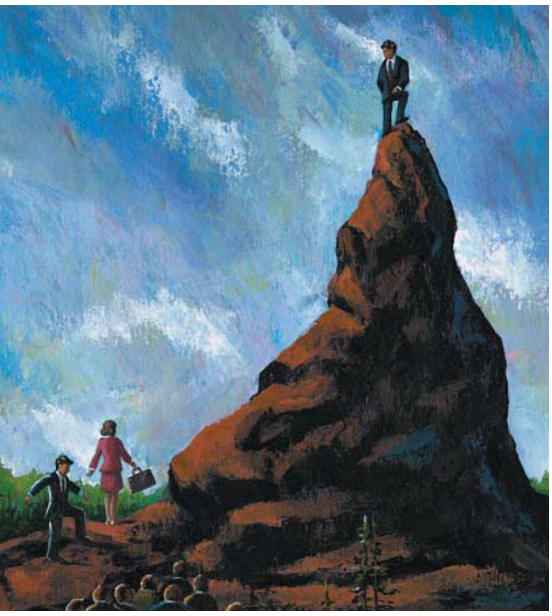
GLIOGENESIS

Oligodendrogenesis on a higher plane



Although oligodendrocytes are widely distributed throughout the adult central nervous system, they originate in restricted domains in the embryonic neural tube. One such domain resides in the ventral neuroepithelium of the developing spinal cord, and it has been suggested that this domain might supply the full complement of oligodendrocytes across the dorsoventral axis. However, two recent reports in *Neuron* identify a more dorsal domain that could be responsible for a second phase of oligodendrogenesis.

Ventrally, oligodendrocytes are produced in the pMN domain, which initially generates motor neurons, but later switches to producing oligodendrocytes under the influence of sonic hedgehog (SHH) signalling and the transcription factors NKX6.1 and NKX6.2. To find out whether oligodendrocytes could be generated in the absence of these factors, Cai *et al.* and Vallstedt *et al.* examined mouse embryos from an *Nkx6.1*$^{-/-}$;*Nkx6.2*$^{-/-}$ double mutant line, and Cai *et al.* also investigated a *Shh*$^{-/-}$ line. In both cases, the pMN domain failed to produce oligodendrocytes. Nevertheless, some oligodendrocyte precursor cells (OLPs) — identified by the expression of *Olig2* and *PDGFRα* (platelet-derived growth factor receptor α) — were still generated, albeit some time after the usual time of onset of oligodendrogenesis. These OLPs originated near the midline in the dorsal spinal cord.

On their own, these findings do not necessarily indicate that the dorsal spinal cord normally produces oligodendrocytes — the OLPs could have migrated from the ventral neural tube, or the dorsal neuroepithelium could have been respecified in the mutant embryos. However, closer inspection of wild-type embryos revealed that an *Olig2*-expressing domain is normally present in the dorsal spinal cord, and in both mutant and wild-type embryos, the cells in this domain also expressed the dorsal neuroepithelial markers *Pax7* and *Mash1*. In addition, Cai *et al.* showed that if the dorsal spinal cord was explanted at embryonic day 11.5 (before the onset of oligodendrogenesis) and grown in

CELL BIOLOGY OF THE NEURON

The making of polarity

Neurons are the masters of membrane specialization. Normally, each polarized neuron has one axon and many dendrites, but it is not clear how this neuronal polarity is formed and maintained. Two recent reports in *Cell* suggest that glycogen synthase kinase 3β (GSK3β) might be a key factor in translating extracellular cues into changes in cytoskeletal organization.

In culture, embryonic hippocampal neurons are initially nonpolarised, with immature neurites, and one of these neurites then grows out to become an axon. Jiang and colleagues found that GSK3β is present in all processes in both polarized and nonpolarized neurons. However, the distribution of phosphorylated GSK3β, which is inactive, is more interesting. This is mainly present in the tips of axons in polarized neurons.

Overexpression of a constitutively active GSK3β mutant inhibits axon formation without affecting the number of dendrites. By contrast, both the inhibition of GSK3β activity by pharmacological and peptide inhibitors and the suppression of GSK3β expression by short-hairpin RNAs result in the formation of multiple axon-like processes. Not only do these processes look like axons and express axonal markers, they can also support synaptic vesicle recycling — a basic feature of functional axons. Among the kinases that might phosphorylate GSK3β and regulate its activity, AKT is differentially localized in axons. Therefore, the authors went on to test whether it promotes axon formation by functioning as an upstream inhibitor of GSK3β. Overexpression of a constitutively active AKT mutant resulted in the formation of multiple axons, which could be partially reversed by co-transfection of GSK3β.

But how does GSK3β regulate axon formation? Axon specification is thought to involve elongation of an immature neurite, and microtubule assembly in the tip of the neurite is essential. In the second study, Yoshimura and colleagues identified a substrate of GSK3β, collapsin response mediator protein 2 (CRMP2), which is involved in regulating axon formation and might be the missing link between GSK3β activity and microtubule organization. GSK3β phosphorylates CRMP2, thereby reducing its ability to bind to tubulin, the building block of microtubules. Like dephosphorylated GSK3β, nonphosphorylated CRMP2 is predominantly present in the tips of axon growth cones, and

culture, the tissue still generated OLPs. Therefore, OLP production in the dorsal spinal cord does not require signals or cellular contribution from the ventral neural tube.

