

# Axons find their way in the snow

Yimin Zou

In February 2009, Keystone, Colorado, hosted the third Symposium on 'Axonal Connections: Molecular Cues for Development and Regeneration', organized by Marie Filbin, John Flanagan and Liqun Luo. Researchers from diverse backgrounds spent the week discussing the latest findings in axon guidance, synapse formation, dendrite development and axon regeneration. The meeting was held jointly with another Keystone Symposium on 'Neurodegenerative Diseases: New Molecular Mechanisms', and the two meetings profited from the lively discussions fuelled with questions from both fields in the joint sessions, which featured topics of common interest, such as axon degeneration, regeneration and neural stem cells.

## Introduction

The third Keystone Symposium on axon guidance and regeneration, which took place in Keystone, CO, USA, this February, featured exciting advances in the understanding of the function of molecular cues in the formation of axonal connections and of the mechanisms that underlie the failure of regeneration, as well as efforts to promote regeneration in the central nervous system (CNS). As axon degeneration is an important component of neurodegeneration and is also receiving increasing attention in the studies of neurodegenerative diseases, the meeting was held concurrently with the Keystone Symposium on neurodegenerative diseases, organized by Valina Dawson and David Holtzman. Many groundbreaking discoveries were presented during these two meetings. This review provides a brief discussion of the most prominent themes in the axonal connections meeting and the joint sessions, ranging from the mechanisms and functions of guidance cues to RNA-based mechanisms, target selection, synapse formation, axon degeneration and regeneration, and advances in stem cell research.

## Secreted axon guidance cues

Secreted axon guidance cues are of great importance for the wiring of the nervous system, and new insights into the mechanisms that underlie the actions of some of these cues – morphogens and neurotrophins – were presented at the meeting.

Morphogens are secreted signaling proteins and form concentration gradients that specify cell fate and axonal connections (for a review, see Zou and Lyuksyutova, 2007). Yimin Zou [University of California (UC), San Diego, La Jolla, CA, USA] reported that Wnt family proteins control the guidance of a number of axons along the anterior-posterior axis of the CNS and that this Wnt-dependent guidance event requires two signaling pathways – Wnt/planar cell polarity and atypical protein kinase C (aPKC)-dependent signaling (Lyuksyutova et al., 2003; Wolf et al., 2008). The components of these two signaling pathways, which are

essential for early cellular polarity in epithelia, appear to persist in growth cones, thus potentially allowing navigating growth cones to respond to directional or polarity cues in the CNS.

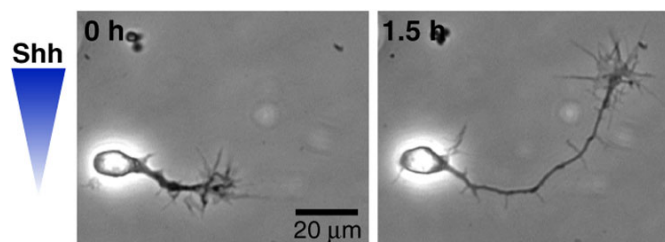
Sonic hedgehog (Shh) attracts commissural axons to the floor plate before they cross the midline (Charron et al., 2003; Okada et al., 2006). Frédéric Charron [Montreal Clinical Research Institute (IRCM), Montreal, Canada] described a modified Dunn's chamber assay that his laboratory has employed to elucidate how Shh signals direct axon guidance (Fig. 1). Using this assay, they showed that Src family kinases are required for Shh-mediated axon attraction. Gary Bassell (Emory University, Atlanta, GA, USA) showed that Src-signaling-dependent axon turning (Leung et al., 2006; Yao et al., 2006) depends on the transport of  $\beta$ -actin mRNA to the growth cone and on local translation. This supports the idea that in addition to regulating the expression of key components of the axon guidance system, local protein translation might participate in determining the direction of axon growth.

