Starring activity

During development, activity-dependent release of ATP from axons is important for promoting myelination, as it inhibits proliferation of oligodendrocyte progenitor cells and stimulates their differentiation into a premyelinating stage. However, it is adenosine, a hydrolysed product of ATP, rather than ATP itself, that has a crucial role in this process. Now,

the results of a study by Tomoko Ishibashi and colleagues show that neuronal activity can also influence the myelinating activity of mature oligodendrocytes, and that this effect is mediated by astrocytes as a result of ATP stimulation.

In a co-culture study, the researchers found that stimulation of dorsal root ganglion (DRG) neurons with a pattern of electrical activity that is known to induce axonal release of ATP increased myelination of axons by mature oligodendrocytes. The effect was mimicked by 2MeSATP, a non-hydrolysable form of ATP, as well as by an agonist of P2X, a type of ATP receptor.

As cytokines, such as leukaemia inhibitory factor (LIF) and ciliary neurotrophic factor, are known to promote the myelinating activity of mature oligodendrocytes, Ishibashi *et al.* tested their involvement in activity-induced myelination. A LIF-blocking antibody markedly decreased myelination of DRG axons induced by electrical stimulation. In addition, there was a prolonged elevation of LIF release in the culture medium in response to axonal firing, which could be blocked by apyrase, an enzyme that rapidly degrades extracellular ATP. In the absence of electrical stimulation, 2MeSATP had a similar effect on LIF production.

The most probable source of LIF in the CNS is astrocytes and microglia. The researchers found that astrocytes, but not microglia, were present in the co-cultures, and that electrical activity in DRG axons increased the level of LIF

mRNA in astrocytes. In monoculture studies, addition of 2MeSATP led to a significant increase in the LIF concentration in the culture medium of astrocytes, but not that of oligodendrocytes, which confirms that ATP might affect myelination by acting on astrocytes rather than oligodendrocytes.

The percentage of astrocytes in the co-cultures of DRG neurons and oligodendrocytes was about 3%. Increasing this percentage to 5–15% by supplementing the culture with purified astrocytes enhanced myelination of DRG axons by oligodendrocytes. However, this effect was completely abolished when astrocytes from LIF-deficient mice were used. Finally, removing astrocytes from the co-culture led to diminished myelination in response to either electric stimulation or 2MeSATP.

This elegant study reveals a new mechanism, whereby neuronal activity promotes myelination of axons by mature oligodendrocytes at a late stage of development and possibly into adult life. According to the researchers, the activity-dependent mechanism of myelination in adults might constitute an under-appreciated form of plasticity of the nervous system.

Jane Qiu

ORIGINAL RESEARCH PAPER Ishibashi, T. *et al.* Astrocytes promote myelination in response to electrical impulses. *Neuron* **49**, 823–832 (2006)

FURTHER READING Volterra, A. & Meldolesi, J. Astrocytes, from brain glue to communication elements: the revolution continues. *Nature Rev. Neurosci.* **6**, 626–640 (2005)

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In the news

PREMATURE BABIES
FEEL PAIN

Response to pain involves a reflexive action, such as flinching, and a higher-level conscious perception. Premature babies are known to respond reflexively to painful procedures, and now research has shown that they also register pain in the brain's cortex. Essentially, they "feel true pain" says Professor Maria Fitzgerald, who led the research at University College, London, UK (*BBC News Online*, 4 April 2006).

Premature babies can be subject to multiple procedures, such as blood tests and chest drains, on a daily basis. "Nursing staff are not callous in dealing with these babies", says Professor Fitzgerald, explaining that the brains of such babies "... are so immature it was difficult to genuinely know that the pain was going to the brain" (*Daily Telegraph*, 5 April 2006).

Brain imaging techniques used for monitoring the processing of pain in adults are not applicable to newborns, so the team used near-infrared spectroscopy. Sensors were attached to the heads of 18 babies delivered between 25 and 45 weeks post conception, allowing the researchers to measure blood flow to the brain while routine procedures — heel-pricks for blood tests — were performed. The team observed that during these procedures there was a surge of blood and oxygen to the brain, showing that pain was being processed at a cortical level.

