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Gastrin may mediate the carcinogenic effect of *Helicobacter pylori* (HP) on the stomach

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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.

Biography

Helge L. Waldum became M.D. in 1971 at the age of 25 years (University of Oslo, Norway, with a grade reported to the King) and completed two Ph.D.s (University of Tromsø, Norway, 1980 and Université de Paris, France, 1993) and is a specialist in Internal Medicine and Gastroenterology, 1980).

He is Professor at Norwegian University of Science and Technology, Trondheim Norway from 1986 and Head of Department of Gastroenterology and Hepatology, University Hospital of Trondheim, Norway for more than 20 years. He has published more than 350 papers and supervised 18 candidates to Ph.D. Research related to regulation of gastric acid secretion, gastrin and in its target cell, the ECL cell. The role of the ECL cell in physiology, patophysiology and carcinogenesis and the classification of gastric carcinomas have been of particular interest.

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