NEUROSCIENCE

Brain Wiring by Presorting Axons

Specific molecular interactions among axons of mammalian olfactory neurons ensure their orderly arrival along the path from the nose to the brain.

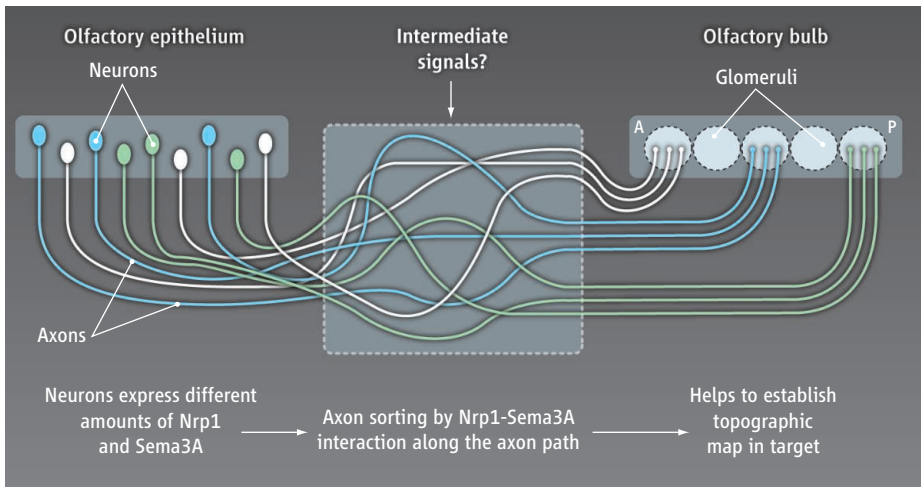
Kazunari Miyamichi and Liqun Luo

Neurobiologist and Nobel Laureate R. W. Sperry proposed an influential chemoaffinity theory half a century ago (*1*) to explain the precision of neuronal wiring in the brain: "The cells and fibers of the brain must carry some kind of individual identification tags, presumably cytochemical in nature, by which they are distinguished one from another almost, in many regions, to the level of the single neurons" (*1*). He suggested that gradients of such identification tags on retinal neurons and on the target cells in the brain coordinately guide the orderly projection of millions of developing retinal axons. This idea was supported by the identification and genetic analysis of axon guidance molecules, including those that direct development of the vertebrate visual system (*2*). But axons not only perceive molecular cues on their targets; they also recognize those on fellow axons. On page 585 of this issue, Imai *et al*. provide a striking example of how axon-axon interactions organize olfactory axons before they reach their target in the brain (*3*).

In the mammalian olfactory system, each olfactory sensory neuron expresses a single type of odorant receptor. Those expressing the same odorant receptor are distributed widely in the nose but converge their axons onto a stereotypical location called the glomerulus in the olfactory bulb of the brain. This wiring results in a discrete map for odor processing (*4*), but how do 1000 different classes of olfactory sensory neurons converge their axons so precisely in the brain? Although odorant receptors may act as "identification tags" during axon targeting (*5*), many classic axon guidance molecules are involved in this process.

Olfactory sensory neurons are distributed in a convoluted two-dimensional nasal epithelium that can be viewed along two axes, anterior-posterior and dorsomedial-ventrolateral. Mapping along the dorsomedial-ventrolateral axis appears similar to that in the visual system (*2*): Odorant receptors are expressed in overlapping bands along this axis that correlate with the positions of target glomeruli along the dorsal-ventral axis of the olfactory bulb (*6*). Classical axon guidance molecules, such as Neuropilin-2, Slit-1, and Robo-2, have been implicated in establishing the coarse topography along this axis (*7*, *8*). By contrast, neurons expressing the same odorant receptor distribute randomly across the entire anterior-posterior axis. An important advance was made a few years ago (*9*). It was shown that odorant receptors define differential levels of cyclic adenosine monophosphate (cAMP) signaling, which results in differential gene expression. One such target is the gene encoding Neuropilin-1 (Nrp1), a receptor for the axon guidance molecule Semaphorin-3A (Sema3A) (*10*). Imai *et al*. reinforce this model by showing that genetic alteration of *Nrp1* expression in mouse olfactory sensory neurons indeed causes a corresponding shift of target sites along the anterior-posterior axis of the olfactory bulb.

