



Following the same nerve track toward different cell fates

Chaya Kalcheim and Hermann Rohrer

Science **345**, 32 (2014);

DOI: 10.1126/science.1257175

This copy is for your personal, non-commercial use only.

If you wish to distribute this article to others, you can order high-quality copies for your colleagues, clients, or customers by [clicking here](#).

Permission to republish or repurpose articles or portions of articles can be obtained by following the guidelines [here](#).

The following resources related to this article are available online at www.sciencemag.org (this information is current as of July 3, 2014):

Updated information and services, including high-resolution figures, can be found in the online version of this article at:

<http://www.sciencemag.org/content/345/6192/32.full.html>

A list of selected additional articles on the Science Web sites **related to this article** can be found at:

<http://www.sciencemag.org/content/345/6192/32.full.html#related>

This article **cites 10 articles**, 6 of which can be accessed free:

<http://www.sciencemag.org/content/345/6192/32.full.html#ref-list-1>

This article appears in the following **subject collections**:

Neuroscience

<http://www.sciencemag.org/cgi/collection/neuroscience>

lowest Landau level are filled. At small electric fields, the ground state is spin polarized (canted antiferromagnetic), and above a critical field the ground state transitions to become layer polarized (see the figure, panel A). What is new is that the lifted orbital degeneracy due to the electric field induces a spin-layer coherent phase (coherent superpositions of Landau levels with the same orbital index but different spin and valley indices) separating the fully spin and fully layer polarized phases (see the figure, panels B and C). Maher *et al.* additionally track the electric field-induced phase transitions of FQHSS, observing weak electron-hole asymmetry reminiscent of the Kou *et al.* findings. The phase transitions in the FQHSS tend to match those observed in the parent QHSS, indicating that the fractionally charged quasiparticles inherit the same symmetries as their parent electrons and couple to symmetry-breaking terms with similar strength. The $\nu = 4/3$ and $5/3$ states are exceptions, exhibiting a phase transition at zero electric field where their parent $\nu = 2$ state does not, suggesting that the competition between ground state phases in the QHSS and FQHSS may be exceedingly complex.

It is remarkable that these three studies, using independent measurement and sample fabrication techniques, draw consistent conclusions about the nature of a system with so many degrees of freedom. Another recent study (10) examined FQHSS in high-quality suspended bilayer graphene and found rather different results, observing only two fully developed states at $\nu = -1/2$ and $-4/3$. The $\nu = -1/2$ state is especially intriguing, as it is expected to be non-Abelian (behaving as neither a boson nor fermion) and is not of the same origin as any of the FQHSS observed on the substrate-supported devices of Kou *et al.* or Maher *et al.* This result further demonstrates the wide variability of FQHSS in bilayer graphene, in contrast to monolayer graphene, in which the FQHS sequence is similar across all experiments. Though considerable work is necessary to fully understand the rich phase diagram of bilayer graphene, these studies open exciting pathways toward realizing and controlling the exotic emergent states. ■

REFERENCES

1. K. S. Novoselov *et al.*, *Nature* **438**, 197 (2005).
2. Y. Zhang *et al.*, *Nature* **438**, 201 (2005).
3. C. R. Dean *et al.*, *Nat. Phys.* **7**, 693 (2011).
4. A. Kou *et al.*, *Science* **345**, 55 (2014).
5. K. Lee *et al.*, *Science* **345**, 58 (2014).
6. P. Maher *et al.*, *Science* **345**, 61 (2014).
7. E. McCann, V. I. Fal'ko, *Phys. Rev. Lett.* **96**, 086805 (2006).
8. J. K. Jain, *Phys. Rev. Lett.* **63**, 199 (1989).
9. M. Yankowitz *et al.*, <http://arxiv.org/abs/1401.5145> (2014).
10. D. K. Kiet *et al.*, *Nano Lett.* **14**, 2135 (2014).

