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**Precancerous nature of intestinal metaplasia**

Takeuchi C, Yamashita S, Liu Y, et al. [Precancerous nature of intestinal metaplasia with increased chance of conversion and accelerated DNA methylation](https://gut.bmj.com/content/73/2/255). Gut 2024; 73:255-267. doi: 10.1136/gutjnl-2023-329492

Takeuchi et al., investigated the precancerous nature of intestinal metaplasia (IM). IM occurs when normal stomach lining cells transform into intestinal-like cells and has long been considered a risk factor for gastric cancer. However, whether IM itself is precancerous or paracancerous has remained debatable.

The study involved obtaining gastric mucosal samples from gastric cancer (GC) patients, a GIST (gastrointestinal stromal tumour) patient, and an intestinal sample from a neuroendocrine tumour patient. Gastric and intestinal crypts were prepared from the gastric mucosa for methylation analysis, with alcian blue staining used to differentiate IM from non-IM crypts. IM crypts exhibited a unique DNA methylation profile termed an “epigenetic footprint.” IM cells experienced accelerated induction of aberrant DNA methylation, likely due to increased NOS2 (Nitric oxide synthase 2) expression and resultant heightened DNA methyl transferase activity. This epigenetic instability suggests that IM cells have a higher chance of converting into cancer cells compared to non-IM cells. IM mucosa showed dynamic enhancer reprogramming, particularly in regions associated with higher NOS2 expression. Notably, interleukin-17A, secreted during extracellular bacterial infection, upregulated NOS2 expression in IM-derived organoids.

In summary, IM cells appear to have a precancerous nature, potentially increasing their likelihood of converting into cancer cells. Abnormal NOS2 expression contributes to accelerated DNA methylation induction, highlighting the importance of epigenetic alterations in gastric cancer development. The study provides valuable insights into molecular mechanisms underlying IM’s role in gastric cancer development and disease progression.