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Editorial

Beyond the Endoscope: The Promise of Blood-based Biomarkers for Gastric Mucosal Changes

Jia Shen[1,2], Lihua Ren[1*] and Hong Chen[1*]

[1]*Department of Gastroenterology, Zhongda Hospital, Southeast University, Nanjing, Jiangsu, China;* [2]*School of Medicine, Southeast University, Nanjing, Jiangsu, China*

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The antralization of the gastric mucosa, a process wherein the oxyntic gastric body epithelium adopts a phenotypical resemblance to the antral mucosa, represents a critical yet reversible juncture in the gastric carcinogenesis cascade.[1] Traditionally, its identification has been solely reliant on histopathological examination of invasively obtained biopsy specimens, creating a significant diagnostic bottleneck. Economical, convenient, and non-invasive testing methods are more worthy of being found and applied to the wider population.[2]

The present study by Ye *et al*.[3] identified a distinct association between antralization and specific alterations in both peripheral blood parameters and gastric mucosal markers. These include elevated peripheral lymphocyte counts, reduced serum lipopolysaccharide (LPS) levels, increased expression of trefoil factor-2 (TFF2), mucin 6 (MUC6), and MUC5B, and decreased expression of MUC5AC in the proximal gastric mucosa. The findings suggest that these biomarkers may help identify the presence of antralization, particularly in high-risk populations for gastric cancer, such as individuals with current or past *Helicobacter pylori* (*H. pylori*) infection. The study's prospective design and the use of pathological confirmation as the diagnostic gold standard lend considerable robustness to its conclusions. The findings can be distilled into two congruent signatures: a systemic circulatory profile and a local tissue-specific mucin profile.

The identification of higher plasma lymphocyte counts coupled with lower serum LPS levels in the antralization group is intriguing. The lymphocytosis may reflect a sustained, albeit dysregulated, immune response to chronic *H. pylori*-driven inflammation, a well-known driver of antralization and metaplastic changes. The significantly reduced LPS level is particularly fascinating. As a key component of Gram-negative bacterial cell walls (including *H. pylori*), LPS is a potent trigger of innate immunity. Its decreased systemic levels could suggest increased consumption or sequestration at the site of active mucosal inflammation, a hypothesis that warrants further mechanistic investigation. Crucially, this combination presents a compelling case for a liquid biopsy approach. A simple blood test that could stratify patients based on their risk of harboring pre-neoplastic changes would be a monumental shift from current endoscopic-heavy surveillance strategies.

The detailed analysis of mucin and trefoil factor expression provides a compelling molecular correlate to the histological changes of antralization. The down-regulation of MUC5AC (a mucin characteristic of normal gastric surface epithelium) and the concomitant up-regulation of TFF2, MUC6, and MUC5B (markers associated with antral and metaplastic lineages) offer a precise protein-level definition of this process. This "mucin switch" is not merely descriptive; it provides actionable targets for immunohistochemical diagnostics, potentially improving inter-observer agreement among pathologists and allowing for a more objective grading of antralization severity.[4]

While the identified systemic and tissue biomarker signatures provide promising, minimally invasive avenues for diagnosing antralization,[5–7] this study underscores the necessity for further rigorous validation. A blood-based diagnostic approach utilizing elevated lymphocyte counts and reduced LPS levels, with chromogranin A as an auxiliary negative indicator, could enable more rapid clinical assessment.[8] At the tissue level, the coordinated "mucin/TFF switch" (TFF2, MUC6, and MUC5B up-regulation; MUC5AC down-regulation) may, upon validation, serve as a molecular diagnostic criterion superior to endoscopic observation alone. Furthermore, extending the findings by Liu *et al*.,[9] TFF2 emerges not only as a diagnostic biomarker but also as a potential therapeutic target for intercepting the progression from antralization to gastric cancer. This could facilitate early screening, dynamic monitoring, and even therapeutic modulation of antral gastritis, particularly in the elderly, in whom antralization incidence rises with age, potentially positioning it as a supplementary stage in the Correa cascade. Although previous studies have linked biomarkers such as Pdx-1, BCL-2, and Ki-67 to antral gastritis,[10,11] the underlying regulatory mechanisms remain largely unexplored. Investigating these pathways may furnish a basis for reversing antral gastritis through targeted interventions.

Despite these promising insights, the current study has limitations. The cohort size is modest, underscoring the need for validation in larger, multi-ethnic populations. The strong association with *H. pylori* infection, while consistent with established knowledge, prompts the question of whether these biomarkers retain diagnostic utility in *H. pylori*-negative antralization, an increasingly relevant clinical scenario.[12] Moreover, the study establishes an as-

[*]**Correspondence to:** Lihua Ren and Hong Chen, Department of Gastroenterology, Zhongda Hospital, Southeast University, Nanjing, Jiangsu 210009, China. ORCID: https://orcid.org/0000-0003-1726-3686 (LR); https://orcid.org/0000-0002-7918-4839 (HC). Tel: +86-18262636296 (LR); +86-13951690225 (HC), E-mail: renlihuaxy@126.com (LR); njchenhong66@163.com (HC)

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sociation but not causality between lymphocyte counts, LPS levels, and antralization, pointing toward a critical direction for future mechanistic research. Finally, advancing diagnostic precision will require the integration of more foundational techniques to identify additional specific and sensitive biomarkers, thereby overcoming the limitations of single-marker approaches.

In conclusion, the study by Ye *et al*.[3] successfully bridges a critical gap in gastroenterology by moving the diagnosis of a pre-neoplastic condition from a purely tissue-based morphological assessment to an integrated model incorporating systemic immunological parameters and specific molecular alterations. It provides a foundational biomarker toolkit that aligns perfectly with the goals of modern precision medicine: to enable early, non-invasive detection, improve risk assessment, and facilitate the monitoring of therapeutic interventions for precancerous conditions. This work marks a significant step toward making the "liquid biopsy for gastric pre-neoplasia" a tangible reality.

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Conflict of interest

The authors declare that there are no conflicts of interest.

Author contributions

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