

2nd International Conference on Gastroenterology & Urology: Gastrin may mediate the carcinogenic effect of *Helicobacter pylori* (HP) on the stomach - Helge Waldum - Norwegian University of Science and Technology

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Gastrin is central to gastric carcinogenesis, and being a peptide hormone it can only directly affect gastrin receptor cells. Gastrin induces histamine release from the ECL cell, and its proliferation. Any disease that has long-term hypergastrinemia in both animals and humans predisposes to gastric malignancy. A direct carcinogenic effect of Hp on the stomach mucosa may be excluded as infection in the antrum alone, on the contrary, protects against stomach cancer. Moreover, even with inflammation in the oxyntic mucosa, a predisposition to gastric cancer necessitates the development of atrophic gastritis. Where gastric hypoacidity by secondary microbes predisposes secondary microbiological infections to gastric cancer, tumors should be expected to develop across the stomach, not just in the oxyntic mucosa.

Accordingly, the pathogenic factor for carcinoma development secondary to Hp infection could be hypergastrinemia itself. If so, the sole target cell established for gastrin, the ECL cell, must play a significant role in gastric carcinogenesis. This was a matter of peculiar controversy and it was even claimed that there was no proliferation of the ECL cell in man although it was clearly shown that this cell proliferates in rodents. Since the ECL cells occur in clusters in patients with hypergastrinemia, the reluctance to accept that the ECL cell does divide was difficult to understand. It was subsequently accepted that the ECL cell was proliferating and producing gastric NETs. In general, however, the role of ECL cells in gastric carcinogenesis was denied, except for NE carcinomas (NECs). Nevertheless, gastric NETs and gastric carcinomas occur both with increased frequency in patients with autoimmune gastritis, and with enhanced sensitivity when applying immunohistochemistry we may demonstrate that gastric carcinomas expressed NE markers in patients with pernicious anemia. In a broader analysis of gastric carcinomas in general, we might infer that a small proportion might actually be

categorized as NE tumors, and then those categorized as diffuse according to Laurén in particular.

Among diffuse-type gastric carcinomas, the NE differentiation in the signet ring subgroup is particularly pregnant. These carcinomas are PAS positive, but don't express clear mucin markers. It is noteworthy that experts in the classification of tumors tend to rely more on unspecific histochemical methods than on more specific ones such as immunohistochemistry and in-situ hybridization. Based on our results it appears that the bulk of diffuse type gastric carcinomas can develop from secondary ECL cells to long-term gastrin hyper-stimulation. Though some intestinal type gastric carcinomas also express NE markers, most do not. Nonetheless, gastrin and the ECL cell may be involved in the tumor genesis of intestinal type gastrin carcinomas by releasing not only histamine but also a factor such as REG I which has a stimulating effect on the proliferation of stem cells and could therefore predispose to carcinoma growth. In addition, as noted earlier, children born with an irregular homozygous mutation in one of the genes coding for the proton pump and thus becoming anacidic and hypergastrinemic from birth developed ECL cell NETs and gastric carcinoma at a young age further supporting the central role of gastrin and the ECL cell in gastric carcinogenesis. Similarly, the latest epidemiological studies that identify those patients who have used long-term PPIs also support such a view have increased risk for gastric cancer. A combination of Hp infection and PPI treatment leads to an rise in additives, at least in serum gastrine. The gastrin receptor is expressed in both diffuse and intestinal cancer cells, which supports implicitly the presence of a gastrin receptor on the oxyntic stem cell as well. Nevertheless, it has been confirmed quite recently that the enterochromaffin (EC) cell in the small intestine, a cell closely related to the ECL cell, was involved in stem cell dynamics suggesting a