Neurotrophins, which regulate the growth, differentiation and survival of nerve cells, also play roles in the formation of axonal connections. David Ginty (Johns Hopkins Medical Institute, Baltimore, MD, USA) presented insights into the role of neurotrophins and their mechanisms of action in the wiring of somatosensory fibers. He showed that nerve growth factor (NGF) regulates the expression of the receptor for glial cell line derived neurotrophic factor (GDNF), RET, and its co-receptors GFR $\alpha$ 1 and GFR $\alpha$ 2, and that its expression in turn depends on GFR/RET signaling (Luo et al., 2007). NGF also regulates the expression of other genes that are RET independent. RET is required for the C-fiber innervation of all epidermal targets; however, RET is only required for the central, but not the peripheral, projections of other dorsal root ganglion neuron populations.

GDNF and membrane-bound ligands of the ephrin A family have previously been shown to cooperate in regulating hindlimb motor axon guidance, particularly in the early dorsal-ventral patterning of motor axons (Kramer et al., 2006). Rüdiger Klein (Max Planck Institute of Neurobiology, Martinsried, Germany) and co-workers have examined the behavior of limb-innervating motor axons co-cultured with cells that ectopically express ephrin A5 and report that GDNF partially suppresses ephrin A5-induced growth cone collapse, which indicates that, at least in some cases, repulsive guidance also needs a growth-stimulating component, which in this case is mediated by GDNF/RET signaling.

## Cell adhesion molecules

Several talks discussed the function of cell adhesion molecules and their signaling pathways in axonal guidance. One such molecule is the Down syndrome cell adhesion molecule (Dscam) protein, a member of the immunoglobulin (Ig) superfamily of proteins. The fly *Dscam* gene is highly complex; through alternative splicing, up to 19,008 different isoforms can be formed. Dscam isoform specificity is involved in a number of axonal wiring processes, and genetic evidence suggests that the molecular diversity of Dscam is functionally required for the wiring specificity of afferent somatosensory projections in the CNS (Chen et al., 2006). Using a BAC-based transgenesis platform developed by Hugo Bellen's laboratory (Baylor Medical School, Houston, TX, USA), Dietmar Schmucker and co-workers (Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA) systematically manipulated the *Dscam* gene and altered the number of alternatively spliced exons.



**Fig. 1. Axon turning in a sonic hedgehog gradient.** A commissural neuron isolated from an E13 rat embryo is exposed to a gradient of sonic hedgehog (Shh) (represented to the left of the figure, with the highest concentration of Shh at the top) in a Dunn chamber. One and a half hours after application of the gradient, the axon of the commissural neuron has turned towards the higher Shh concentrations. Image courtesy of Patricia T. Yam and Frédéric Charron.

They report that reducing the maximal number of isoforms from 19,008 to just 396 in all neurons causes severe connectivity defects. When examining single mechanosensory neurons, they observed an almost complete absence of secondary and higher order branches, which indicates a robust repulsion among branches and fibers within the CNS. Remarkably, clear axonal connectivity defects are also observed when the isoform diversity is only reduced cell-autonomously in isolated sensory neurons. It is clear that a few hundred isoforms of Dscam are not enough to sufficiently ‘diversify’ fly neurons (Yao et al., 2006).

Cell adhesion molecules can also serve as receptors for secreted axon guidance cues. Yi Rao (Peking University, Beijing, China) reported collaborative work with Jane Wu (Northwestern University, Chicago, IL, USA) on the signaling mechanisms of Dscam as a new Netrin receptor (Ly et al., 2008; Andrews et al., 2008; Liu et al., 2009). He reported that this pathway involves the phosphorylation of the Src family kinase Fyn, the focal adhesion kinase (FAK) and of the adapter protein P130<sup>CAS</sup>, leading to the activation of the small GTPases Rac and Cdc42 and to actin polymerization. He also discussed the function of Robos, another group of Ig superfamily proteins, which are known receptors for the secreted axon guidance cue Slit. Interestingly, Slit increases the surface presentation of its own receptor, Robo1. This process is mediated by ubiquitylation by Usp33. Therefore, Slit appears to positively regulate its own signaling, a process that might be involved in regulating the Slit response during midline crossing.

