Pathobiology of the Gastric Mucosa

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I.   One of the most interesting developments in our knowledge of gastric mucosal pathobiology has been the recognition of the relationship between *Helicobacter* infection, chronic gastritis, induction of lymphoid follicles in the mucosa (MALT)[c] and gastric lymphoma. Difficulties in distinguishing histologically between florid reactive lymphoid hyperplasia, sometimes termed "pseudolymphoma," and lymphoid neoplasia have long been recognized. More recently, monoclonality of lymphoid proliferations and the presence of gene rearrangements have been taken as evidence of transformation to a neoplastic state, and molecular techniques have increased our sensitivity over histology in detecting these lesions. However, the demonstration by Isaacson's group, subsequently confirmed by others, that early MALT lymphomas, diagnosed by morphologic and molecular criteria are not autonomous but are driven by specific *Helicobacter* antigens in the presence of T cells and regress upon elimination of the *Helicobacter* infection, is both intriguing and important [1, 2]. First, it has altered our management of patients with early MALT lymphomas of the stomach. Second, it raises as yet unanswered questions about the long-term outcome of these lesions: for example, following regression of the initial tumor, does a population of "tumor" cells remain in the mucosa with the potential for re-emergence if the bacterium is incompletely eradicated or if reinfection occurs, as a few early reports suggest [3]. How can we distinguish reliably between "early" or antigen-dependent lymphoid proliferations and those that are truly autonomous and that, therefore, will not respond to antibiotic therapy? Moreover, it prompts a semantic question concerning the definition of neoplasia: recognizing that its development is a multi-step process, how do we now define when neoplastic transformation has occurred in this setting? Are these early MALT "lymphomas" true neoplasms, or are they merely reactive monoclonal lymphocytic reactions to a persistent foreign antigen, best defined as pre-neoplastic? Finally, it raises fundamental questions as to what molecular changes occur in mucosal B-cells during the progression from reactive gastritis to low-grade and high-grade maltoma and how *Helicobacter pylori* elicits them. The availability of a mouse model of *Helicobacter*-induced gastric maltomas offers an opportunity to compare the roles of products generated by *Helicobacter* and those produced by inflammatory cells in a similar system [4]. In association with studies on readily accessible human gastric biopsy tissue, this may lead to elucidation of the pathogenesis of this interesting lymphoproliferative process.

II.   The morphologic changes that occur in the mucosa affected by chronic gastritis have been well recognized for many years, although the histologic terminology has been a matter of some dispute. Chronic inflammation, as seen in *Helicobacter*-associated and

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[c]*Abbreviations:* MALT, mucosa-associated lymphoid tissue; ECL, enterchromaffin-like (cell); GRP, gastrin-releasing peptide; MEN, multiple endocrine neoplasia.

autoimmune gastritis, may lead to profound changes in the acid secreting mucosa, culminating in complete loss of several functionally important components of the epithelial cell population, notably the chief and parietal cells. The process by which this occurs is poorly understood, and it is not clear why residual epithelial stem cells fail to differentiate in a normal fashion. Moreover, it is not known with certainty if regeneration of acid-secreting glands can occur in this setting once the inflammatory processes are ablated, or if gastric atrophy is a fixed condition, as one study suggests, in which no regression of atrophy was detected during up to one year following eradication of *Helicobacter* [5]. A remarkable feature of the atrophic gastric mucosa is its propensity to develop intestinal metaplasia. Although several varieties of intestinal metaplasia are described, all are characterized by epithelial differentiation that is more akin to that seen in the small intestine (often with Paneth cells, absorptive enterocytes and goblet cells) or in the large intestine, as if the differentiation program in the stem cell had been switched. Whether such differentiation packages are under the control of homeobox genes is not known. However, elucidation of the mechanisms controlling this process is important, as it is well-recognized that intestinal metaplasia of the incomplete or colonic type is a precursor of the intestinal type of gastric andenocarcinoma. Moreover, atrophic gastritis is itself a usual prerequisite for enterochromaffin-like (ECL) cell hyperplasia or neoplasia in the mucosa of the gastric body/fundus.

III. Gastric epithelial dysplasia, defined as an unequivocal neoplastic transformation, is being increasingly recognized. At present, the diagnosis of dysplasia rests on morphologic features, and it is commonly evaluated as being high- or low-grade. The management of patients with a diagnosis of gastric dysplasia is still a matter of controversy. Weinstein has recommended that all patients with this diagnosis should have extirpation of the dysplastic mucosa, either by endoscopic mucosectomy or by resection, following careful mapping of its extent by endoscopy with multiple biopsies [6]. It is generally accepted that gastrectomy is advisable in cases of high-grade gastric dysplasia. However, since there is much subjectivity in diagnosing dysplasia, and in particular in distinguishing between low-grade dysplasia and reactive atypia, many favor a more conservative approach in cases of low-grade dysplasia, with careful follow-up, repeat evaluation with multiple biopsies and independent review of the biopsy material by an experienced gastrointestinal pathologist. If low-grade dysplasia is confirmed, extirpation would, at present, appear to be the treatment of choice, since low-grade dysplasia has been reported to progress to carcinoma within only two years of diagnosis [7].