"Since pain information is transmitted ... from 25 weeks, there is the potential for pain experience to influence brain development from an early age" says Professor Fitzgerald (*Guardian*, 5 April 2006). It is hoped that the research will lead to better pain-relief protocols for premature babies. Neil McIntosh, professor of child life and health at Edinburgh University did point out, however, that whereas "... a large number of units give nothing for heel-pricks ... with a painful procedure like a chest drain, virtually no one would not give analgesia" (*Guardian*).

Ruth Williams

CIRCADIAN RHYTHMS

SCN synchronicity...hup, two, three, four

It would be most inconvenient if your stomach thought it was time for breakfast while your eyelids thought it was bedtime. Luckily, neurons of the suprachiasmatic nucleus (SCN), which control the internal circadian rhythm, spontaneously synchronize so that their target neurons in peripheral tissues receive correctly time-coordinated signals. But how do the SCN neurons stay in sync? The results of new work reveal that interneuronal signalling via vasoactive intestinal polypeptide (VIP) is required.

Maywood and colleagues focused on VIP signalling, as it had previously been implicated in SCN circadian rhythmicity. To further investigate this association, the team looked at expression of the clock gene period (*Per*) in mice that lacked VIP receptor 2 (VIPR2). In normal mice, *Per* expression is temporally controlled by a feedback mechanism

that results in a 24-hour periodicity between expression peaks. The group used a *Per1* transgene containing a bio-luminescent reporter and, in real time, measured the amount of light emitted from SCN slices in culture over a number of days. Compared with wild-type mice carrying the transgene, *Vipr2*^{-/-} mice showed low levels of bio-luminescence and an imprecise periodicity. Furthermore, using video microscopy to continuously image the slices, the researchers were able to determine that rather than the regularity of the feedback loop mechanism having been lost from all cells, the cells had instead lost synchronicity. Therefore, loss of VIP signalling both reduced the expression levels of *Per* and disrupted interneuronal synchronicity.

Expression of *Per* can be suppressed by hyperpolarization of SCN neurons. Therefore, to determine

“ ... SCN neurons continually signal to each other to maintain synchronicity of the body clock.”

CANCER

Developing patterns

cases of anaplastic astrocytoma and glioblastoma using microarrays. Three clusters of tumour samples were identified with differential expression of 108 survival related genes — 35 of which were robust markers of the three tumour subtypes. One subtype was found to express genes associated with the normal brain and the process of neurogenesis (known as the proneural subtype), another expressed proliferation associated genes (the proliferative subtype) and a third subtype expressed genes associated with angiogenesis and mesenchymal origin (the mesenchymal subtype). Patients with the proneural subtype had better prognosis (median survival 174.5 weeks) than those with either the proliferation (60.5 weeks) or mesenchymal subtypes (65 weeks). Profiling of an independent set of 31 glioblastoma cases confirmed the prognostic value of this classification. The authors then compared the signatures of 26 pairs of matched specimens — primary and recurrent astrocytoma from the same patient — and found that on recurrence tumours tend to shift towards the mesenchymal phenotype.

whether membrane depolarization might rescue the expression level of *Per* (and synchronicity) in *Vipr2^{-/-}* mice, the team depolarized the SCN slices and found that both *Per* expression levels and interneuronal synchronicity of the feedback loops did revert to that of the wild type. The same result was observed when gastrin-releasing peptide (GRP), which activates electrical firing of SCN neurons, was added to the slices. However, once depolarization or GRP treatment ceased, the cells of the SCN gradually (over a period of days) lost synchronicity and *Per* expression levels dropped.

Taken together, the findings of Maywood *et al.* indicate that synchronicity of SCN neurons cannot be achieved by one initial signal but instead requires continued signalling (through VIP). Much like marching soldiers sing together to keep in sync, SCN neurons continually signal to each other to maintain synchronicity of the body clock.

