

**2nd International Conference on Gastroenterology & Urology: Classification of gastric carcinomas - Helge Waldum
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The prevalence of gastric cancer has decreased but poor prognoses. Better information about carcinogenesis and the cells of origin should be obtained to enhance diagnosis. Usually, stomach cancer is localized to one of the three mucosae; cardiac, oxyntic, and antral. In addition, not only the stem cell but also the ECL cell can proliferate and cause tumours. The stem cell is likely to give rise to an intestinal type, whereas in the diffuse type, the ECL cell may be significant. Gastrin elevation may be the carcinogenic factor for *Helicobacter pylori*, as well as the recently identified increased risk of gastric cancer due to treatment with proton pump inhibitors. Nevertheless, the stomach contains at least two distinct mucosae (oxyntic and antral), which makes it unusual that in most cases carcinomas arising in the stomach are lumped together as gastric carcinomas. In general there was no attempt to differentiate between antral and oxyntic mucosae based carcinomas. The boundary between oxyntic mucosa and antral mucosa is however not as sharp as previously thought. Generally speaking, if any distinction has been made between gastric carcinomas based on location, this has been made between proximal tumors located in the heart region and distal tumors including those in the oxyntic and antral mucosa. The mature cells differentiated from the stem cell mainly do not divide although there is some evidence of proliferation of certain chief cells playing a role in the development of the so-called polypeptide-expressing metaplasia (SPeM).

In addition, in the gastric mucosa several different types of cells have the capacity to differentiate and thus give rise to carcinomas. In addition to the stem cells present in both the oxyntic and the antral mucosa, neuroendocrine (NE) cells can also differentiate into the other epithelial cells. The ability of NE cells to divide has been shown most convincingly for the enterochromaffin-like (ECL) cell producing histamine which is one of the most abundant NE cells in the

stomach. This ability has also been indirectly indicated by the case reports describing ghrelinomas (developing from A-like cells)

There are many different systems for classifying the gastric carcinomas. As defined by Borrmann, classification may be based on gross appearance (polypoid, fungal, ulcerated, and infiltrative). Gastric carcinomas exhibit microscopic similarity to intestinal mucosa; a feature used in most of the classification schemes based on microscopy. The classification system of the World Health Organization (WHO) distinguishes between subtypes of the papillary, tubular, mucinous and signet-ring cells. Ming finally classified gastric carcinomas into two types, those with an expanding and those with a pattern of infiltrative growth. Improvement in molecular technology has made it possible over the past decades to determine mutations in carcinomas and thus classify these findings. Tumor mutation analyzes can guide the selection of treatment strategies, especially when there are driver mutations. Analyzes of mutations do not usually give indication of the origin cell. It is possible that specific mutations can usually be important in carcinogenesis, and occur during tumorigenesis in various cell types. Therefore, both mutation analyzes of malignant tumors as well as actual marker analyzes with regard to the cell of origin and its regulation of growth would be useful with regard to both treatment prophylaxis and prevention of the carcinomas. The stem cell in oxyntic mucosa is located in the glands' isthmus region and causes all types of exocrine cells in the oxyntic mucosa to develop. The mature cells differentiated from the stem cell principally do not divide although there is some evidence for proliferation of some chief cells playing a role in the development of the so-called spasmolytic polypeptide-expressing metaplasia (SPeM).

The origins of the endocrine cells in the oxyntic mucosa are unknown. This is in contrast to the antral

mucosa where the stem cell has also been shown to grow into endocrine cells, experimentally. Stem cells located in the antral mucosa are likely to develop into all types of epithelial cells in the glands, including NE cells consisting of cells similar to G-, D- and A-like.

Malignant epithelial tumors of the stomach have traditionally been classified as adenocarcinomas based upon glandular growth pattern and/or mucin positivity. Mucin positivity has been assessed by histochemical methods (PAS and Alcian Blue), both methods being unspecific. However, it is not easy to distinguish between neuroendocrine and exocrine derived malignant tumors as evidenced by the reclassification of gastric tumors occurring in the African rodent *Mastomys* by Soga from adenocarcinoma to neuroendocrine ECL cell carcinomas (GANN Monograph 1969; 8:15-26), and by the similar reclassification of the malignant oxyntic tumors found in mice/rats after long-term dosing with inhibitors of acid secretion by Havu in the middle of the eighties (Digestion 1986; 35 Suppl 1:42-55). We asked ourselves whether such a misclassification also could occur in man. In our first study (Eur J Gastroenterol Hepatol 1991; 3:245-49) we found that some of the tumor cells in carcinomas of diffuse type according to Lauren showed neuroendocrine differentiation and, interestingly, that virtually all tumor cells were positive for chromogranin A in a cancer of a young woman with a 2-years history of flushing after meals (thought to be food allergy, but was histamine flushing). We then went on to collect tumor samples from the operation theater together with blood for serum analyses. In 1998, we published our second study (Cancer 1998; 83:435-44) where we confirmed that a proportion of gastric carcinomas of diffuse type expressed neuroendocrine markers. Later, we used immunohistochemistry with tyramide signal amplification and confirmed that a large portion of gastric carcinomas of diffuse type actually were of neuroendocrine origin (Histochem J 2000; 32:551-56). Interestingly, virtually all carcinomas taken from patients with long-term marked hypergastrinemia (atrophic gastritis with or without pernicious anemia) could be classified as ECL derived (APMIS 2002; 110:132-39). By using chromogranin A immune

electronmicroscopy we could show that tumor cells contained secretory granules (Appl Immunohistochem Mol Morphol 2010; 18:62-68.) In recent time we have applied in situ hybridization by the use of a new commercially available method (RNAscope) which has improved sensitivity and specificity compared to conventional in-situ hybridization (Appl Immunohistochemical Mol Morphol 2013; 21:185-89). We have confirmed neuroendocrine mRNA expression in signet tumor cells, but no expression of mRNA for different mucins. In conclusion, gastric carcinomas of diffuse type are of neuroendocrine and more specifically of ECL cell origin. PAS positivity in these tumor cells is not due to mucin.