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COMMENTARY

The Innovation

Decoding the interplay: *Helicobacter pylori* infection, tumor immune microenvironment, and immunotherapy outcomes in gastrointestinal cancers

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Received: July 31, 2024; Accepted: March 10, 2025; Published Online: March 14, 2025; https://doi.org/10.1016/j.xinn.2025.100880

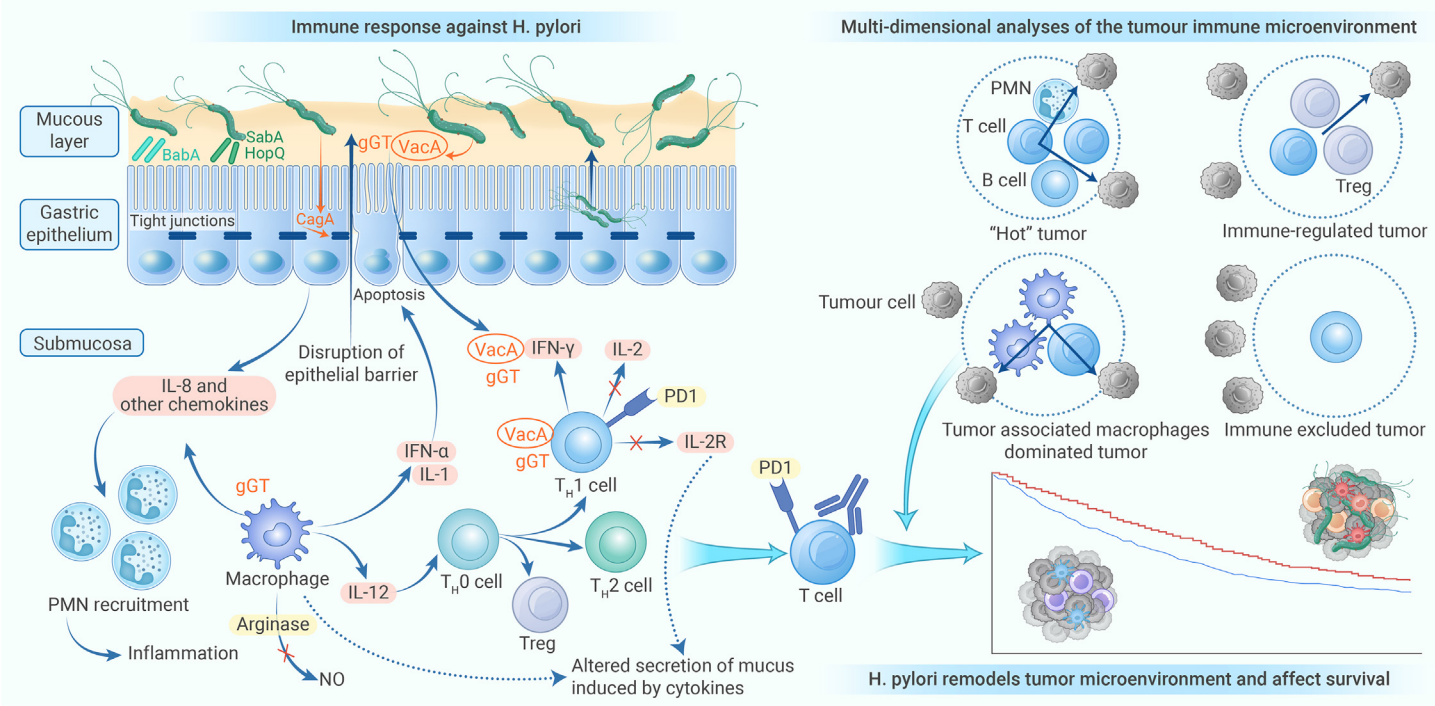
Citation: Mejias-Luque R. and Gerhard M. (2025). Decoding the interplay: *Helicobacter pylori* infection, tumor immune microenvironment, and immunotherapy outcomes in gastrointestinal cancers. The Innovation **6(5)**, 100880.

The tumor microenvironment is a complex and heterogeneous milieu characterized by the interaction between diverse cellular and non-cellular constituents. This intricate ecosystem, intrinsic to gastrointestinal (GI) cancers, encompasses elements such as the local microbiome, specific species like *Helicobacter pylori*, distinct immune cell subsets, and stromal cell components. The interplay between these components intricately contributes to the modulation of tumor progression dynamics and shapes the responses of GI neoplasms to therapeutic interventions. A comprehensive understanding of these nuanced interactions is pivotal to elucidate the underlying complexities of GI cancers, thereby providing avenues for the strategic manipulation of these networks, leading to more efficacious therapeutic strategies.