The findings of Cai *et al.* and Vallstedt *et al.* support a model in which the dorsal domain is responsible for a phase of oligodendrogenesis that begins around embryonic day 14.5 — 2 days later than in the ventral spinal cord. It was not possible to determine whether the dorsal OLPs develop into mature myelinating oligodendrocytes, because the mutants that were investigated in these studies died at birth. Therefore, further studies will be required to establish what contribution, if any, the dorsal domain makes to the oligodendrocyte population of the mature spinal cord.

Heather Wood

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its overexpression also results in the formation of multiple axons. Overexpression of nonphosphorylated CRMP2 can counteract the effect of GSK3β on axon growth, which indicates that GSK3β regulates neuronal polarity through CRMP2. Interestingly, neurotrophin 3 and brain-derived neurotrophic factor (BDNF) — factors that promote axon formation by activating the AKT–GSK3β pathway — decrease CRMP2 phosphorylation in neurons.

The two studies put together an interesting theory of how a particular neuronal process can be selected to form an axon. In nonpolarized neurons, all neurites contain the active form of GSK3β and phosphorylated CRMP2, which has low tubulin-binding activity. This blockade of microtubule assembly can be removed by extracellular cues that activate AKT, which, in turn, phosphorylates and inactivates GSK3β. Whether other pathways are involved and how they might fit into the picture remains to be seen.

Jane Qiu

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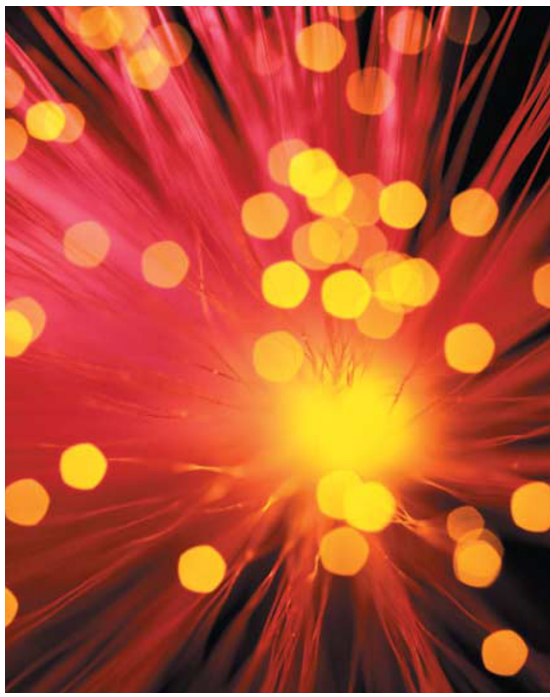
SENSORY TRANSDUCTION

Seeing the light



Three studies have shown that melanopsin — a pigment that is found in the type of retinal ganglion cell that allows light to entrain the circadian clock — can function as a photopigment in other types of cell. As well as confirming that melanopsin is photosensitive, the studies reveal that it is closer in some ways to invertebrate photopigments than to other photopigments in vertebrates.

Circadian entrainment in mammals relies on a set of intrinsically photoreceptive retinal ganglion cells (ipRGCs). Although these contain melanopsin, and lose their photoreceptive properties if melanopsin is removed, it has not previously been shown that melanopsin itself is the photopigment in these cells. To show that melanopsin is not only necessary, but also sufficient, for photosensitivity, three groups expressed the pigment in different types of cell — *Xenopus* oocytes, human embryonic kidney (HEK293) cells and a mouse neuronal cell line called neuro-2a. In each case, the expression of melanopsin caused the cells to become photosensitive.

The three groups also investigated the signalling pathways that mediated phototransduction in the transfected cells. Molyan *et al.* found that, in neuro-2a cells, melanopsin signals through a G-protein signalling pathway to regulate the opening of an intrinsic ion channel. In *Xenopus* oocytes and HEK293 cells, according to Panda *et al.* and Qiu *et al.*, the activation of melanopsin by light can trigger the opening of TRPC3 calcium channels — a mammalian homologue of the TRP and TRPL channels, which are involved in phototransduction in *Drosophila*. The activation of TRPC3 channels in these cells also involves signalling through a G-protein pathway, and the signalling pathway is similar to that found in invertebrate photoreceptors.

Photosensitive opsins, such as melanopsin, use 11-*cis*-retinaldehyde as a chromophore. When light converts 11-*cis*-retinaldehyde to all-*trans*-retinaldehyde, it creates a conformational change in the opsin that triggers G-protein activation. In vertebrate photoreceptors, the chromophore is converted back to 11-*cis*-retinaldehyde through a complex pathway in the retinal pigment epithelium, but in invertebrates the opsins themselves can carry out the photoisomerase activity that is needed to regenerate the chromophore. Both Melyan *et al.* and Panda *et al.* provide evidence that melanopsin resembles invertebrate opsins in that it has an intrinsic photoisomerase activity that can convert all-*trans*-retinaldehyde into 11-*cis*-retinaldehyde.

Although further studies are needed to pin down the exact mechanism by which melanopsin mediates phototransduction in ipRGCs, these three studies provide proof that melanopsin can function as a photopigment, and also point towards an invertebrate-like signalling mechanism. In a fourth study that investigated the melanopsin-driven dispersal of melanosomes in cultured *Xenopus* melanophores, Isoldi *et al.* also found evidence for a signalling pathway that resembled those in invertebrate photoreceptors. This similarity between ipRGCs and invertebrate photoreceptors could give valuable insights into the biology and evolution of the circadian light-entrainment system in vertebrates.

Rachel Jones

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