cmgh
CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

# LATS Dance: Molecular Choreography Between a Chronic Human Pathogen and Its Host

Gastric adenocarcinoma is the third leading cause of cancer-related death in the world, with 5-year survival rates of less than 30%. Recently, the Cancer Genome Atlas Network identified 4 molecular subtypes of gastric cancer; however, in all anatomic regions of the stomach, chromosomal instability tumors with intestinal-type histology predominate. This subtype progresses through a series of well-orchestrated histologic steps from normal mucosa to nonatrophic gastritis and atrophic gastritis (lesions with high potential for reversibility), to intestinal metaplasia and dysplasia (typically irreversible lesions), and, ultimately, adenocarcinoma. The annual incidence of gastric cancer is estimated to be 0.1% for patients with atrophy, but increases 2.5-fold for patients with intestinal metaplasia, underscoring the premalignant potential of this lesion.

*Helicobacter pylori* is the strongest known risk factor for gastric adenocarcinoma; however, only a subset of infected persons ever develop cancer. Contact between *H pylori* and gastric epithelial cells is critical for inducing injury, and a strain-specific bacterial determinant that augments cancer risk is the *cag* type IV secretion system, which translocates the oncoprotein Cytotoxin-associated gene A (CagA) into epithelial cells. After translocation, CagA undergoes tyrosine phosphorylation and activates a eukaryotic phosphatase Src homology region 2 (SH2)-containing protein tyrosine phosphatase 2 (SHP-2), leading to carcinogenic cellular responses. Nonphosphorylated CagA also exerts pathologic effects via induction of proinflammatory signaling, activation of $\beta$-catenin, and disruption of apical–junctional complexes. Importantly, CagA can activate intracellular molecular pathways that regulate gastric-to-intestinal cell transdifferentiation.

In addition to promoting carcinogenesis, *H pylori* has cleverly evolved mechanisms to suppress the host immune response, which facilitates its chronic lifestyle. For example, *H pylori* flagellin is a noninflammatory molecule in terms of its ability to activate Toll-like receptor 5. *H pylori* lipopolysaccharide contains an anergic lipid A core that induces an attenuated Toll-like receptor 4–mediated response. Finally, activation of the intracellular receptor Nucleotide-binding oligomerization domain containing 1 (NOD1) by *H pylori* suppresses subsequent nuclear factor-$\kappa$B–dependent signaling via activation of a NOD1-dependent negative feedback loop. In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Castro et al[1] provide fresh insights into the molecular underpinnings that regulate both *H pylori*–induced premalignant lesions and microbial persistence within the stomach.

By using a panel of in vitro cell culture systems, Castro et al[1] reported that *H pylori* up-regulates Large tumor suppresor kinase 2 (LATS2), a critical constituent of the Hippo signaling pathway, as well as its upstream kinase Yes-associated protein 1 (YAP1), in a CagA-dependent manner. Induction of these molecules, however, varies in tempo and is characterized by an early and transient activation of YAP1. This subsequently is followed by LATS2 activation, which then exerts an inhibitory brake on further activation of YAP1. The homeostatic role of LATS2 is corroborated further by loss-of-function experiments showing that LATS2 inhibits carcinogenic phenotypes, including epithelial-to-mesenchymal transition, invasion, and intestinal metaplasia. Viewed in isolation, these results suggest that up-regulation of YAP1 induced by *H pylori* is followed by activation of LATS2, which then orchestrates a negative feedback loop to dampen YAP1 overexpression and maintain a homeostatic epithelial phenotype, potentially promoting microbial persistence.

However, biology rarely is straightforward and additional experimentation has shown the complexity of such host–microbial interplay. In vivo corroboration studies using human and mouse samples infected with *H pylori* showed that LATS2 and YAP1 are co-overexpressed within replicative progenitor cell zones in both the gastric antrum and corpus. Furthermore, using molecular silencing techniques, Castro et al[1] found that LATS2 and YAP1 have the capacity to positively regulate each other after infection with *H pylori*. Thus, this chronic pathogen can manipulate the YAP1–LATS2 signaling axis in a multitude of directions.

This study provides novel information regarding how a chronic pathogen may affect carcinogenesis and persistence within its cognate host; more importantly, it establishes a framework for future directions. The topography of LATS2 and YAP1 co-overexpression in vivo localizes to the stem and progenitor cell niche. Recent studies have highlighted the importance of stem cell manipulation by *H pylori*, which occurs in a *cag* type IV secretion system–dependent manner. Based on this, future work should use primary organoid models that can be manipulated experimentally to examine the effects of LATS2 and YAP1 on stem cell phenotypes on a deeper level. Tissue-specific inactivation of LATS2 and/or YAP1 in genetic mouse models also would be useful not only for organoid studies but also to determine the long-term effects of removing these signaling molecules on the development of gastric neoplasia in vivo. Do differences in the composition of gastric microbial communities affect this signaling hub, which may explain some of the discordant results when comparing patterns of in vitro activation with results observed in vivo? Finally, there were other downstream LATS2-independent targets identified to be transcriptionally up-regulated by YAP1 activation, including Connective tissue growth factor (*CTGF*) and Cysteine-rich angiogenic inducer 61 (*CYR61*) . What roles do these targets

exert in manipulation of the host response by *H pylori*? Collectively, the findings from this study have opened a gateway not only for understanding the development of gastric cancer but also for defining mechanisms through which *H pylori* can persistently colonize its human host.

*GIOVANNI SUAREZ, PhD*
Department of Medicine
Vanderbilt University Medical Center
Nashville, Tennessee

*RICHARD M. PEEK JR, MD*
Department of Medicine
Department of Pathology, Microbiology and Immunology
Department of Cancer Biology
Vanderbilt University Medical Center
Nashville, Tennessee

## Reference

1. Molina-Castro SE, Tiffon C, Giraud J, Boueuf H, Sifre E, Giese A, Belleannée G, Lehours P, Bessède E, Mégraud F, Dubus P, Staedel C, Varon C. The hippo kinase LATS2 controls *Helicobacter pylori*–induced epithelial–mesenchymal transition and intestinal metaplasia in gastric mucosa. Cell Mol Gastroenterol Hepatol 2020;9:257–276.

**Correspondence**
Address correspondence to: Richard M. Peek Jr, MD, Division of Gastroenterology, Hepatology, and Nutrition, Vanderbilt University Medical Center, 1030C MRB IV, 2215B Garland Avenue, Nashville, Tennessee 37232-2279. e-mail: richard.peek@vumc.org.

**Conflicts of interest**
The authors disclose no conflicts.

**Funding**
Supported by National Institutes of Health grants R01CA077955, R01DK058587, P01CA116087, and P30DK058404.

**Most current article**


2352-345X
https://doi.org/10.1016/j.jcmgh.2019.09.007