Ruth Williams

ORIGINAL RESEARCH PAPER Maywood, E. S. *et al.* Synchronization and maintenance of timekeeping in suprachiasmatic circadian clock cells by neuropeptidergic signaling. *Curr. Biol.* **16**, 599–605 (2006)

So, what are the main features of each subtype, and how do they relate to neurogenesis? The poor prognosis subtypes showed features of tumour cell proliferation or angiogenesis that were almost absent from the better prognosis proneural subtype. In addition, although poor prognosis subtypes expressed markers of undifferentiated neural stem cells and/or transit amplifying cells (progenitor cells), the proneural subtype expressed markers of neuroblasts or neurons. At the genomic level, most of the proliferative and mesenchymal tumours had losses on chromosome 10, which includes the *PTEN* (phosphatase and tensin homologue) locus, and gains on chromosome 7, which contains the *EGFR* (epidermal growth factor receptor) locus, whereas proneural tumours did not have these alterations. Notch pathway elements, including *DLL3*, were overexpressed in proneural tumours. The authors then investigated whether the phenotypes associated with changes in the Notch pathway and the Akt pathway (which is activated by changes in *PTEN* and *EGFR*) were directly associated with patient survival, and found that levels of *PTEN* and *DLL3*

mRNA formed a highly significant predictive model of survival in high-grade astrocytoma. These findings are intriguing, as both the Notch and Akt pathways have been implicated as key regulators in neurogenesis.

The authors propose a model for human gliomas in which all molecularly defined subtypes arise from cell types of similar origin, but that differential activation of signalling pathways leads some tumours to maintain more undifferentiated neural-stem-cell-like or transit-amplifying-cell-like phenotypes, whereas others adopt a phenotype closer to that of neuroblasts or immature neurons. Further confirmation of the correlation between stem cell biology and glioma aggressiveness should produce a useful molecular signature prognostic model.

Ezzie Hutchinson, Chief Editor,
Nature Reviews Cancer

ORIGINAL RESEARCH PAPER Phillips, H. *et al.* Molecular subclasses of high-grade gliomas predict prognosis, delineate a pattern of disease progression, and resemble stages in neurogenesis. *Cancer Cell* **9**, 157–173 (2006)

RESEARCH HIGHLIGHTS

NEUROENDOCRINOLOGY

Hormonal hippocampus

Growth hormone (GH), which is primarily produced in the pituitary and known for its role in body growth and development, is also expressed in the hippocampus, where its function is not clear. Now, Donahue and co-workers report that the expression of endogenous hippocampal GH in rats is regulated by age, sex and response to stress.

The authors first showed that the level of GH mRNA in the adult hippocampus was more than double that in juveniles. They then compared the levels in adult males and females at different stages of oestrus. Relative to adult males, females in proestrus (a stage associated with ovulation and high blood oestrogen levels) had elevated hippocampal GH mRNA expression, whereas dioestrus females (which had relatively low levels of oestrogen in the blood) did not.

Interestingly, the opposite effect was seen for the growth hormone receptor (GHR) and its downstream effector insulin-like growth factor 1 (IGF1) — expression of both molecules was downregulated by oestrogen. As GH production in the pituitary is normally regulated by negative feedback from IGF1, the authors suggest that the induction of GH mRNA by oestrogen might be due to downregulation of IGF1.

As the production of GH expression is enhanced by learning, and because stress is known to have different effects on learning in males and females, the authors investigated whether the expression of GH in the hippocampus is affected by stress. Exposure to brief, intermittent tail shocks increased the expression of GH mRNA in the hippocampus of males and dioestrus females. However, the already high level of GH mRNA expression in the oestrus or proestrus female hippocampus was not affected by stress. Interestingly, the inverse correlation with IGF1 expression was seen in stressed females, but not in stressed males, suggesting that the elevation of GH after stress is regulated by IGF1 in females but by a different mechanism in males.