### Establishing topographic maps

A common feature of axonal connections are topographic projections, in which two parts of the nervous system are linked in such a way that the spatial and positional information is continuously preserved from the donor to the recipient areas. Several talks discussed the mechanisms by which the topographic organization of axonal connections can be achieved. An elegant study from Hitoshi Sakano’s group (University of Tokyo, Tokyo, Japan) showed that axons of olfactory sensory neurons self-sort along the anterior-posterior axis of the CNS as they travel in the axon bundle on the way to the olfactory bulb (Fig. 2). This axon-axon self-sorting is thought to be mediated by repulsive interactions of neuropilin 1 (Nrp1) and semaphorin 3A (Sema3A). Similar axon sorting is also important to maintain a topographic order along the dorsal-ventral axis, which is mediated by Nrp2 and Sema3F. Eric Williams (Cornell University, New York, NY, USA), by contrast, explored the importance of the target region in the

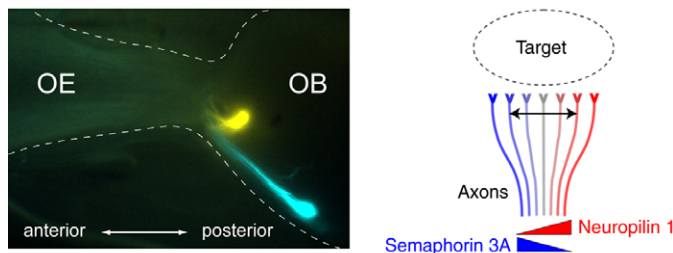
olfactory bulb. Using laser microdissection and microarrays, he found that protocadherins (Pcdhs) display subtle expression gradients in parts of the olfactory bulb, and that misexpressing Pcdh10 caused targeting defects in the olfactory glomeruli, the convergence points for olfactory axons that express the same odorant receptors. In addition, published work also suggests that a Slit1 gradient in the olfactory bulb plays a role in dorsal-ventral zonal segregation of olfactory axons (Cho et al., 2007). Both these studies highlight the role of the target zone in the topographical migration of olfactory axons. Studying topographic connections in the visual system, Uwe Drescher (King’s College London, London, UK) investigated the control of axon branching in the optic tectum, which is important for the formation of visual maps. His data support the idea that a balance between ephrin A reverse signaling and EphA forward signaling results in topographic branching. Here, axonal ephrin As exert their function by controlling the branch-promoting activity of the neurotrophin receptor TrkB (Ntrk2) (Marler et al., 2008).

### Making connections: synapse formation and dendrite morphogenesis

Understanding how neural activity and experience shape the development of the nervous system and, later, modify its mature circuits is essential for understanding the overall development and function of the nervous system. Michael Greenberg and colleagues (Harvard Medical School, Boston, MA, USA) have identified a new function for activity- and experience-dependent transcription in regulating the formation or maintenance of inhibitory synapses on excitatory neurons. A mutation in the binding site in the brain derived neurotrophic factor (*Bdnf*) promoter IV for the transcription factor cAMP response element binding protein (CREB), or the functional disruption of the transcription factor NPAS4 by RNAi or a conditional knockout strategy, results in fewer inhibitory synapses. CREB is a key activity-dependent regulator of transcription. Therefore, activity- or experience-dependent transcription controls the homeostatic balance between synaptic excitation and inhibition, which might be altered in several mental disorders (Hong et al., 2008; Lin et al., 2008).

Axons contain the presynaptic components of neuronal connections. To complete neuronal circuits, axons need to find the correct postsynaptic cells, and sometimes the specific postsynaptic subcellular regions, to make synapses. The morphology of dendrites, which host the postsynaptic parts of neuronal connections, is therefore intimately related to axonal connections.

