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Molecular targets and biological modifiers in gastric cancer

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The overall survival of gastric cancer patients remains poor despite efforts and advances in its prevention, diagnosis, and treatment. The development of new therapies is crucial for the effective control of this disease. An increasing number of genetic and epigenetic alterations have been associated with distinct histological types of gastric cancer. In this review, we will discuss the involvement of E-cadherin, *EGFR*, *ERBB2*, MMR genes, *KRAS*, and *PIK3CA* in the development and progression of gastric cancer and their role as biomarkers or as novel putative targets for therapy.

Gastric cancer (GC) is one of the most common forms of cancer in Europe.[1] In 2000, there were 192,000 new cases with 158,000 deaths. In Southern Europe, Portugal shows the highest incidence of GC (as estimated by GLOBOCAN 2002).[2] Despite advances in prevention and diagnosis, the overall outcome of the patients has remained poor. The overall 5-year survival is around 23%. This is largely due to the advanced stage of disease at presentation, so that most patients only receive palliative treatment. Moreover, in the various multimodal therapy regimens that are used to improve the patients' prognosis, the majority of patients do not respond to treatment. In summary, the prediction of therapy response in GC is very limited, and the high prevalence of incurable disease produces a large burden on patients, which has a huge effect on health care resources. In this review, we will focus on putative alternative therapeutic strategies based on the identification of molecular targets and biological modifiers in GC.

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Overview of GC

Carcinomas of the stomach are very heterogeneous from the morphologic standpoint. This heterogeneity is amply reflected in the diversity of histopathological classifications on record, which are based on different approaches: histologic profile, degree of differentiation, pattern of growth, and histogenesis.[3]

Laurén's classification[4] individualizes two main types of gastric carcinoma—intestinal and diffuse—which display different clinicopathologic profiles and often occur in distinct epidemiologic settings. Intestinal carcinoma is more prevalent in elderly persons of the masculine gender, whereas diffuse carcinoma tends to occur in younger individuals, mainly females, and frequently depicts hereditary conditioning. The incidence of intestinal carcinomas is steadily decreasing in most countries, in contrast to diffuse carcinomas, whose incidence is quite stable or even increasing.[5] The classification proposed by Carneiro and coworkers[6] highlights the heterogeneity of gastric carcinoma, individualizing mixed and solid carcinomas. By univariate analysis, the survival of the patients with mixed carcinomas

was shown to be significantly worse than that of patients with pure histologic type of tumors. In a multivariate analysis using the Cox's model, Carneiro's classification kept its independent prognostic significance, emerging as the second most important factor after TNM staging and before venous invasion.[6]

About 90% of GC cases appear in a sporadic setting, whereas familial clustering is observed in the remaining 10%.[7] Of these, only 1% to 3% is hereditary.[8]

Among the cases with familial aggregation of GC, several situations can be identified: cases, in which the histopathology of the tumors is unknown, simply designated as familial GC (FGC) and cases in which it is possible to have information on the histopathological type of one or more GCs. The latter group encompasses specific syndromes/diseases as follows: hereditary diffuse GC (HDGC), familial diffuse GC (FDGC), and familial intestinal GC (FIGC).[9]

Histopathological features of HDGC

As fully described below, truncating germline E-cadherin gene (*CDH1*) mutations were identified in 1998 as a causal genetic defect for HDGC by Guilford and coworkers.[10] Shortly afterward, the International Gastric Cancer Linkage Consortium (IGCLC) defined the following criteria for identification of HDGC families: (1) two or more documented cases of diffuse GC in first/second-degree relatives, with at least one diagnosed before the age of 50; or (2) three or more cases of documented diffuse GC in first/second-degree relatives, independent of age.[11] Furthermore, the IGCLC recommended that carriers of *CDH1* truncating germline mutations should be offered the possibility of being submitted to intensive screening and/or prophylactic gastrectomy.