The sexual dimorphism in hippocampal GH mRNA expression, and the response of GH to stressful experiences, suggest that GH might have a role in hippocampal functions that differ between males and females.

Daniel McGowan

ORIGINAL RESEARCH PAPER Donahue, C. *et al.* Growth hormone is produced within the hippocampus where it responds to age, sex and stress. *Proc. Natl Acad. Sci. USA* **103**, 6031–6036 (2006)

NEURODEGENERATIVE DISORDERS

Switch to the potassium channel

Misfolded and aggregated proteins generally take the centre stage of aetiological research into many neurodegenerative disorders, including Huntington's disease, Parkinson's disease, spinocerebellar ataxia (SCA) and Alzheimer's disease. However, the results of a new study suggest that potassium channel dysfunction could also be involved. Reporting in *Nature Genetics*, Pulst and colleagues show that, in two families with SCA, mutations in the voltage-gated potassium channel gene *KCNC3* are to blame. Is it time for a switch in our thinking about neurodegeneration?

SCA can manifest a wide spectrum of motor disorders, such as ataxia, dysarthria and oculomotor abnormalities, and also other neurological symptoms such as cognitive decline, epilepsy and psychiatric disorders. So far, 12 SCA-associated genes have been identified. Although the functions of the majority of these genes are unknown, the causative mutations are mostly in the form of expanded polyglutamine

stretches (suggesting protein misfolding and aggregation pathways in disease progression).

Pulst's group had previously characterized a Filipino family with late-onset SCA and, through linkage analysis, showed that the candidate genomic locus was within a 4 cM region on chromosome 19q13. Encouragingly, this 4 cM was within

a region previously identified in a French family with early-onset SCA and mental retardation. Using additional genetic markers, the team was able to narrow their search to a region of just 800 kb, which contained ~40 genes — one was *KCNC3*. The expression of *KCNC3* in Purkinje cells of the cerebellum (involved in motor coordination) made it a prime suspect. And the researchers' suspicions were confirmed when they carried out sequencing analyses and found that the gene was mutated in both families.

In the Filipino family, the mutation gave rise to a single amino acid substitution affecting the main voltage-sensing domain of *KCNC3*. In the French family, the mutation caused a different amino acid substitution, this time affecting the protein's cytoplasmic domain, which controls pore opening. To investigate the effect on function, the team overexpressed the two mutant variants in *Xenopus* oocytes and compared channel activity with that of the wild-type protein. Using a voltage clamp analysis, they found that the Filipino mutation resulted in the total loss of channel activity (no detectable current), whereas the French mutation altered the voltage sensitivity of *KCNC3* such that pores were open longer (prolonged current).

NEURODEGENERATIVE DISORDERS

Malicious multimers

Alzheimer's disease is frequently preceded by a decline in memory function, which is thought to be due to changes in synaptic function rather than neuronal loss. Reporting in *Nature*, Lesné and colleagues show that memory deficits in middle-aged Alzheimer mice are caused by a soluble amyloid- β ($A\beta$) protein assembly.

Tg2576 mice, which express mutant human $A\beta$ precursor protein, develop memory deficits without neuronal loss at 6 months of age. Following this initial decline, memory function is stable for 7–8 months before declining further. There is good evidence that $A\beta$ is responsible for this memory

decline, but its levels increase rapidly with age, which contrasts with the period of stability reported in these mice. To explain this paradox, the authors postulated the existence of a specific oligomeric $A\beta$ species that would be detectable in *Tg2576* mice from 6 months of age and remain at a similar level throughout middle age.

Immunoblotting of extracellular-enriched protein extracts from 6-month-old mice revealed the presence of putative $A\beta$ monomers (4 kDa), trimers (14 kDa), hexamers (27 kDa), nonamers (40 kDa) and dodecamers (56 kDa). These oligomers were all resistant to denaturation by SDS/urea, a common

denaturant of globular proteins. However, increasing concentrations of hexafluoroisopropanol, a solvent that disrupts hydrogen bonds, led to their progressive dissociation into monomers, confirming that they are composed of multiples of the same peptide. The 56 kDa $A\beta$ assembly, which the authors termed $A\beta^*56$, first appeared at 6 months of age and remained at a similar level throughout middle age, indicating that levels of $A\beta^*56$ were inversely correlated with memory deficits in *Tg2576* mice.