Interestingly, some axon guidance cues also regulate synapse formation, although the mechanisms involved are still being investigated. Alex Kolodkin and David Ginty (Johns Hopkins University, Baltimore, MD, USA) have shown previously that the axon guidance cue Sema3F, a semaphorin receptor, modulates synapse transmission (Sahay et al., 2005). At the meeting, Kolodkin presented recent findings that in *Sema3F* and *Nrp2* (another semaphorin receptor) knockout mice, many dendritic spines are enlarged, when compared with wild-type controls, and have multiple postsynaptic densities, which are sites of active synapses. He further reported that another semaphorin receptor, plexin A3 (but not plexin A4) is involved in regulating spine morphology. By contrast, Sema3A/Nrp1 mediates basal dendrite morphology, but not spine morphology. Therefore, secreted semaphorin proteins have profound roles in neural circuit development, and members of this family serve distinct and contrasting functions in the regulation of dendrite morphology, which might be mediated by distinct receptor molecules.



**Fig. 2. Axon self-sorting in olfactory sensory neurons.** (Left) Dorsal view of an axonal projection from the olfactory epithelium (OE) to the olfactory bulb (OB) of a transgenic mouse (left). Axons projecting to the anterior OB [yellow, ORI7-dnPKA-YFP (Imai et al., 2006)] and those projecting to the posterior OB (cyan, ORI7-CFP) are presorted in the axon bundle. (Right) The pre-target axon-axon interactions, mediated by axonal semaphorin 3A (blue) and neuropilin 1 (red), are important to establish the anterior-posterior topography of the olfactory map. OR, odorant receptor; dnPKA, dominant-negative protein kinase A. Image courtesy of Takeshi Imai and Hitoshi Sakano.

In terms of synapse formation, Wnts and Netrin are known to be inhibitory factors of synaptogenesis in *C. elegans* (Klassen and Shen, 2007; Poon et al., 2008). Their anterior-posterior and dorsal-ventral expression gradients in the worm body are thought to help pattern the spatial distribution of the excitatory synapses of dopaminergic motoneurons on muscles. Kang Shen and colleagues (Stanford University, Palo Alto, CA, USA) reported a new mechanism involving cyclin-dependent kinase as well as a parallel Ckd5/p35 pathway that mediates the inhibition of synapse formation by both Wnts and Netrin.

Looking into dendrite development, Liqun Luo (Stanford University, Palo Alto, CA, USA) showed that a N-methyl-D-aspartate receptor (NMDR), NR2B, is involved in dendritic morphogenesis. Using mosaic analysis with double markers (MADM), the Luo laboratory created single-cell knockouts of the *Nr2b* (*Grin2b*) gene. *Nr2b* knockout caused an increase in the number of primary apical dendrites in dentate gyrus granule cells and in the barrel cortex, which indicates that NR2B is normally required for dendritic pruning. Therefore, it appears that molecules involved in synaptic function or related to those that function in synapses have additional functions in the development of neuronal connections.

### Mechanisms of neuronal and axonal degeneration

Although a number of genes that are involved in neurodegenerative disorders have been identified, it remains unclear how mutations in these genes lead to neurodegeneration. Huda Zoghbi (Baylor College of Medicine, Houston, TX, USA) illustrated the newest findings in the understanding of the complex pathogenetic mechanisms leading to spinocerebellar ataxia type I (SCA1), a neurodegenerative disease linked to the expansion of a polyglutamine repeat in the protein ataxin 1 (Atxn1). She reported that a specific serine residue outside of the Atxn1 polyglutamine tract is crucial to SCA1 pathogenesis, and that polyglutamine expansion alters protein-protein interactions by enhancing the normally limited interactions between Atxn1 and certain proteins that are mediated by this serine, at the cost of the normal interactions with other proteins. These findings underscore the importance of proper protein conformation and of the normal balance of protein-protein interactions in the health of neurons (Zoghbi and Orr, 2009).