Current knowledge on the morphologic steps underlying the development of HDGC stems from detailed studies performed in stomachs that were totally mapped, encompassing prophylactic gastrectomy specimens, and total gastrectomies performed in patients referred from chromoendoscopic surveillance programs.[12-18] In most specimens, at least one focus of early invasive diffuse GC was identified. In North American families, early invasive carcinoma was not restricted to any topographic region in the stomach: foci were identified from cardia to prepyloric region, without evidence of antral clustering.[12,13] In New Zealand Maori families, a predilection was observed for the occurrence of early invasive carcinomas for the distal stomach and the body-antral transitional zone.[15,16] Reasons for the different anatomical localization of the cancer foci in the aforementioned studies remain to be clarified.

As precursors of the invasive cancers, two distinct types of lesions were identified in prophylactic gastrectomies: (1) in situ signet ring cell carcinoma, corresponding to the presence of signet ring cells within basal membrane, generally with hyperchromatic and depolarized nuclei (Figure 1); and (2) pagetoid spread of signet ring cells below the preserved epithelium of glands/foveolae (Figure 1).[14]

Model of development of HDGC

On the basis of the findings in prophylactic gastrectomies, a model for the development of diffuse GC in E-cadherin mutation carriers was proposed,[14] encompassing the following lesions: mild nonatrophic gastritis, in situ signet ring cell carcinoma, pagetoid spread of

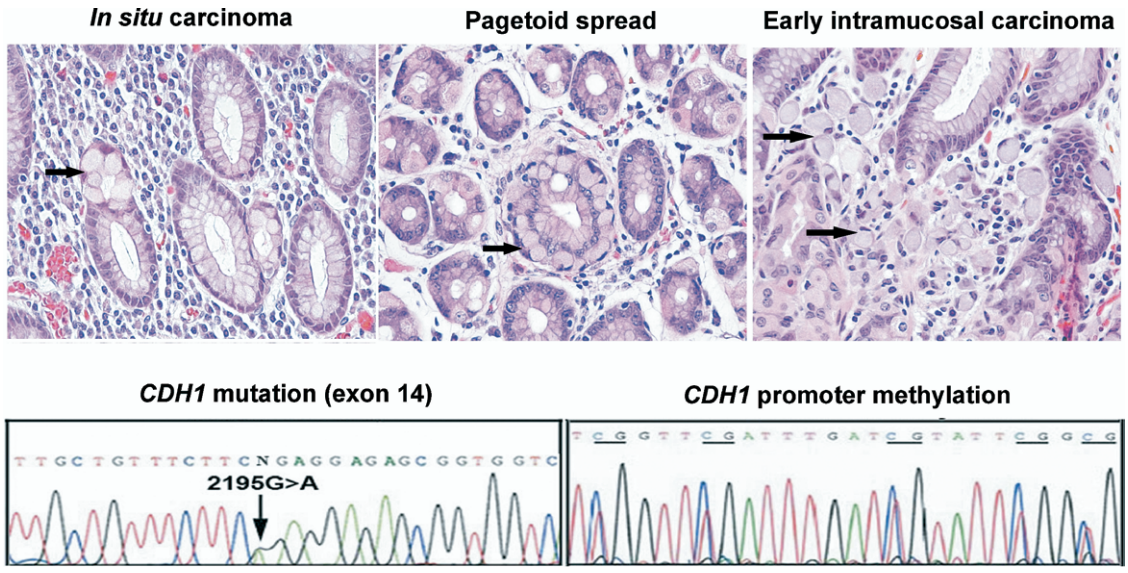

Figure 1 Morphological steps in the development of HDGC encompassing in situ carcinoma, pagetoid spread, and early intramucosal carcinoma (upper panel). Sequencing analysis of a germline mutation in exon 14 of *CDH1* gene (lower panel, left). *CDH1* promoter methylation in a tumor from the same family, determined in bisulphite treated DNA by PCR and sequencing (lower panel, right).