10.1126/science.1256545

NEUROSCIENCE

Following the same nerve track toward different cell fates

Schwann cell precursors can become either neurons or glia

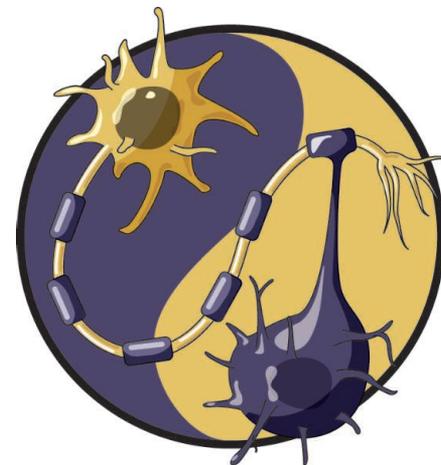
By Chaya Kalcheim¹ and Hermann Rohrer²

The autonomic nervous system controls the activity of internal organs such as the heart, lung, and gut, maintaining homeostasis of body functions in response to changing external conditions (1). It is composed of two antagonistic branches, sympathetic and parasympathetic. The former is essential for adapting to activity (i.e., fight-and-flight), whereas the latter is important at rest. Sympathetic neurons form ganglia along the body axis; parasympathetic ganglia are distributed all over the body. On page 87 and page 82 in this issue, Espinosa-Medina *et al.* (2) and Dyachuk *et al.* (3) challenge current views on how the parasympathetic nervous system is formed. These ganglia arise from progenitor cells that migrate along nerve fibers to peripheral targets. Known as Schwann cell precursors, these cells had previously been thought to give rise only to non-neuronal cells. Moreover, the nerve tracks include the very nerve fibers that ultimately innervate the parasympathetic neurons once they reach their destination and mature.

Both sympathetic and parasympathetic neurons derive from neural crest cells that emigrate from the neural tube (precursor to the brain and spinal cord) during early vertebrate development (4, 5). This migration to sites of ganglion formation and the molecular control of neuron differentiation have been well delineated for sympathetic ganglia, but the formation of parasympathetic ganglia has remained unclear (6, 7). Espinosa-Medina *et al.* and Dyachuk *et al.* demonstrate that parasympathetic ganglia are formed not by the aggregation of migrating neural crest cells but rather from Schwann cell precursors derived from neural crest cells. The Schwann cell precursors track along outgrowing axons from neurons in the developing hindbrain and transiently display a dual identity—part Schwann cell precursor and part parasympathetic neuron progenitor.

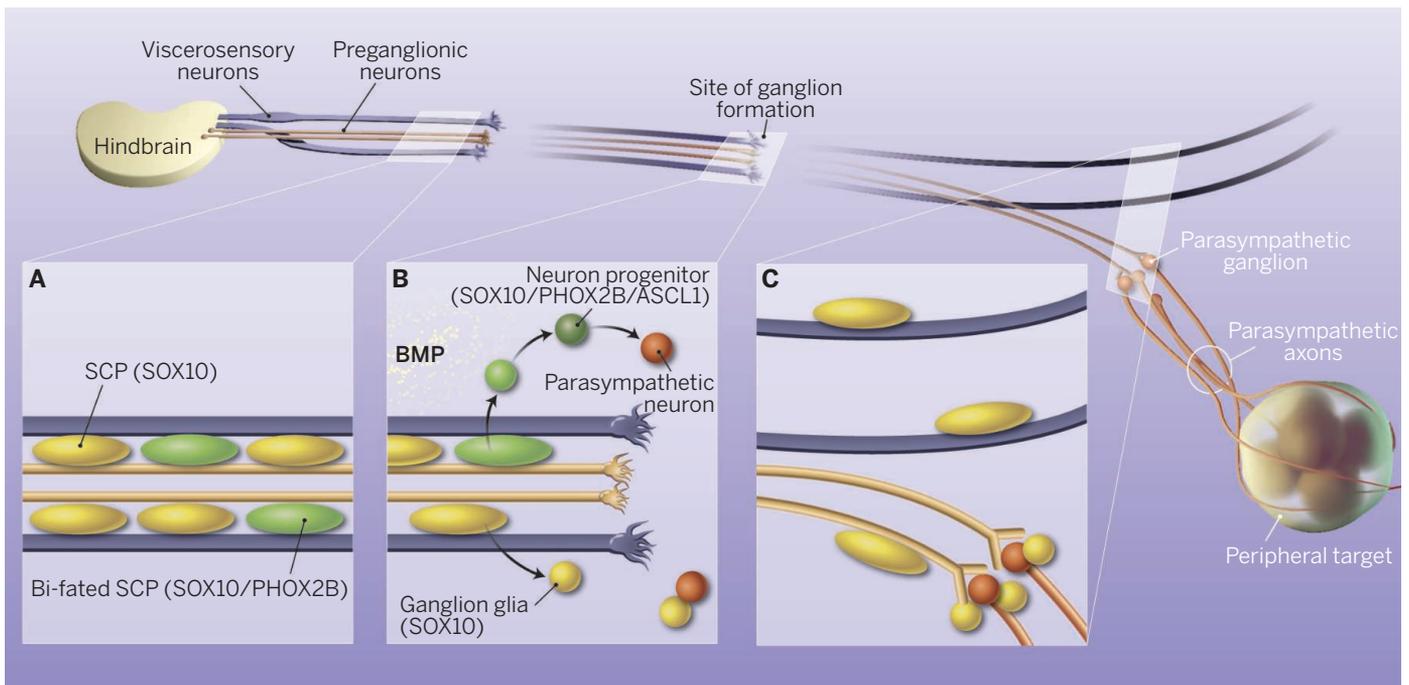
During mouse embryonic development, two parasympathetic ganglia (sphenopalatine and lingual) in the head are absent when a facial nerve that emanates from the hindbrain is partially eliminated (8).