Strikingly, Imai *et al*. found that axons that project to different regions of the olfactory bulb segregate before reaching their final target. Genetic experiments revealed that this pre-target sorting is mediated by Nrp1 and Sema3A. Interestingly, cAMP signaling regulates *Nrp1* and *Sema3A* expression in opposite directions: Higher cAMP signaling up-regulates *Nrp1* and down-regulates *Sema3A*. Thus, each olfactory sensory neuron class expresses complementary amounts of Nrp1 and Sema3A according to the level of cAMP signaling. This reflects the odorant receptor it expresses, regardless of the neuron's cell body position along the anterior-posterior axis of the nasal epithelium. As axons travel toward the olfactory bulb, repulsive interactions between Sema3A and Nrp1 gradually sort them according to the amounts of this ligand-receptor pair, and hence according to the odorant receptors they express (see the figure). Indeed, the absence of Sema3A from only olfactory sensory neurons affected not only pre-target axon sorting but also the final projection sites in the olfactory bulb.



Wiring through sorting. Olfactory sensory neurons with different expression levels of Nrp1 and Sema3A are intermingled in the olfactory epithelium of the mouse nose. Repulsive axon-axon interaction by this ligand-receptor pair gradually sorts axons within the bundle before they reach their olfactory bulb target in the brain. Intermediate cues may orient the order of axons within the bundle. A, anterior; P, posterior.

Axon-axon interactions alone cannot provide the stereotyped polarity of axon order within the bundle projecting to the olfactory bulb. Imai *et al*. suggest that *Sema3A* expression in glia cells that surround the axon bundle is biased, which could orient the order of axons within the bundle to their environment. This hypothesis will be validated if the absence of *Sema3A* in these intermediate regions randomizes the polarity of axon order within the bundle.

The contribution of semaphorins to axon-axon interactions was first described in the fly olfactory system (*11*, *12*). In that model organism, pre-target axon sorting was not examined, but axon-axon interactions were shown to occur at the target (*11*). Two different olfactory sensory neuron populations project their axons with a temporal difference to the fly antennal lobe (corresponding to the mouse olfactory bulb). Sema1A that is expressed by early-arriving axons to the antenna constrains the target choice of late-arriving axons

Howard Hughes Medical Institute, Department of Biology, Stanford University, Stanford, CA 94305, USA. E-mail: lluo@stanford.edu

CREDIT: C. BICKEL/*SCIENCE*

Downloaded from www.sciencemag.org on July 30, 2009

Published by AAAS

from the maxillary palp, likely through repulsive interaction with Plexin-A, a receptor for Sema1A (*11*). Thus, the same family of axon guidance molecules plays a role in axon-axon interactions in the fly and mouse olfactory systems, implying an evolutionally convergent strategy for olfactory circuit formation.

After the coarse olfactory map in the mouse is established by the processes described above, axon-axon interactions among those that target neighboring glomeruli further refine the map through attractive and repulsive interactions (*13*, *14*). Thus, wiring specificity of complex neural circuits is achieved through stepwise mechanisms, involving axon sorting along the path (*3*, *15*), at the targets (*11*, *13*), and pre- and postsynaptic recognitions. As well, the individual identification tags originally proposed by Sperry for pre- and postsynaptic matching can serve at multiple steps to ensure the precise wiring of the brain.

References and Notes

1. R. W. Sperry, *Proc. Natl. Acad. Sci. U.S.A.* **50**, 703 (1963).
2. L. Luo, J. G. Flanagan, *Neuron* **56**, 284 (2007).
3. T. Imai *et al.*, *Science* **325**, 585 (2009); published online 9 July 2009 (10.1126/science.1173596).
4. R. Axel, *Sci. Am.* **273**, 154 (October 1995).
5. G. Barnea *et al.*, *Science* **304**, 1468 (2004).
6. K. Miyamichi, S. Serizawa, H. M. Kimura, H. Sakano, *J. Neurosci.* **25**, 3586 (2005).
7. E. M. Norlin *et al.*, *Mol. Cell. Neurosci.* **18**, 283 (2001).
8. J. H. Cho, M. Lepine, W. Andrews, J. Parnavelas, J. F. Cloutier, *J. Neurosci.* **27**, 9094 (2007).
9. T. Imai, M. Suzuki, H. Sakano, *Science* **314**, 657 (2006); published online 21 September 2006 (10.1126/science.1131794).
10. T. S. Tran, A. L. Kolodkin, R. Bharadwaj, *Annu. Rev. Cell Dev. Biol.* **23**, 263 (2007).
11. L. B. Sweeney *et al.*, *Neuron* **53**, 185 (2007).
12. M. Lattemann *et al.*, *Neuron* **53**, 169 (2007).
13. S. Serizawa *et al.*, *Cell* **127**, 1057 (2006).
14. T. Kaneko-Goto, S. Yoshihara, H. Miyazaki, Y. Yoshihara, *Neuron* **57**, 834 (2008).
15. T. Bozza *et al.*, *Neuron* **61**, 220 (2009).

