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Jena L. Chojnowski, Heidi A. Trau, Kyoko Masuda, Nancy R. Manley

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Authors: Jena L. Chojnowski[1], Heidi A. Trau[2], Kyoko Masuda[3], and Nancy R. Manley[*]

Department of Genetics, Paul D. Coverdell Center, 500 DW Brooks Drive, University of Georgia, Athens, GA, 30602

*Author for correspondence: nmanley@uga.edu, fax 706-583-0691.

[1] Current address: Department of Natural Sciences, University of South Carolina Beaufort, One University Boulevard, Bluffton, SC 29909, USA

[2] Current address: Department of Physiological Sciences, Eastern Virginia Medical School, 700 W Olney Road, Lewis Hall, Norfolk, VA 23507, USA

[3] Current address: The Institute of Frontier Medical Sciences, Kyoto University, 53 Shogoin-Kawahara-cho, Sakyo-ku, Kyoto-shi, Kyoto, 606-8397 Japan

Abstract

Hoxa3^{null} mice have severe defects in the development of pharyngeal organs including athymia, aparathyroidism, thyroid hypoplasia, and ultimobranchial body persistence, in addition to defects of the throat cartilages and cranial nerves. Some of the structures altered in the *Hoxa3*^{null} mutant embryos are anterior to the described *Hoxa3* gene expression boundary: the thyroid, soft palate, and lesser hyoid horn. All of these structures develop over time and through the interactions of multiple cell types. To investigate the specific cellular targets for HOXA3 function in these structures across developmental time, we performed a comprehensive analysis of the temporal and tissue-specific requirements for *Hoxa3*, including a lineage analysis using *Hoxa3*^{Cre}. The combination of these approaches showed that HOXA3 functions in both a cell autonomous and non-cell autonomous manner during development of the 3rd and 4th arch derivatives, and functions in a neural crest cell (NCC)-specific, non-cell autonomous manner for structures that were *Hoxa3*-negative by lineage tracing. Our data indicate that HOXA3 is required for tissue organization and organ differentiation in endodermal cells (in the tracheal epithelium, thymus, and parathyroid), and contributes to organ migration and morphogenesis in NCCs. These data provide a detailed picture of where and when HOXA3 acts to promote the development of the diverse structures that are altered in the *Hoxa3*^{null} mutant. Data presented here, combined with our previous studies, indicate that the regionally restricted defects in *Hoxa3* mutants do not reflect a role in positional identity (establishment of cell or tissue fate), but instead indicate a wider variety of functions including controlling distinct genetic programs for differentiation and morphogenesis in different cell types during development.