In recent years, a growing interest has emerged in unraveling the complex connections between the tumor immune microenvironment and the outcomes of immunotherapy in GI cancers. Two noteworthy studies, conducted by Jia et al.[1] and Chen et al.,[2] provide valuable insights into different facets of this complex relationship. Jia et al. explore the impact of *H. pylori* infection on immune checkpoint inhibitor (ICI) responses in various GI cancers,[1] while Chen et al. delve into a multi-dimensional analysis of the tumor immune microenvironment in gastric cancer (GC).[2] While both studies already provide valuable insight, their combined findings offer an even more comprehensive understanding of the interplay between infectious agents, immune responses, and the efficacy of immunotherapy in the context of GI malignancies.

The study by Jia et al. involved a large cohort of patients with GI cancers and utilized various analyses to investigate the impact of *H. pylori* on immune-related progression-free survival (irPFS) and immune-related overall survival (irOS) in patients with GC who received anti-PD-1/PD-L1 therapy. The authors reported that *H. pylori*-positive patients with GC exhibited longer irPFS and a trend of longer irOS compared to *H. pylori*-negative patients. This observation is supported by the higher densities of PD-L1+ cells and non-exhausted $CD8^+$ T cells in *H. pylori*-positive GC. Furthermore, the transcriptomic analysis revealed similarities between *H. pylori*-positive GC and tumors with favorable immunotherapy responses, suggesting a potential link between *H. pylori* infection and enhanced response to ICIs in GC.

The study involved a large sample size of 10,122 patients who underwent 13C-urea breath tests, with a subset of 2,460 patients receiving anti-PD-1/PD-L1 therapy. The inclusion of patients with different GI cancers, such as esophageal cancer (EC) and colorectal adenocarcinoma (CRC), provides a unique approach to a better understanding of the similarities and differences in the interaction of microbes, tumor microenvironment, and therapy response across various GI malignancies. The subsequent analysis of 636 patients with Epstein-Barr virus-negative microsatellite-stable GC who were treated with anti-PD-1/PD-L1 therapy further corroborates the conclusions drawn. The study's findings also extend to CRC, where the authors observed a negative impact of *H. pylori* infection on the treatment response to anti-PD-1/PD-L1 immunotherapy in DNA-mismatch-repair-deficient/microsatellite-instability-high patients with CRC. This comprehensive analysis of the effects of *H. pylori* infection on different types of GI cancers underscores the complexity of the interactions and emphasizes the need for highly personalized approaches in immunotherapy for patients with GI cancer.



Interplays among *Helicobacter pylori* infection, tumor immune microenvironment, and immunotherapy outcomes in gastrointestinal cancers.

The opposing effects of *H. pylori* on immunotherapy outcomes in different types of cancer underline the need for a tailored approach to patient management, with a specific focus on *H. pylori* testing as part of immunotherapy for GI cancer. This has significant implications for clinical practice, as it suggests that *H. pylori* status may serve as a potential biomarker for predicting treatment response and guiding therapeutic decisions in patients with GI cancer. This study paves the way for further research into the mechanistic underpinnings of *H. pylori*-mediated immunomodulation and its implications for personalized immunotherapy strategies in GI cancers. Together, the findings have the potential to influence clinical practice, patient management, and the development of personalized treatment approaches in GI oncology.

It should be mentioned that the study's retrospective nature and potential confounding factors, such as prior *H. pylori* eradication therapy and other comorbidities, could influence the observed associations and outcomes. Future prospective studies with controlled interventions and long-term follow-up are required to validate the findings and elucidate the underlying mechanisms of *H. pylori*-mediated immunomodulation in GI cancers and especially the potential effects of eradication therapy, with the ultimate goal of improving treatment outcomes and patient care in the field of GI oncology.

Several mechanisms are conceivable to explain how *H. pylori* may influence these outcomes. First, *H. pylori* infection is associated with chronic inflammation and immune dysregulation in the gastric mucosa. This bacterium induces a local inflammatory response characterized by the infiltration of neutrophils, macrophages, T cells, B cells, and plasma cells, which leads to a chronic inflammatory environment. At the same time, this chronic infection creates a highly tolerogenic local environment dominated by regulatory T cells, immunosuppressive cytokines, and expression of PD-1/PD-L1 and, thus, an immunosuppressive milieu that facilitates tumor evasion from immune surveillance. In line with this, *H. pylori*-positive GCs exhibit higher densities of PD-L1+ $CD8^+$ T cells. In addition, *H. pylori* infection has been shown to directly induce DNA damage and interfere with DNA repair capabilities.[3] *H. pylori*-positive GCs have a higher tumor mutational burden and are more often microsatellite unstable, which usually goes along with higher infiltration of immune cells, specifically CD103+ $CD8^+$ T cells, which are responsive to PD-L1 blockade.

