Neural crest cell origin and signals for intrinsic neurogenesis in the mammalian respiratory tract

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Rationale: Our study investigates the innervation of the respiratory tract during mouse embryonic development with a focus on identification of cell origin and essential developmental signals for the resident, or intrinsic, neurons.

Methods: We characterize the intrinsic neurogenesis in the respiratory tract using lineage tracing and mouse mutants.

Results: We show that these intrinsic neurons are derived from neural crest cells and cluster to form ganglia that reside in the dorsal trachea and bronchi with diminishing frequency. Comparison of intrinsic neurogenesis between wildtype, *GDNF-/-*, *NRTR-/-* and *Ret-/-* embryos, in combination with lung organ cultures, has identified that Ret signaling, redundantly activated by GDNF and neurturin, is required for intrinsic neurogenesis in the trachea and primary bronchi. In contrast, Ret deficiency has no effect on the innervation of the rest of the respiratory tract, suggesting that the majority of respiratory innervation is controlled independent of Ret signaling by neurons whose cell bodies are located outside of the lung, so-called extrinsic neurons. Furthermore, although the trachea and the esophagus and their intrinsic neurons share foregut endoderm and neural crest cell origins, respectively, signals required for their intrinsic neurogenesis are divergent.

Conclusion: Together, our results not only establish the neural crest lineage of intrinsic neurons in the pulmonary tract, but also identify regional differences in the abundance and developmental signals of intrinsic neurons along the pulmonary tract and in the esophagus.