To show a causative effect for $A\beta^*56$ in memory loss, the authors purified this assembly to homogeneity, and injected it into the lateral ventricles of young rats that were then subjected to tests of spatial learning and memory. Relative to controls, acquisition of spatial information was not impaired in rats injected with $A\beta^*56$, but

DEVELOPMENT

Synaptic development and branch dynamics

As potassium channels also regulate intracellular calcium concentrations, the authors suggest that longer duration of electrical activity spikes might increase calcium influx and lead to neuronal death. They argue that this latter phenotype is potentially worse than total loss of channel activity, which might explain the different severities and onset ages observed between the Filipino and French families.

There are several reports that link alterations in potassium channel expression with Huntington's disease, Parkinson's disease and Alzheimer's disease. The finding that mutations in the potassium channel gene *KCNC3* are responsible for SCA in two families suggests that, in addition to investigating protein misfolding and aggregation in the aetiology of neurodegenerative diseases, researchers might also benefit from considering the role of potassium channels.

Ruth Williams

ORIGINAL RESEARCH PAPER Waters, M. F. *et al.* Mutations in voltage-gated potassium channel *KCNC3* cause degenerative and developmental central nervous system phenotypes. *Nature Genet.* **38**, 447–451 (2006)

long-term spatial memory was. Tests performed 10 days later, with no further injection of A β *56, showed no difference between the groups, indicating that memory impairment is due to a transient physiological effect rather than permanent neuropathology.

These findings suggest that A β *56 might be the principal cause of memory deficits in *Tg2576* mice, independent of plaques and neuronal loss, prompting a search for its correlate in humans as a potential therapeutic target. It remains to be determined how A β *56 affects synaptic function, and what effects might be attributed to the various other higher-order A β assemblies.

Daniel McGowan

ORIGINAL RESEARCH PAPER Lesné, S. *et al.* A specific amyloid- β protein assembly in the brain impairs memory. *Nature* **440**, 352–357 (2006)

The development and refinement of topographic maps in the brain depends on dynamic changes in the precise arrangement of axonal branches. Two articles in *The Journal of Neuroscience* provide a window onto the growth of presynaptic axonal branches during the early development of living retinal ganglion cells. Both studies report that synaptogenesis and synaptic maturation make important contributions to the growth and stabilization of axonal branches.

In these two studies, the authors tracked over time the effects of synaptic development on axonal branch dynamics in retinal ganglion cells projecting from the retina to the optic tectum in the midbrain. They used two-photon time-lapse imaging of the GFP (green fluorescent protein)-labelled synaptic vesicle protein synaptophysin. This was co-expressed with cytosolic dsRED (discosoma red fluorescent protein) to mark arbor structure. They then quantified the levels of synaptophysin at individual synapses to provide a measure of the extent of maturation or disassembly of synapses over time, and related this to structural changes in axonal arbors.

In their study of retinal ganglion cells of albino *Xenopus laevis* tadpoles, Ruthazer and colleagues found that presynaptic sites that were intensely labelled with GFP-tagged synaptophysin had more presynaptic vesicles and were more stable. Synapses were the sites

of new branch additions, so that axon arbor development was clearly affected by synapse formation and stabilization. Ruthazer and colleagues were particularly interested in branch elimination and observed that strong synapses stabilized branches against retraction. Meyer and Smith confirmed this close association between the timecourse of synaptic development and the growth of axonal arbors in a study of retinal ganglion cells in living zebrafish larvae.

“... synaptogenesis and synaptic maturation make important contributions to the growth and stabilization of axonal branches.”

