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Long-term proton pump inhibitor administration induces atrophic corpus gastritis and promotes adenocarcinoma development in Mongolian gerbils infected with *Helicobacter pylori*

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The association between chronic active gastritis and pre-neoplastic conditions as well as invasive cancer of the stomach was established several decades ago. The risk of progression depended on the severity and distribution of gastritis, with cancer in particular occurring in subjects with pan-gastritis. Subsequently, *Helicobacter pylori* was recognized as the primary cause of chronic active gastritis, and it was demonstrated that the pattern of gastritis corresponded with the colonization pattern of *H. pylori*. We and others then showed both in animals and in humans that this pattern of colonization and associated gastritis primarily depended on the level of acid output (1–2). Although this hypothesis was widely accepted, it led to intense debate when dealing with the safety of long-term treatment with profound acid suppressors. An elegant, long-awaited study from Japan in this issue of Gut provides compelling evidence that the pattern of *H. pylori* colonization depends on acid output and that this influences the long-term progression to neoplasia (3).

The current study was based on experiments in gerbils, one of the well established animal models for the study of *Helicobacter* spp.-induced gastric disease (4). Gerbils, used sparingly for biomedical research, were first reported as a model for experimental *H. pylori* infection in 1991 (5). Interestingly, the gerbil has been shown to have particular relevant features that can be used to address whether *H. pylori* can induce gastric cancer. Japanese investigators have noted intestinal metaplasia, atrophy, and gastric ulcers in gerbils experimentally infected with *H. pylori* (6–7). Following these findings, others noted that gerbils infected with *H. pylori* from periods ranging from 15 to 18 months develop gastric adenocarcinoma (8–9). The gastric cancers were clearly documented histologically. Vascular invasion and metastases were not observed in either study.

The histological progression of *H. pylori* associated disease in the gerbil closely resembles that observed in humans, including early appearance of intestinal metaplasia, well-differentiated histologic patterns of gastric malignancy, and antral location of the gastric

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cancers. The development of cancer in the gerbil is also preceded by invagination of atypical glands (cystica profunda) into the submucosa. The association with gastric ulcers in this model continues to be of interest, given clinical studies in human patients indicating a link between gastric ulcer disease and gastric cancer (10). Although most of the tumors in the *H. pylori* gerbil model originate in the pyloric region of the stomach, significant changes in the oxyntic mucosa consistent with chronic atrophic gastritis are also observed. Glandular tissue in the gastric body and fundus are replaced by atrophy and hyperplastic epithelium of the pseudopyloric type. A similar type of gastric atrophy (loss of oxyntic glands and neck cell hyperplasia) has also been reported in *H. felis* or *H. pylori*-infected C57BL mice (11–12).

The gerbil appears to be uniquely susceptible to *H. pylori*-induced gastric neoplasia, and further characterization of the gerbil model has provided important clues on gastric cancer progression and host-bacteria interaction. The unusual susceptibility of this animal species to gastric cancer using fairly standard *H. pylori* strains underscores once again the overriding importance of host factors in determining the outcome from gastric *Helicobacter spp.* infection (13). Further, a possible role for altered gastrin physiology in the pathogenesis of gastric cancer has been raised by several recent studies. In Mongolian gerbils, *H. pylori* leads to marked elevation of serum gastrin levels which coincide temporally with increases in gastric mucosal proliferation rates (14). This is consistent with experiments in inbred (FVB/N) mice that were rendered moderately hypergastrinemic through an insulin-gastrin (INS-GAS) transgene. In this model there is increased mucosal proliferation and progressive atrophy, and gastric carcinomas develop in20 months old INS/GAS mice (15). Infection of these hypergastrinemic mice with *H. felis* and *H. pylori* accelerates tumorigenesis, with the majority (85%) of infected male mice developing gastric cancer within 8 months after colonization. We recently reported that this chronic, progressive process is enhanced by co-colonization with enteric flora (16).

Using this well described and reproducible gerbil model, Japanese investigators have conducted a very important study, examining the potential effect of PPI therapy on progression of *H. pylori* associated disease (3). The male gerbils were divided into four groups: *H. pylori* (ATCC43504)-positives and –negatives, with and without administration a PPI (omeprazole 100 mg/kg body weight/day). At the end point of the 6 months experiment, the authors provided detailed analysis of gastric pathology including morphometric severity of parietal cell loss. The authors made a concerted effort to address confusion in the literature with respect to what constitutes a “gastric adenocarcinoma” in a Mongolian gerbil model and how to differentiate an “invasive carcinoma” from “heterotopic glands” that are frequently encountered in these models during the early course of the disease. The ability to differentiate glandular herniation into the submucosa from the true invasion is an important consideration in evaluating rodent models of *H. spp*. induced gastric cancer. Indeed with these histopathological criteria in mind the results were remarkable and provide considerable support for previously published literature in humans. *H. pylori* –negative male gerbils did not develop gastritis, metaplasia, or cancer irrespective of PPI treatment. *H. pylori* –positive gerbils all developed gastritis, and most also developed metaplasia during the later stages of disease. Treatment with omeprazole in *H. pylori* –positive animals accelerated progression to atrophy and enhanced hypergastrinemia, resulting in a significantly increased incidence of

gastric cancer (3). The authors emphasize that hypergastrinemia might be promoting the development of *H. pylori* gastric cancer. Given gender susceptibility to *H. pylori* associated gastric cancer in humans and rodent models, additional studies using *H. pylori* female gerbils on chronic PPI theraphy should provide additional interesting insights.

Overall, the findings in the current paper support previous findings by us and others showing the increased risk of gastric atrophy in *H. pylori* infected patients on PPI therapy (2, 17–19). In humans, it remains to be shown whether chronic PPI therapy in *H. pylori* infected individuals also increases the further progression to metaplasia, dysplasia and neoplasia. These studies will require longer term follow-up of this subset of patients. In the meantime, the current findings in this paper support the argument regarding the importance of considering *H. pylori* eradication in patients on long-term PPI treatment to cure gastritis, lower gastrin levels, and prevent progression to atrophy, dysplasia and gastric cancer. This recommendation is consistent with European guidelines on *H. pylori* treatment in humans (20).

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