IV. While it is well recognized that ECL cells are increased in prominence in the mucosa of the body/fundus in atrophic gastritis, there is dispute as to how this occurs. Possibilities include proliferation of ECL cells, proliferation of precursor stem cells in the gastric gland necks, a shift in the differentiation spectrum of existing uncommitted epithelial cells towards the ECL phenotype, increased longevity of ECL cells (e.g., by inhibition of ECL cell apoptosis) and selective destruction of other epithelial cell types resulting in a relative increase of ECL cells [8]. Loss of other epithelial elements in atrophic gastritis complicates quantitation of absolute ECL cell numbers or mass, but in patients with severe hypergastrinemia (1,000-10,000 pg/ml) of other etiologies, there is a clear increase in volume density, cross-sectional area and number of profiles of ECL cells in microscopic sections [9]. No evidence of ECL cell proliferation was found in the normal human stomach or in gastritis in a recent study in which double-staining with the endocrine cell marker chromogranin A and the proliferation marker Ki67 was performed, suggesting that the ECL cells may be terminally differentiated [10]. However, if ECL cell precursors that had not yet synthesized chromogranin were proliferating, they would not have been detected

in this analysis. It has been suggested that in chronic gastritis, when epithelial cells expressing class II antigens are being subjected to attack by cytotoxic T-cells, the ECL cells, which lack these antigens, may survive unimpaired. Such a mechanism might account for the increased prominence of ECL cells in chronic gastritis, especially the micronodular form, but it would not explain the diffuse hyperplasia observed in patients with gastrinoma and severe hypergastrinemia. It seems likely, therefore, that gastrin has an effect either on proliferation of ECL cells or their precursors, or on the longevity of differentiated ECL cells. The reversibility of ECL cell hyperplasia in rats in which hypergastrinemia is controlled supports this concept. Endocrine cells generally are long lived and have a proliferation rate that is low relative to many other cell populations, and, therefore, a very slight (and potentially undetectable) increase in the rate of proliferation, or a subtle increase in longevity of these cells, could have marked effects on their numbers. Nevertheless, at some point in the development of ECL cell neoplasia it is evident that a proliferative process must occur, leading to invasion through the muscularis mucosae, to the development of aggregates of these cells in the sub-mucosa and ultimately to metastatic dissemination. Further clarification of these events is needed.

ECL carcinoids are exclusively found in the nonantral mucosa of patients with type A autoimmune atrophic gastritis or with the multiple endocrine neoplasia (MEN-1) syndrome (i.e., in the presence of hypergastrinemia and a genetic predisposition or immunological factors). They are of essentially benign nature. In contrast, sporadic gastric carcinoids are mostly multihormonal and gastrin independent (i.e., found in normogastrinemic patients without any background gastropathy) [11, 12]. They are not restricted to the nonantral mucosa and often behave like neuroendocrine carcinomas.

Omeprazole therapy results in hypergastrinemia, but to date, there have been no reports of the development of carcinoidosis in patients using this medication. In one detailed study of the effects of five-year omeprazole therapy, ECL cell hyperplasia occurred in a proportion of patients but seemed to be more closely associated with chronic gastritis than with the use of the drug; in no case was ECL cell dysplasia observed [13]. In chronic gastritis, the increase in ECL cells typically develops over a very long period of time. It is possible that more prolonged use of omeprazole will be seen to have similar effects. A minority of patients on omeprazole have significant hypergastrinemia (500-800 pg/ml). Usually, they also have advanced atrophic gastritis and may, therefore, be at increased risk of ECL cell proliferation. It has been suggested that *Helicobacter* should be eliminated in these patients since it increases the rise in gastrin due to omeprazole.

V.   The complex components of the interaction of *H. pylori* with the gastric mucosa are beginning to be dissected and unraveled. Evidence is accumulating that down-regulation of somatostatin may be an important factor in this process [14]. Decreased secretion of somatostatin would mean de-inhibition of the G-cells and, thus, explain the hypergastrinemia of patients with antral gastritis due to *H. pylori*. Whether this occurs directly, for example through production of an H_3 agonist as suggested by Megraud, as a secondary response to inflammation as seen in the rectum in proctitis, or as a result of the effect of virulence factors such as *cagA* and *vacA* on D-cells, is unknown. Also, direct stimulation of the gastrin producing G-cells by inflammatory cytokines has been recently described [15].

As more has been learned about the apparent virulent factors of *H. pylori*, it has been become evident that there is marked variation in their expression in different strains; this, and the potential for studying strains deleted of specific virulence factors, opens the way for distinguishing between those factors that are significant in the pathogenesis of chronic gastritis from those that are not, and for investigating the mechanisms involved. On the other hand, information that is emerging concerning the inflammatory response to *H.*

pylori, both in terms of cellular elements and cytokines, will also contribute to our understanding of the processes by which mucosal injury is mediated and may contribute to the development of strategies for vaccine production. In this context, it has been suggested that mucosal injury in *H. pylori* gastritis is due to an inappropriate Th1 response, and that if a Th2 response is provoked the infection could be satisfactorily cleared without significant residual mucosal damage [16].

In patients with duodenal ulcer and *H. pylori* gastritis, unstimulated acid secretion returns to normal following *Helicobacter* eradication [17]. Currently, results relating to maximally stimulated acid secretion in duodenal ulcer patients are conflicting. Data from patients without duodenal ulcers are not available. After *Helicobacter* eradication, both the response of gastric acid secretion to gastrin releasing peptide and the serum gastrin levels decrease, though the fall in gastrin is markedly variable from patient to patient. The reasons for this variability in the gastrin response are unclear, but may be related to *Helicobacter* load, the duration of infection or the severity of the gastritis. Gastrin releasing peptide is a neurotransmitter (not a hormone) and has the capacity to stimulate gastrin and somatostatin secretion if infused intravenously. In the case of *H. pylori* infection (i.e., impaired somatostatin response), GRP has an unrestrained effect on gastrin and gastric acid secretion, which is reversed after *H. pylori* eradication [18].

Despite the remarkable advances in our knowledge of the pathobiology of the gastric mucosa since the discovery of *H. pylori*, the complexities of the immune response to this pathogen and of the cross-talk between the mucosal inflammatory, stromal and epithelial cells and their cytokines and hormones remain a formidable challenge.

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