Through careful analysis of changes in levels of synaptophysin over time, and branch extension and lifetime, both sets of authors showed that the presence of stabilized synaptic contacts directly influenced the extent to which branches stabilized, rather than being a consequence of branch stabilization. These data suggest a model in which synaptogenesis and synaptic maturation influence the growth of axonal arbors by stimulating the formation and extension of new branches, and by selectively stabilizing them.

Ruthazer and colleagues also showed that visual stimulation enhanced the stability of arbors that contained more maturing synapses, whereas it induced retraction of newly formed, exploratory branch tips.

These two studies provide firm evidence for the participation of synaptic development in the shaping of topographic maps, and shed light on the mechanisms involved in this process.

Alison Rowan

A *Xenopus* retinal ganglion cell axon expressing dsRED and GFP-tagged synaptophysin imaged *in vivo*. Image courtesy of H. Cline, Cold Spring Harbor Laboratory, USA, and E. Ruthazer, Montreal Neurological Institute, Canada.

ORIGINAL RESEARCH PAPERS Ruthazer, E. S., Li, J. & Cline, H. T. Stabilization of axon branch dynamics by synaptic maturation. *J. Neurosci.* **26**, 3594–3603 (2006) | Meyer, M. P. & Smith, S. J. Evidence from *in vivo* imaging that synaptogenesis guides the growth and branching of axonal arbors by two distinct mechanisms. *J. Neurosci.* **26**, 3604–3614 (2006)

FURTHER READING Innocenti, G. M. & Price, D. J. Exuberance in the development of cortical circuits. *Nature Rev. Neurosci.* **6**, 995–965 (2005)

AXON GUIDANCE

The worm that turned

During nervous system development, new connections and networks are established by the growing neuronal axons and dendrites. In the case of the mechanosensory neurons of the nematode worm *Caenorhabditis elegans*, these neurite extensions advance along the anteroposterior body axis. However, two new papers report that, in worms with mutated WNT proteins, the anterior/posterior trajectories of these neurites can become completely reversed.

The WNT family of proteins are known to regulate various developmental processes, including asymmetrical cell division, cell fate determination and axon guidance. They are secreted proteins that act on target cells, over long distances, through interaction with their cell surface receptors. Both teams observed that in worms with mutations in one of these receptors (LIN-17), the polarity of the mechanosensory neuron PLM was often reversed such that the anterior process was short and unbranched, much like the posterior process of the wild type, and the posterior process was long and branched, like the anterior process of the wild type.

The inverted neuronal processes observed in LIN-17 mutants indicated that WNT proteins might be involved in mechanosensory neuron polarity in *C. elegans*. *C. elegans* has five WNT proteins: CWN-1, CWN-2, EGL-20, LIN-44 and MOM-2. The authors found that specific combinations of WNT mutations could indeed produce inverted PLM neurons, and also inverted ALM neurons (another class of mechanosensory neuron).

Interestingly, Prasad and Clark found that PLM and ALM neurons were also inverted in worms mutant for VPS-35, a component of the retromer complex that mediates endosome-to-Golgi trafficking. They went on to show that the VPS-35 mutation disrupted WNT signalling, and that the ALM and PLM polarity defect could be rescued in these mutants by specific expression of VPS-35 in WNT-expressing cells.

WNT signalling controls a large repertoire of developmental functions, including cell fate decisions and cell growth/migratory guidance. The WNT proteins are highly conserved from invertebrates to vertebrates, and it is therefore possible that WNT signalling could also influence neuronal polarity in mammalian development.

Ruth Williams

ORIGINAL RESEARCH PAPERS Hilliard, M. A. & Bargmann, C. I. Wnt signals and Frizzled activity orient anterior-posterior axon outgrowth in *C. elegans*. *Dev. Cell* **10**, 379–390 (2006) | Prasad, B. C. & Clark, S. G. Wnt signalling establishes anteroposterior neuronal polarity and requires retromer in *C. elegans*. *Development* **133**, 1757–1766 (2006)

PAIN

Cut the mustard

Mustard, garlic and chilli peppers all contain components that stimulate nociceptors, triggering pain, inflammation and hypersensitivity. These molecules target TRP receptors — a family of excitatory cation channels — and identifying the specific receptors for individual molecules could help to elucidate the mechanisms that underlie nociception and how pain is sensed. Writing in *Cell*, Bautista and colleagues report that TRPA1 is the sole receptor of the noxious components of mustard oil and garlic, and also link this receptor with inflammatory responses to environmental toxins.