In both normal development and pathological conditions, axons are often destroyed. An emerging theme is that there appears to be an active axon destruction program that causes axon degeneration in development and disease. P75 (NGFR) is known to be a major mediator of axon degeneration. Freda Miller (University of Toronto, Toronto, Canada) showed that BDNF acts via P75 to mediate sympathetic axon degeneration by dampening the axon survival pathway through the Ras/MAPK cascade. Marc Tessier-Lavigne and co-workers (Genentech, South San Francisco, CA, USA) found that a member of the tumor necrosis factor (TNF) receptor family, death receptor 6 (DR6; TNFRSF21), mediates a developmental axon degeneration pathway that is important for normal axon pruning. Blocking DR6 function causes a delay of axon pruning in vitro and in vivo. They also found that axon degeneration requires caspase 6 rather than caspase 3, which is involved in cell body death, and that N-terminal amyloid precursor protein (APP) (1-286) is a regulated ligand for DR6. This developmental pathway, which is involved in forming normal axonal connections, could be 'hijacked' during the pathogenesis of Alzheimer's disease (Nikolaev et al., 2009).

Soluble oligomers of amyloid- $\beta$  are thought to be the pathogenetic agents in Alzheimer's disease, but their receptor has not been found. Using expression cloning, Stephen Strittmatter and colleagues (Yale University, New Haven, CT, USA) found that the cellular prion protein is a receptor for soluble amyloid- $\beta$  oligomers and mediates amyloid- $\beta$ -induced synaptic dysfunction (Lauren et al., 2009). Interestingly, Nogo receptor (NgR; RTN4R) has been shown previously to bind APP and to regulate amyloid- $\beta$  plaque deposition (Park et al., 2006a), and subcutaneous injection of NgR ectodomain removes brain amyloid- $\beta$  and improves spatial memory in transgenic mouse models of Alzheimer's disease (Park et al., 2006b). It will be interesting to test whether this APP-NgR interaction has additional functions than plaque deposition, such as causing axon degeneration.

The intracellular mechanisms of axon degeneration are poorly understood. The Wallerian degeneration slow (Wlds) mouse strain, which displays greatly decelerated degeneration of the distal segment of severed axons (known as Wallerian degeneration), provides an opportunity for understanding this process. Taking advantage of *Drosophila* genetics, Marc Freeman (University of Massachusetts, Worcester, MA, USA) studied the mechanisms by which the Wlds protein, a chimeric protein comprising a short fragment of the ubiquitin assembly protein UFD2 (UBE4B) and the full-length nicotinamide adenine dinucleotide (NAD) synthetic enzyme nicotinamide mononucleotide adenylyltransferase 1 (Nmnat1), prevents Wallerian degeneration. They reported that the NAD biosynthetic activity of Nmnat1 and a 16 amino acid region in the N-terminus of Wlds are required for sparing the severed axons from degeneration (Avery et al., 2009).

These findings demonstrate the progress that is being made in understanding the molecular mechanisms that underlie degeneration and disease, which brings with it hope for potential future therapeutic intervention.

### Axon regeneration

Damage to CNS axons causes permanent loss of function, partly because CNS axons fail to regenerate. Myelin and the glial scar that forms after nerve damage are thought to be the main sources of cues inhibitory to CNS axon regeneration. After spinal cord injury, axons also die back, which adds another obstacle to regeneration. Jerry Silver (Case Western Reserve University, Cleveland, OH, USA) showed that ED1-positive macrophages, which are found

abundantly in the lesion sites after spinal cord injury, attack the adult sensory axons in culture, which might be the underlying mechanism of axon retraction. In addition, the lesioned tissue appears to produce a 'trophic oasis', which leads to regenerating axons stalling in, rather than exiting, the lesion site.

Lack of growth potential is another reason why CNS axons cannot regenerate. Using optic nerve regeneration as a model system, Zhigang He (Harvard Medical School, Boston, MA, USA) showed that intrinsic growth potential could be enhanced by regulating the balance of PI3 kinase/PTEN signaling and that the inhibition of PTEN caused dramatic regenerative growth. This enhanced regeneration is in part caused by reactivating the mTOR growth pathway in retinal ganglion cells (Park et al., 2008). He presented his latest work, which shows that corticospinal tract regeneration is also improved by reactivating the mTOR pathway, but that this improvement is less effective than that seen in the optic nerve. This finding highlights once again that the spinal cord is a particularly tough environment for inducing regeneration.