This pointed to a role for cranial nerves in parasympathetic neuron development. Extending these findings to additional parasympathetic ganglia in the mouse head and trunk, Espinosa-Medina *et al.* used genetic methods to delete other cranial nerves—the glossopharyngeal nerve and/or the vagus nerve. The authors observed that the generation of parasympathetic neurons that constitute the otic ganglion—which stimulates a salivary gland—depends on the presence of the glossopharyngeal cranial nerve.



Formation of the cardiac ganglion—which innervates the heart—depends on the presence of the vagus nerve. Detailed analysis revealed that both parasympathetic ganglia arise from cells that accompany the cranial nerve fibers as they grow toward the site of parasympathetic ganglion formation. These migrating cells express the transcription factor SOX10, which indicates their crest cell origin and is a marker for future Schwann cells. During their migration, however, they also turn on the expression of another transcription factor, PHOX2B, which is a marker for autonomic neurons. They therefore assume a bi-fated precursor

¹Department of Medical Neurobiology, Institute for Medical Research Israel-Canada (IMRIC) and The Safra Center for Brain Research (ELSC), Hebrew University of Jerusalem, Hadassah Medical School, Jerusalem, Israel. ²Research Group Developmental Neurobiology, Max Planck Institute for Brain Research, Frankfurt/M, Germany. E-mail: kalcheim@cc.huji.ac.il; hermann.rohrer@brain.mpg.de



Bi-fated progenitors. (A) So-called Schwann cell precursors (SCPs) associate with outgrowing mixed viscerosensory and visceromotor nerve fibers from the embryonic mouse hindbrain. (B) At sites of future parasympathetic ganglion formation, these precursors detach from the nerve and change expression of certain factors to follow a neuron cell fate [likely in response to bone morphogenetic protein (BMP)] or a non-neuronal (Schwann cell or ganglion glia) fate. (C) Differentiated parasympathetic neurons innervate targets and are themselves innervated by visceromotor neurons from the hindbrain.

sor identity for neuronal and non-neuronal cells. At later stages, when the migrating cells that will become parasympathetic neurons begin to cluster and detach from the cranial nerve, SOX10 expression decreases (see the figure). Interestingly, the bi-fated precursor cells (expressing both transcription factors) are not restricted to cranial nerves but are also found in developing limb nerves where they generate a small ganglion composed of autonomic neurons that express PHOX2B.