Until now, it was not known whether TRPA1 was the exclusive target of the irritants allyl isothiocyanate and allicin — the noxious components of mustard oil and garlic, respectively. Using live-cell calcium imaging, the authors showed that only cultured

trigeminal neurons from TRPA1-deficient mice were insensitive to either of the agents. Interestingly, deletion of this sensory gene also led to behavioural changes in the mice. Application of mustard oil to the paws would be expected to elicit flinching and paw licking. However, TRPA1-deficient mice showed neither of these responses. Furthermore, the mustard-oil-treated paws of the mutant mice were less swollen and sensitive to pain than those of wild-type mice.

Activation of sensory nerve endings in the lungs by irritants triggers neurogenic inflammation, which can aggravate conditions such as asthma. Structural similarities between one such agent — acrolein — and the potent ingredients in mustard oil and garlic prompted the authors to investigate whether this compound would also activate TRPA1. Indeed, only cells expressing TRPA1 showed

VISION

Under the spotlight

The third, or parietal, eye of lizards and other lower vertebrates mediates the detection of dawn and dusk instead of conventional image-forming vision. The parietal eye photoreceptors resemble their lateral eye counterparts (rods and cones) in morphology, but could produce a hyperpolarizing light response most sensitive to blue light, as well as an unusual depolarizing light response most sensitive to green light — a curious phenomenon known

as chromatic antagonism. Writing in *Science*, Chih-Ying Su and colleagues reveal the molecular machinery that underlies these pathways of light detection in the parietal eye.

By screening a parietal eye cDNA library from the side-blotched lizard, the researchers identified pinopsin, the blue-sensitive pigment in rods and cones that is known to drive the hyperpolarizing response, as well as a new pigment, which they named

A side-blotched lizard, which has a third, or parietal, eye containing the unusual photoreceptors. Image courtesy of J. Finn and K.-W. Yau, Johns Hopkins University, Maryland, USA.

a strong response to acrolein. As acrolein is also a toxic by-product of the metabolism of some chemotherapeutic drugs, these findings have therapeutic implications for the treatment of disorders such as asthma and cancer.

TRPA1 is also thought to mediate other sensory processes. It has been implicated in the perception of extreme cold and sound, and the depolarization of nociceptors in response to proalgesic agents such as bradykinin, which stimulates pain-sensing neurons, leading to hypersensitivity to heat or touch.

Mice lacking TRPA1 had normal hearing functions and sensitivity to cold, suggesting that TRPA1 is not involved in the initial detection of these conditions.

By contrast, administration of bradykinin evoked a considerably lower response in TRPA1-deficient mice, suggesting a role for TRPA1 in nociceptor excitation.

The identification of TRPA1 as the sole receptor responsible for the response to irritants in mustard oil and garlic not only provides insights into the mechanisms that underlie pain sensation, but also has therapeutic implications. Blocking TRPA1 activity has the potential to prolong cancer therapy and alleviate the symptoms of pulmonary diseases, such as asthma.

Samantha Barton

ORIGINAL RESEARCH PAPER Bautista, D. M. *et al.* TRPA1 mediates the inflammatory actions of environmental irritants and proalgesic agents. *Cell* **124**, 1269–1282 (2006)

parietopsin. Double immunostaining showed that pinopsin and parietopsin co-localized in the same photoreceptor outer segment, where phototransduction takes place.