16. We thank L. Sweeney for helpful comments.

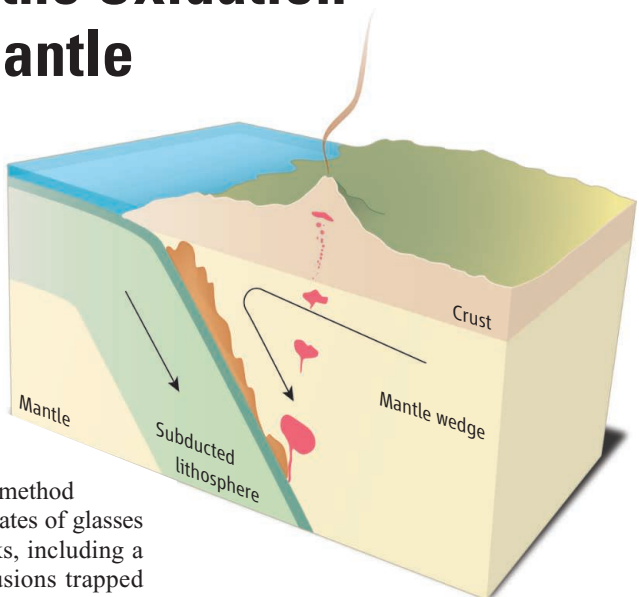
10.1126/science.1178117

GEOCHEMISTRY

Ironing Out the Oxidation of Earth's Mantle

Marc M. Hirschmann

Subduction processes cause magmas from volcanoes in island arcs to become more oxidized and may influence the oxidation state of the entire mantle.



Oxidizing mantle rocks and magmas. Subduction of oceanic lithosphere carries oxidized surface rocks into Earth's interior. These rocks, including sediments and hydrothermally altered basalts, are rich in water, which is released into the overlying mantle wedge, as indicated by the region in brown. This process initiates melting in the mantle wedge, which in turn leads to formation of volcanoes in island arcs such as Japan and Indonesia. Regions where silicate melt is present are shown schematically in red. Kelley and Cottrell show that the subducted, volatile-rich geochemical component found in island arc volcanoes is also associated with oxidation, strongly suggesting that the fluids added from the subducted lithosphere to the mantle wedge are rich in an oxidizing agent such as ferric or sulfate ions. The mantle wedge is dragged into the deeper mantle by viscous coupling to the subducted lithosphere (curved arrow).

CREDIT: P. HUEY/*SCIENCE*

Lavas from island arc volcanoes form when the crust is recycled into the mantle at subduction zones (see the figure). These lavas are more oxidized than those produced at mid-ocean ridge volcanoes. On page 605 of this issue, Kelley and Cottrell (*1*) use a high–spatial resolution method to determine iron oxidation states of glasses from a suite of volcanic rocks, including a broad sampling of tiny inclusions trapped in minerals from arc volcanoes that have not undergone degassing. They correlate these measurements with dissolved water and trace element concentrations determined by other microanalytical techniques, and link the oxidation of arc volcano magmas with oxidants in the fluids that infiltrate the mantle wedge above subduction zones, as opposed to other processes, such as volcanic degassing in surface regions.

The lavas produced at arc volcanoes—adjacent to oceanic trenches in Japan, Chile, Indonesia, and other places around the Pacific "ring of fire"—are created when cold rocks from near Earth's surface are returned to the mantle at a subduction zone (see the figure). It may seem paradoxical that cold materials lead to volcanism, but the subducted rocks release fluids that rise and induce partial melting in the overlying mantle wedge. The partial melts are buoyant, and once they segregate from the mantle, they create arc volcanoes.

The fact that arc magmas are more oxidized than mid-ocean ridge magma has been attributed to subduction processes, but recently, new methods analyzing vanadium in arc lavas have challenged this supposition (*2*). Because vanadium takes on different oxidation states depending on its environment, its geochemical behavior can be used to infer the oxidation state during partial melting. Studies based on this method suggested that the mantle wedge beneath island arcs (see the figure) is no more oxidized than is the mantle in other regions (*2*). This could indicate that the oxidized character of arc volcanic rocks derives from near-surface processes, such as fractional crystallization or volcanic degassing.

However, the results of Kelley and Cottrell suggest a different explanation. Using microscale x-ray absorption near-edge spectroscopy, they determined the iron oxidation state of the lavas and found that it correlates with water content. They argue that the oxidation state of arc magmas is affected mainly by the proportion of subduction fluid added to the source. Thus, the oxidation process must occur near where the subducted rock meets the mantle wedge. The oxidation state is also proportional to trace element indicators of subduction influence, although more data will be required before a strong correlation can be established.

The study by Kelley and Cottrell shows that the increase in oxidation state is not an arti-

Department of Geology and Geophysics, University of Minnesota, Minneapolis, MN 55455, USA. E-mail: marc.m.hirschmann-1@umn.edu

Downloaded from www.sciencemag.org on July 30, 2009

Published by AAAS