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Following the same nerve track toward different cell fates

By Chaya Kalcheim and Hermann Rohrer

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., flight-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 (spenopalatine 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.
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 morphogenic 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.

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 cell populations that express SOX10 and the transcription factor ASCL1. The latter is a marker for neuronal commitment. The authors also detected the neuronal marker PHOX2B (expressing PHOX2B and SOX10) 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 control 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