The hyperpolarizing response of rods and cones in lateral eyes is mediated by the G protein transducin- α . Interestingly, Su *et al.* found that photoreceptors in the parietal eye do not contain transducin- α , but express its close relative gustducin- α — the G protein that mediates bitter and sweet transduction in taste buds — as well as $G\alpha_o$, the α -subunit of G_o . Co-localization studies showed that gustducin- α and $G\alpha_o$ are also expressed in the same photoreceptor outer segment.

The researchers next examined the signalling pathways of light detection in the parietal eye using single-cell recordings. Similar to transducin- α , gustducin- α activates a cyclic GMP (cGMP) phosphodiesterase and

closes cGMP-gated cation channels in response to a flash of green light, thereby hyperpolarizing the membrane. By contrast, $G\alpha_o$ inhibits the phosphodiesterase and opens the same ion channels in response to a flash of blue light, thereby depolarizing the membrane.

The pinopsin–gustducin- α pair is similar to the signalling components in vertebrate rods and cones, whereas the parietopsin– $G\alpha_o$ coupling resembles that in some invertebrate photoreceptors. Therefore, the researchers suggest that the third eye is more primitive, and that image-forming lateral eyes might have evolved from their parietal ancestor but inherited only one G-protein pathway.

Jane Qiu

ORIGINAL RESEARCH PAPER Su, C.-Y. *et al.* Parietal-eye phototransduction components and their potential evolutionary implications. *Science* **311**, 1617–1621 (2006)

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IN BRIEF

DEVELOPMENT

UNC-6/Netrin induces neuronal asymmetry and defines the site of axon formation.

Adler, C. E. *et al.* *Nature Neurosci.* **9**, 511–518 (2006)

A defining characteristic of neurons is the ability to form long neurites, but the mechanisms leading to neuronal asymmetry and process elongation are poorly understood. Evidence that guidance information might direct the earliest stages of asymmetric neuronal growth comes from observations that neurons usually extend their first stable process in the exact direction that will be taken by the eventual axon. Adler and colleagues show that netrin (UNC-6) and its receptor UNC-40, which are known for their role in growth cone guidance, are also active at early developmental stages to generate, maintain and orient asymmetry in *Caenorhabditis elegans* HSN neurons. As the axon forms, UNC-40 and another protein, MIG-10, become localized to the ventral side of HSN neurons, where they mark the leading edge of the growing neuron that defines the site of axon formation.

NEUROTECHNIQUES

Nano neuro knitting: peptide nanofiber scaffold for brain repair and axon regeneration with functional return of vision.

Ellis-Behnke, R. G. *et al.* *Proc. Natl Acad. Sci. USA* **103**, 5054–5059 (2006)

Ellis-Behnke and co-workers have combined nanotechnology and biomedicine to stimulate axonal regeneration following injury in the mammalian visual system. The authors report that a self-assembling peptide nanofiber scaffold (SAPNS) permitted regenerated axons to reconnect to target tissues with sufficient density for functional return of vision in hamsters with severed optic tracts. Because SAPNSs can be broken down into component L-amino acids, are synthetic and free of contaminants, and are immunologically inert, they represent a viable technology for tissue repair and treatment of CNS trauma.

AGEING

Early and simultaneous emergence of multiple hippocampal biomarkers of aging is mediated by Ca^{2+} -induced Ca^{2+} release.

Gant, J. C. *et al.* *J. Neurosci.* **26**, 3482–3490 (2006)

Numerous Ca^{2+} -related electrophysiological processes in the hippocampus are dysregulated with age. These include processes involved in the Ca^{2+} -dependent slow afterhyperpolarization, spike accommodation, Ca^{2+} action potential and whole-cell Ca^{2+} currents. L-type voltage-gated Ca^{2+} channel activity is also increased with age. These findings suggest a possible common mechanism of Ca^{2+} dysregulation in age-related cognitive impairment. Now Gant *et al.* provide evidence that changes in Ca^{2+} -induced Ca^{2+} release from ryanodine receptors on the endoplasmic reticulum underpin Ca^{2+} dysregulation in hippocampal neurons during ageing.