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No *H. pylori*, no adenocarcinoma for autoimmune gastritis patients

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Previous studies have noted that atrophic gastritis is the pathological finding most-correlated with the development of gastric adenocarcinoma [1]. Worldwide, the most common cause of atrophic gastritis is chronic infection with *H. pylori*. This general loss of acid secreting parietal cells is associated with the development in the corpus of metaplastic lineages including pyloric metaplasia (also known as spasmolytic-polypeptide-expressing metaplasia (SPEM) or pseudopyloric metaplasia) and intestinal metaplasia as direct sequelae of atrophy. The intestinal metaplasia lineages can develop in both the corpus and the antrum. In contrast with *H. pylori* infection, direct destruction of parietal cells through the production of anti-parietal cell antibodies (most prominently antibodies against the H/K-ATPase) in patients with autoimmune gastritis induces profound atrophy in the corpus, sparing the antrum. While it has been known that autoimmune gastritis is associated with a higher incidence of ECL cell carcinoids in the stomach [2], the risk for adenocarcinoma has been controversial [3, 4, 5]. Many studies have failed to discriminate between cancer arising from *H. pylori* infection and that emanating from the primary results of autoimmune gastritis. This has led to confusion in how these patients should be followed with endoscopy, especially in younger patients.

In this issue of *Gut*, Massimo Rugge and colleagues present the results of an important study which clarifies the relationship of autoimmune gastritis with gastric adenocarcinoma versus carcinoid [6]. This study, which followed prospectively 211 patients with autoimmune gastritis, but without *H. pylori* infection, definitively demonstrates that autoimmune gastritis, on its own, is not a significant precursor for gastric adenocarcinoma. Rather, as reported previously, Rugge, et al. demonstrate that autoimmune gastritis leads to an increased incidence of ECL cell carcinoids in the stomach. These studies provide the most definitive data to date that, in the absence of *H. pylori* infection, the risk of adenocarcinoma is not significant for autoimmune gastritis patients.

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If atrophic gastritis with extensive loss of parietal cells is considered as pre-carcinogenic, why do the *H. pylori* negative autoimmune gastritis patients fail to demonstrate increases in adenocarcinoma? The answers may lie in the precancerous milieu and its influence on gastric lineages. The present investigation reports that pyloric or pseudopyloric metaplasia was far more commonly observed in autoimmune gastritis patients than intestinal metaplasia. This finding is supported by previous investigations [7, 8]. Since pyloric metaplasia/SPEM is considered a direct response to significant gastric mucosal injury [9], these lineages would be considered predominantly reparative. Increasing evidence suggests that pyloric metaplasia gives rise to intestinal metaplasia in the corpus of the stomach (Figure 1). Glands with intestinal metaplasia can be further sub-classified as either incomplete intestinal metaplasia (containing both intestinal lineages and SPEM lineages) or incomplete intestinal metaplasia (containing absorptive and Paneth cell lineages). Incomplete intestinal metaplasia is considered the lesion with the highest risk for progression to adenocarcinoma [10]. The present study does not report whether the intestinal metaplasia observed in autoimmune gastritis patients was complete or incomplete intestinal metaplasia. Nevertheless, a previous study of 20 *H. pylori*-negative autoimmune thyroiditis/gastritis patients found only complete intestinal metaplasia in these patients, compared with patients with gastric adenocarcinoma-associated chronic gastritis, who predominantly demonstrated incomplete intestinal metaplasia. Since incomplete intestinal metaplasia is most highly associated with risk for gastric adenocarcinoma [10], it seems more likely that the stomachs of autoimmune gastritis patients are mostly populated with pyloric metaplasia and complete intestinal metaplasia (Figure 1). In rodent studies, treatment for up to a year with the parietal cell-specific toxic drug DMP-777, which causes profound parietal cell loss without inciting a significant immune infiltrate, induced prominent SPEM without the development of intestinal metaplasia or dysplasia [11]. It thus seems that the presence of a pro-carcinogenic immune infiltrate may be needed. In mouse studies, M2-macrophages have been recognized as critical for the promotion of metaplasia and progression towards dysplasia [12, 13]. It is therefore important that, while prominent macrophage infiltrates were observed in the metaplastic mucosa of adenocarcinoma patients with chronic *H. pylori*-associated gastritis, significantly fewer macrophages were found in the atrophic mucosa of autoimmune gastritis patients without *H. pylori* [7]. Thus, while autoimmune gastritis patients certainly demonstrate prominent lymphocytic infiltrates, the lack of macrophages may lead to a more benign pattern of metaplasia and abrogate against the increased risk for adenocarcinoma. Why chronic loss of parietal cells from *H. pylori* infection versus anti-parietal cell antibodies in autoimmune gastritis would elicit different immune responses remains a mystery.

