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GASTRIC CANCER. A FLEETING GLIMPSE AT ITS GENETIC EVIDENCES

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Genetic and epigenetic alterations are involved in gastric cancer (GC) development and progression by activating growth-promoting pathways and inactivating tumor-suppressive pathways. Genetic alterations like point mutations as *p53, KRAS, PIK3CA, ARIDIA, MLL3* and *MLL* mutations, small insertions and deletions, chromosomal gains and losses, gene amplifications as *PIK3CA, C-MET, ERBB4* and *CD44* are frequently found in GC, suggesting that they have a key and critical role in gastric human tumorigenesis. Epigenetic alterations enclose aberrant DNA methylation, histone modifications, nucleosome positioning, noncoding RNAs and microRNAs. Aberrant DNA methylation in the promoter region of gene (CpG island) is known to repress transcription of its downstream gene. Therefore, a tumor suppressor gene can be permanently inactivated by this mechanism.

GC is prevalently an epigenetic phenomenon in which more than 90% of the heritable alterations are of epigenetic origin. In the early steps of gastric carcinogenesis, for example, aberrant methylation caused by *Helicobacter pylori* (*H. pylori*) has also an extensive role[11, 16]. Multiple factors besides bacterial infection, like dietary habits, smoking and genetic polymorphisms determine the risk of GC development. Various genetic aberrations and epimutations become critical during the initiation and progression of GC.

Today it is well recognized that a number of epigenetic abnormalities in intestinal metaplasia and adenoma are precursors of GC. This multistep pathogenesis of intestinal-type GC is an accepted paradigm but the pathogenesis of the diffuse type is not fully understood, despite of the role of *H. pylori* infection, there are no known histologic precursor lesions of this type of GC. During the progressive stages of the GC carcinogenesis, CpG island hypermethylation and repetitive DNA hypo-methylation increase from chronic gastritis to GC [14]. The analysis of the profile of genetic / epigenetic alterations in GC has provided new insights into the genes defaults and identifies molecular targets to the therapeutics approaches in selected patients. Within the profiles of these patients cohorts, recently, point mutations and gene amplifications of a large number of target genes can be analyzed by bench top next-generation sequencers[6], and a comprehensive DNA methylation can be analyzed using a bead array[3], since these mechanisms are shown to be the most frequently observed causes of gene modification[16].

In an integrated analysis of cancer-related pathways of 55 gastric cancers within the growth-promoting pathways, the *WNT* pathway was activated only in two cases through mutations of the genes that encode β catenina, but in 49 cases the activation was due to potentially aberrant methylation of its negative regulators, the *AKT/mTOR* pathway was activated by mutations of its coding gene *PIK3CA* in four cases and the *MAPK* pathway was activated in 11 cases through mutations and gene amplifications of *ERBB2* and *KRAS*[16]. In this study, between the tumor repressive pathways, the inactivation was observed in the cell cycle regulations in 13 cases by aberrant methylation of *MHL* in two gastric cancers. The p53 was inactivated by mutations of *TP 53* in 19 of these GC and by potentially aberrant methylation of it downstream in 38 cases. The cell adhesion was affected by mutations of *CDH1* in two cases but none of the 50 GC had heavy aberrant methylation of *CDH1*; that is interesting because this suppressor gene is known to be important for the diffuse-type histology.

Familial clustering under a dominant inheritance causes 12% of gastric cancer[4]. Swedish database showed that when a parent had GC, the offspring risk was almost 1.6 fold increased only at ages older than 50 years, whereas the risk of probed siblings was near six fold increased, but only when the diagnosis was earlier than 50 years[7]. These transmission patterns were probably environmental and seen according with the easier transmission pattern of *H. pylori* infection observed in siblings.

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Hereditary diffuse gastric cancer is an inherited gastric cancer predisposition syndrome that is associated with germline transmission of a *CDH1* mutation[5]. Since there is 75% lifetime risk of developing diffuse-type gastric cancer in a gene carrier of this mutation, a prophylactic total gastrectomy should be considered when his or her age reaches the mid 20s[1].

Peculiar genetic features contribute to GC. Campanholo et al.[2] in a report that accompanies this editorial studied one of them, the variant polymorphism-765 G>C of the *COX-2* gene. Their original contribution refers to the increased association between the polymorphism in GC genotypes and the risk of GC in a suitable Brazilian cohort of the population. Interestingly, the hypomethylation status of *COX2* gene was associated with the intestinal type GC in patients from northern Brazil independently of the status of *H. pylori* infection[12] although it is well established that *H. pylori* contributes to *COX-2* expression in both GC and gastric IM adjacent to the cancer[15].

In MALT lymphomas, apart from several somatic genetic aberrations, including trisomy 3, *p53* mutation/LOH and *p16* deletion[8], some of which have shown to have diagnostic and prognostic value, five non-random chromosomal translocations involving few genes can be detected. These translocations appear to converge to the same nuclear factor kappa B (NF-kB) oncogenic pathway. Even so the lymphoma acquired as a result of *H. pylori* infection is histologically distinct from MALT lymphoma *H. pylori* independent, and that the eradication that leads to its regression can last from a few weeks to 18 months[8], it is very important the early definition of the therapeutic strategies. This is especially relevant since we know now that this independence is a feature of lymphoma progression coincident with the acquisition of additional genetic alterations[8]. In this setting, the article of Lima et al.[10], published in this issue, reports the behavior of the most common structural chromosomal abnormality frequently found in gastric lymphoma, the translocation t(11;18)(q21;q21) that results in a chimeric fusion between the *API2* and *MALT1* genes[8]. As they conclude, the detection of this translocation may be critical for targeting the therapy since it is highly specific for MALT subtype; it has also a high diagnostic value and often is found in gastric MALT lymphoma patients infected with CagA-positive *H. pylori*[8]. As the transcript is almost never found in MALT lymphoma with areas of high-grade transformation, some authors consider it restrict to low-grade cases[9, 13]. Others clinical relationships between the t(11;18) and MALT lymphoma include the association with advanced cases and submucosal involvement, but it is absent in lymphomas restricted to the mucosa[8,13].

In summary, the emerging genetic knowledge related to clinical implications has been recently reported and will produce a steady upgrade on the targeted treatment of gastric malignancies.

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