Model organisms provide unique advantages in understanding the genetic control of axon regeneration. Using the combined power of *C. elegans* genetics and imaging, Andrew Chisholm (UC San Diego, La Jolla, CA, USA) showed that CCAAT/enhancer binding protein (C/EBP) is required for axon regrowth in *C. elegans* and that it might be locally translated in response to injury. As a model system, the zebrafish is particularly well suited for detailed, long-term imaging, and Alvaro Sagasti and colleagues (UC Los Angeles, Los Angeles, CA, USA) showed using live imaging that after a certain developmental stage, regenerating peripheral nerve endings are repelled by their former territories. Further experiments suggest that the NgR pathway is involved in this inhibition.

How do vertebrate CNS axons respond to injury? Wenbiao Gan (Skirball Institute, New York, NY, USA) used two-photon microscopy to introduce small lesions into the mouse cortex and spinal cord and watched how the damaged axons and dendrites failed to regenerate. He noticed that microglial processes responded rapidly to the lesion. In the spinal cord dorsal column, axon die-back and degeneration were observed within two hours. Dying back stops at branch points of the injured axons. These findings visually demonstrate that neuronal processes fail to regenerate after injury in the mature CNS. Furthermore, Gan reported that increased spine plasticity correlates with microglial activation after the brain injury that is associated with craniotomy as well as in mouse models of multiple sclerosis with experimental autoimmune encephalomyelitis (EAE), suggesting that neuroinflammation might promote neuronal plasticity and even facilitate regeneration.

### Adult neurogenesis

In two separate regions – the dentate gyrus of the hippocampus and the anterior subventricular zone – new neurons continue to be born in the mature mammalian brain. These adult stem cells probably contribute markedly to the plasticity of the nervous system in these areas. Using retrovirus-mediated overexpression of the bHLH transcription factor *Ascl1* in the dentate gyrus, Fred Gage (Salk Institute, La Jolla, CA) showed that stem cell fate is highly reprogrammable (Jessberger et al., 2008). Adult-born neurons do form functional synapses (Toni et al., 2008), and the initial contacts were preferably made with pre-existing boutons. In addition, the connectivity of new neurons continues to change for at least two months (Toni et al., 2007). He also discussed the possible functional role that adult neurogenesis might play in memory formation (Aimone et al., 2009).

Fiona Doetsch (Columbia University, New York, NY, USA) showed that the microRNA miR-124 regulates the temporal progression of adult neurogenesis in the subventricular zone. *Sox9* is a target of miR-124 during the transition from the transit-amplifying cell to the neuroblast stage (Cheng et al., 2009).

Hongjun Song (Johns Hopkins Medical Institute, Baltimore, MD, USA) showed that the DNA repair protein Gadd45b is induced by the synchronized activation of mature dentate neurons by electroconvulsive treatment (ECT), which enhances adult neurogenesis. Given that Gadd45b promotes DNA demethylation of the regulatory regions of the *Bdnf* and *Fgfl* genes and is required for activity-dependent neurogenesis, neural activity might regulate neurogenesis by epigenetic mechanisms such as DNA demethylation (Ma et al., 2009).

Understanding the mechanisms of adult neurogenesis and of the integration of adult-born neurons into neural circuits will be invaluable to evaluate the significance of adult neurogenesis and its connection with nervous system disorders.

### Conclusions

More and more evidence suggests that intimate connections exist between axon development and axon plasticity. Common signaling pathways that regulate axon structure are frequently found to be important in both developing and mature axons. The mechanistic links are just beginning to be elucidated, but the synergistic interaction of these research areas promises to drive the discovery and development of therapies for nervous system diseases, especially neurodegenerative disorders, at an accelerating rate. Adult neurogenesis and the incorporation of new adult-born neurons into functional circuits provide fascinating new insights into the structure and the function of the nervous system. Comparing the mechanisms of axonal guidance in adult-born and embryonic neurons will prove insightful for understanding neural circuit development at both stages. This meeting was a nice snapshot of the exciting research in both developmental neuroscience and nervous system disease.

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