While autoimmune gastritis may not increase risk of gastric adenocarcinoma, it seems likely that autoimmune gastritis coincident with chronic *H. pylori* infection might provide excess risk for adenocarcinoma. Furthermore, the autoimmune gastritis patients without *H. pylori* infection demonstrate a continued increased risk for carcinoid tumor development (Figure 1). The results presented by Rugge, et al. demonstrate a prominent progression of atrophy and ECL cell hyperplasia to enteroendocrine cell dysplasia over time. While many have speculated that elevated levels of gastrin may be responsible for carcinoid tumor development from histamine-secreting ECL cells, the exact mechanisms driving this

transition remain elusive. Mouse models of autoimmune parietal cell targeted destruction have shown prominent oxyntic atrophy associated with induction of SPEM, but the ability of these models to replicate the ECL cell carcinoids observed in humans remains unclear [14]. Thus, surveillance endoscopy remains important in autoimmune gastritis patients to identify possible progression of ECL cell hyperplasia in atrophic gastric mucosa to frank carcinoid tumors [15]. The study of Rugge, et al. definitively refocuses the care of autoimmune gastritis to eradication of *H. pylori* when present, and screening endoscopy for progression of lesions towards carcinoid neoplasia.

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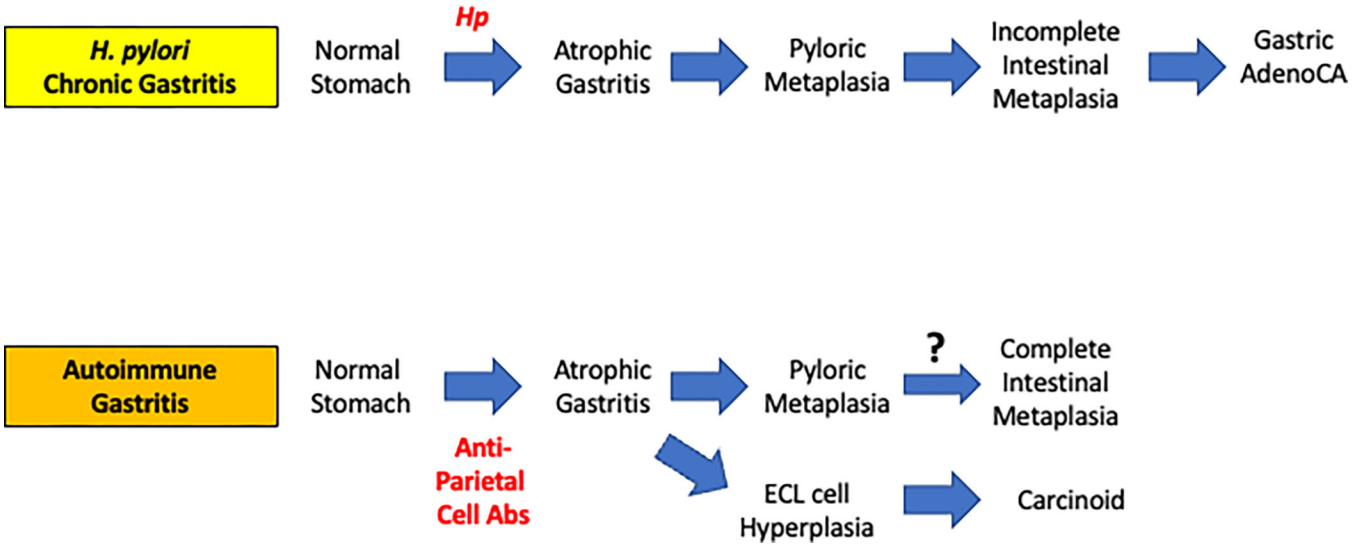

Figure 1: Comparison of lineages changes in *H. pylori*-associated and autoimmune gastritis-associated atrophic gastritis.

Chronic *H. pylori* (*Hp*) infection induces parietal cell loss (atrophic gastritis) followed by induction of pyloric metaplasia. Continued inflammation induces incomplete intestinal metaplasia, which can then develop into gastric adenocarcinoma. In autoimmune gastritis patients, anti-parietal cell antibodies cause atrophic gastritis. Loss of parietal cells leads to subsequent induction of pyloric metaplasia which may progress to complete intestinal metaplasia. Additionally, the atrophic milieu in autoimmune gastritis patients can promote the evolution of ECL cell hyperplasia and eventually carcinoid tumors.