potential direct role for the ECL cell also in intestinal type of gastric cancer. Interestingly, Goetze and colleagues found that a majority of gastric carcinomas located to different sections of the stomach expressed both gastrin and gastrin receptor which may suggest a stimulating autocrine loop. In the same line, Hayakawa and colleagues described that antral stem cells expressed the gastrin receptor that could be stimulated by progastrins but not by amidated gastrins, and that this stimulation had a role to play in carcinogenesis. It is difficult to imagine, however, that the same gastrin receptor would have affinity for amidated gastrin at certain locations and not to progastrins and bind progastrin and nonamidated gastrins at other cellular locations. A gastrin receptor on antral cells (G cells) would be expected to be inhibitory and not stimulating from a biological point of view. In any way, it needs to be shown *in vivo* before a role of autocrine stimulation and progastrins can be accepted in antral carcinogenesis.

It is firmly established that HP infection plays a central role in the pathogenesis of gastric cancer (NE J Med 1991; 325:1127-31) although the mechanism for the carcinogenic effect of HP infection is not clarified. Even before the studies on HP infection, it was well-known that gastric cancer occurred in stomachs with gastritis and particularly atrophic gastritis (JAMA 1962; 179:311-15, Acta Med Scand 1960; 166:455-74). It was also known that patients with duodenal ulcer did not develop gastric cancer (Scand J Gastroenterol 1990; 25:1223-26). These patients never have atrophic gastritis in the oxyntic mucosa as shown by their normal or increased secretion of gastric acid (Gut 1965; 6:427-35). Furthermore, HP infection *per se* seems not to dispose to gastric cancer as mice infected at an early stage leading to tolerance for HP and thus no gastritis in spite of HP infection, do not develop premalignant changes (Gastroenterology 2011; 140: 199-209). Thus, HP infection predisposes to gastric cancer by inducing gastritis. However, the gastritis itself does not lead to cancer as patients with duodenal ulcer have gastritis confined to the antral mucosa but have a reduced risk of gastric cancer (Scand J Gastroenterol 1990; 25:1223-26). Therefore, the carcinogenic effect of atrophic oxyntic mucosal

gastritis due to HP infection must be due to a consequence of atrophic gastritis, for instance increased serum gastrin. It was recently reported that non-atrophic HP induced gastritis in the oxyntic mucosa also could lead to gastric cancer (Int J Cancer 2012; 131:2632-42). However, most of these patients had hypertrophic rugal gastritis, a condition known to be accompanied with hypergastrinemia. It is true that patients with duodenal ulcer have a slight hypergastrinemia (Lancet 1989; 1:1167-68) sufficient to induce hypersecretion of acid due to the potency of gastrin (Life Sci 1990; 46:453-59) but patients with duodenal ulcer due to HP infection have never a marked hypergastrinemia because of the high acidity of the gastric content inhibiting gastrin release. We proposed already in 1993, that the carcinogenic effect of HP infection could be due to hypergastrinemia (Gastroenterology 1993; 105:1264-66), but this point of view has been met with hostility or neglect. We subsequently showed that the ECL cell and not the parietal cell had the gastrin receptor (Scand J Gastroenterol 2001; 36:1128-33). Hypergastrinemia in rodents had previously been shown to induce malignant gastric tumours which initially were classified as adenocarcinomas and subsequently were realized to be ECL cell derived (Digestion 1986; 35, suppl.1:42-55). During the last 25 years we have examined whether human gastric carcinomas also could have been misclassified and that the ECL cell and therefore gastrin also could be of importance in human gastric carcinogenesis (Eur J Gastroenterol Hepatol.1991; 3:245-49, Cancer 1998; 83:435-44, APMIS 1999; 107:1085-92, Histochem J 2000; 32:551-56, APMIS 2002; 110:132-39, J Histochem Cytochem 2006; 54:615-21). Quite recently we could show that the subgroup of gastric carcinomas of diffuse type according to Lauren expresses mRNA for chromogranin A, but not for mucins, further supporting the view that these carcinomas are of neuroendocrine, and more specifically of ECL cell origin, and thus incriminating gastrin in their pathogenesis.