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EDITORIAL

GATA4 in Regional Affairs

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, new work from DeLaForest et al[1] provides striking genetic evidence that the zinc finger containing transcription factor, GATA4, is both necessary and sufficient for glandular hindstomach tissue identity to emerge from the developmentally permissive foregut endoderm. These findings broaden the scope of knowledge about how GATA factors function in tissue patterning and have tantalizing implications for gastrointestinal diseases, particularly Barrett's esophagus, which is a predisposing condition for esophageal adenocarcinoma.

In mammalian development, *Gata4* is expressed broadly in the foregut endoderm (in squamous esophageal/forestomach and glandular stomach precursors) before resolving into the glandular stomach as the organism matures.[2,3] This *Gata4* expression pattern suggests a potential role for the transcription factor in imparting regional identity to the developing stomach. The investigators tested this hypothesis by inactivating *Gata4* in a mouse model using a pan-endodermal Cre driver under the control of the *Shh* promoter. Resulting gastric tissues lacking GATA4 immunoreactivity showed a clear loss of glandular morphology, instead expressing markers of squamous, forestomach-like tissue. Pockets of remaining GATA4-positive cells that escaped Cre activity in the neonatal hindstomach exhibited normal gastric glands, suggesting a cell-autonomous role for GATA4 in imparting hindstomach identity to these tissues. Immunohistology for canonical markers of gastric epithelia confirmed the authors' hypothesis that GATA4 is required for hindstomach epithelial development and maturation, and these observations were strongly substantiated by transcriptome analysis. Conversely, although markers of hindstomach epithelia were substantially diminished in the *Shh-Cre; Gata4*$^{f/f}$ embryos, genes associated with squamous forestomach and esophagus were ectopically expressed in the hindstomach, consistent with the appearance of squamous tissue in these mutants. Excitingly, ectopic expression of GATA4 in the presumptive squamous stomach led to a suppression of a key squamous cell transcriptional regulator, TRP63, and squamous marker genes, such as KRT5. Transcriptome analysis of the mutant embryos either ectopically expressing or lacking GATA4 in the developing stomach showed a homeotic-like conversion between forestomach and hindstomach in a GATA4-dependent fashion. Hundreds of forestomach-enriched genes were upregulated in *Gata4*-knockout hindstomach, while hundreds of hindstomach-enriched genes were upregulated in the *Gata4*-overexpressing forestomach. Many of these genes may be under direct control of GATA4, as evidenced by GATA4 ChIP-seq enrichment at the promoters of these differentially expressed genes. These findings are corroborated in a study earlier this year showing that overexpression of GATA4 could impart glandular identity in the forestomach that is consistent with a transitional epithelium that lies at the glandular/squamous boundary.[4] Taken together, these studies make a compelling case that GATA4 is key factor imparting tissue regionality in the murine stomach.

Importantly, the authors identified that a large fraction of GATA4-regulated transcripts identified in this study are differentially regulated in Barrett's esophagus. This finding opens the possibility that GATA4 orchestrates the transformation of the squamous tissue in Barrett's, just as ectopic GATA4 expression in the murine endoderm triggered a conversion of embryonic forestomach to an identity akin to glandular epithelium. Le Douarin's classic embryology experiments[5] indicate that anterior-posterior identity is gradually lost with developmental time. It will be of interest to determine whether GATA4's ability to induce hindstomach-like epithelial properties in the squamous forestomach is possible in adult animals, making GATA4 an even stronger candidate for initiating Barrett's metaplasias. Fascinatingly, based on ChIP-seq of adult hindstomach, it seems that GATA4 has the capacity to function as an activator of the hindstomach program and a suppressor of the squamous forestomach program. Future studies can resolve what cofactors partner with GATA4 to mediate these divergent outcomes in distinct genomic contexts. This study's ChIP-seq data provide an excellent starting point that could be complemented by protein-interaction studies and functional assays of hindstomach development, potentially using iPS-derived organoid systems.

The discovery by DeLaForest et al[1] adds to the fascinating roles of GATA4 in establishing tissue pattern and provides new avenues through which to decipher its "regionalizing" mechanisms. In pancreatic development, *Gata4* localizes to the exocrine tip, whereas *Gata6* expression is enriched in the ducts.[6] In the intestine, *Gata4* is required to impart proximal distal patterning.[7,8] In the adrenal cortex, nonoverlapping expression of Gata factors are observed. Indeed, the promising correlation between GATA4 targets in the developing hindstomach and transcripts altered in Barrett's metaplasia suggests that clinical insights are likely to be found when GATA4's tissue patterning mechanisms are further elucidated.

MICHAEL PAUL VERZI, PhD
Human Genetics Institute of New Jersey
Cancer Institute of New Jersey
Rutgers Center for Lipid Research
Department of Genetics
Rutgers University
Piscataway, New Jersey

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Correspondence
Address correspondence to: Michael Paul Verzi, PhD, Rutgers University, Genetics, 145 Bevier Road, LSB 127, Piscataway, New Jersey 08854. e-mail: Verzi@biology.rutgers.edu.

Conflicts of interest
The author discloses no conflicts.

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