Together, these factors render *H. pylori*-positive GCs especially susceptible to immunotherapeutic therapies, potentially explaining the observed outcomes in GC.

Secondly, *H. pylori* infection influences the gut microbiota composition, which is known to play a critical role in modulating systemic immune responses. Dysbiosis, or the imbalance of gut microbiota, associated with *H. pylori* can lead to the production of metabolites that either promote or inhibit immune responses. While the alterations of the gastric microbiome upon *H. pylori* infection are well documented, some reports also found a significant change in the intestinal and colonic microbiome of *H. pylori*-infected individuals. This altered microbiome can affect the efficacy of ICIs by influencing the overall immune tone and the specific immune pathways activated in response to cancer cells. The differential outcomes between GC and CRC observed by Jin et al. may also be influenced by the differential effects of *H. pylori* in GI microbiome and immunity. *H. pylori* infection has been shown to alter intestinal and colonic immunity by shifting the balance between regulatory and proinflammatory T cells ($CD4^+$, $CD8^+$, and Th17 cells) toward the latter, creating a proinflammatory milieu in the small intestine and colon. This goes along with a compromised intestinal mucosal barrier function and distinct shifts in the colonic microbiome.[4] Interestingly, *H. pylori*-positive individuals had an unchanged or even higher alpha-diversity than controls, which is often considered an indicator of a healthy gut microbiome. However, significant shifts in individual bacterial taxa were observed in *H. pylori*-positive individuals, with a loss of beneficial short-chain fatty acid (SCFA) producers and an increase in CRC-associated taxa.[5] SCFAs are considered to have a positive effect of immunotherapy in some cancers, and higher levels of fecal SCFAs were associated with PFS.[6,7]

Taken together, several local and systemic effects associated with *H. pylori* infection may account for the findings observed by Jin et al. Still, especially in the light of the continuously evolving landscape of GI oncology, more studies are needed to understand the interplay of microbial factors and the intricate immune environment within tumors.

Chen et al. have conducted a noteworthy multi-dimensional analysis of the tumor immune microenvironment in GC, addressing a significant gap in the current understanding of patient responses to ICIs. This approach is particularly pertinent given the heterogeneous nature of the tumor immune microenvironment and the variable response rates to ICIs observed in clinical practice.

The study's strength lies in its exhaustive analysis of tumor-infiltrating immune cells (TIICs) through multiplex immunohistochemistry. By examining the density and spatial organization of specific immune cell subsets within the tumor microenvironment, the authors have developed a multi-dimensional TIIC signature. This signature, which includes the density of CD4+FoxP3−PD-L1+, CD8+PD-1−LAG3−, and CD68+STING+ cells, as well as the spatial organization of CD8+PD-1+LAG3− T cells, has shown promise in predicting patient response to anti-PD-1/PD-L1 immunotherapy and survival outcomes.

The integration of both standard-of-care and clinical trial data enhances the study's relevance to a broader patient population. One of the most significant aspects of this research is its potential for clinical application. The identification of a multi-dimensional TIIC signature could transform patient stratification for immunotherapy, allowing for more personalized treatment plans and potentially improving outcomes for patients with GC. The study's findings are a next-level evolution of what has long been initiated by the groundbreaking work from Jerome Galon in 2006 initially linking immune cells within human colorectal tumors with clinical outcome PFS[8] and indicates that a single biomarker may not suffice for predicting responses to ICIs due to the complex nature of the immune response to cancer, as well as the continuously evolving therapeutic landscape. This insight is particularly valuable because it promotes a more holistic approach to biomarker development. However, while the study's findings are promising, it is crucial to consider the need for external validation in larger, independent cohorts. Additionally, the study was conducted within a single ethnic population, which may limit the generalizability of the results to other populations with different genetic backgrounds.

The multi-dimensional TIIC signature proposed by the authors provides a higher resolution of the interplay between various immune cells within the tumor microenvironment and their collective impact on the efficacy of immunotherapy. The study exemplifies the importance of a comprehensive approach to understanding biological complexities, especially in oncology. While the study advances our knowledge of the tumor immune microenvironment, it may also pave the way for more effective patient selection for immunotherapy. This research exemplifies the potential of precision medicine in oncology and brings us closer to the goal of tailored treatments for patients with gastric and other highly heterogeneous GI cancers.

Both studies underscore the need for personalized approaches, potential biomarkers, and a more comprehensive understanding of the immune landscape to improve treatment selection and outcomes and patient care in the field of GI oncology. Further research and prospective studies are warranted to validate the findings and explore the underlying mechanisms, with the ultimate goal of improving treatment outcomes and patient care in the field of GI oncology.

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DECLARATION OF INTERESTS

The authors report no conflicts of interest.