Dyachuk *et al.* show that parasympathetic ganglia coalesce 1 or 2 days after the cessation of neural crest cell migration from the neural tube. This temporal gap suggested that these ganglia might not directly derive from neural crest precursors. Lineage tracing revealed that parasympathetic neurons in the mouse head are generated from cells associated with extending cranial nerves that express SOX10 and the transcription factor ASCL1. The latter is a marker for neuronal commitment. The authors also detected the neuronal marker PHOX2B in these cells and the dependence of parasympathetic ganglion formation on cranial nerves. These bi-fated precursor cells also expressed ERBB3, a receptor for neuregulin that is expressed by Schwann cells. In the ERBB3-deficient mice, both precursor cells and parasympathetic neurons are absent, indicating a transition from a bi-fated precursor to a parasympathetic neuron pheno-

type. Conversely, in the absence of ASCL1, the precursor cells remain as Schwann cells.

The findings of Espinosa-Medina *et al.* and Dyachuk *et al.* show that bi-fated precursors, known as Schwann cell precursors, that are present in viscerosensory cranial and vagus nerves are the source of neurons and non-neuronal cells. This extends previous findings showing that these precursors also give rise to skin melanocytes (9) that are restricted to the abdomen and limbs (10) and to endoneurial fibroblasts in the protective connective tissue that surrounds nerves (11). Thus, early developing nerves represent a convenient source of, and pathway to deliver, progenitor cells to distant sites. Interestingly, parasympathetic ganglion development relies completely on this principle, but the presence of bi-fated progenitors (expressing PHOX2B and SOX10) is not restricted to nerves containing preganglionic parasympathetic nerve fibers (2). The discovery of an autonomic ganglion (expressing PHOX2B) along a limb nerve in the developing mouse suggests that parasympathetic ganglia may form transiently and may be eliminated in the absence of preganglionic innervation (12).

Espinosa-Medina *et al.* and Dyachuk *et al.* propose an elegant solution for the wiring of preganglionic autonomic neurons to their peripheral postsynaptic parasympathetic targets. It is yet unclear what signals con-

trol the fate switch in the migrating bi-fated precursor cells, how PHOX2B expression is regulated in these cells, what factors elicit detachment from the cranial nerve and subsequent neuron differentiation, and how progenitors become restricted to a parasympathetic neuronal fate rather than a sympathetic neuronal fate. It would also be interesting to clarify whether individual Schwann cell precursors display stem cell-like properties to generate parasympathetic neurons, melanocytes, and endoneurial fibroblasts or whether they are a heterogeneous cell population that can produce specific combinations of cell fates depending on the spatiotemporal context. ■

REFERENCES

1. W. B. Cannon, *The Wisdom of the Body* (Norton Library, New York, NY, 1963).
2. I. Espinosa-Medina *et al.*, *Science* **345**, 87 (2014).
3. V. Dyachuk *et al.*, *Science* **345**, 82 (2014).
4. N. M. Le Douarin, C. Kalcheim, *The Neural Crest* (Cambridge Univ. Press, Cambridge, ed. 2, 1999).
5. S. Krispin, E. Nitzan, Y. Kassem, C. Kalcheim, *Development* **137**, 585 (2010).
6. H. Rohrer, *Eur. J. Neurosci.* **34**, 1563 (2011).
7. J. C. Kasemeier-Kulesa, R. McLennan, M. H. Romine, P. M. Kulesa, F. Lefcort, *J. Neurosci.* **30**, 13078 (2010).
8. E. Coppola *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **107**, 2066 (2010).
9. I. Adameyko *et al.*, *Cell* **139**, 366 (2009).
10. E. Nitzan, E. R. Pfaltzgraff, P. A. Labosky, C. Kalcheim, *Proc. Natl. Acad. Sci. U.S.A.* **110**, 12709 (2013).
11. N. M. Joseph *et al.*, *Development* **131**, 5599 (2004).
12. S. Furber, R. W. Oppenheim, D. Prevet, *J. Neurosci.* **7**, 1816 (1987).

10.1126/science.1257175