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Considerations about gastric cancer proteomics

Considerações sobre proteômica no câncer gástrico

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ABSTRACT

The frequency of molecular studies aimed to analyze promoter methylation of tumor suppressor genes and global proteomics in gastric carcinogenesis is increasing. Nonetheless, only a few considered the different types of stomach cells, the tumor location and the influence of Helicobacter pylori and Epstein Barr virus infection (EBV). Molecular differences relating to anatomical and histological tumor areas were also recently described. The authors propose a molecular classification of gastric cancer, dividing it into four subtypes: tumors positive for EBV; microsatellite unstable tumors; genomically stable tumors and tumors with chromosomal instability.

Keywords: *Stomach Neoplasms. Proteome. Helicobacter pylori. Herpesvirus 4, Human. Methylation.*

Gastric Cancer (GC) is the third leading cause of death from cancer throughout the world[1]. Its incidence varies substantially among different countries. In Brazil, GC corresponds the fifth major cause of cancer mortality among men and the sixth among women. It is estimated that Brazil will have 20,520 new GC cases in 2016, 12,920 in men and 7,600 in women[2].

The stomach is classically divided into four anatomical regions: cardia, fundus, corpus and pylorus. Each has different glands, cells and functions, showing a heterogeneity in the morphological, cytological and molecular levels[3].Based on this heterogeneity, some classification systems have been proposed to evaluate the gastric tumor's pathological characteristics. For gastric adenocarcinoma, the Lauren's classification is one of the most used systems, in which two major histologic subtypes are the intestinal and the diffuse, the indeterminate subtype being an uncommon one[4]. The World Health Organization (WHO) 2010 classification describes four major histologic patterns of gastric adenocarcinoma: tubular, papillary, mucous and poorly cohesive (including signet ring cell carcinoma), plus uncommon histologic variants[5].

GC is considered a multifactorial disease. However, the factors involved in tumor development and progression, especially in the genetic pathways, remain unclear. Among the risk factors involved are: genetic predisposition[6], diet[7], alcohol consumption, smoking[8], and chronic *Helicobacter pylori* or Epstein-Barr virus (EBV) infection.The International Agency for Research on Cancer (IARC) classifies *H. pylori* and EBV as a class-I carcinogen[9,10] , and both are known to up-regulate DNA methyltransferases (DNMT)[11]. GC lesions have shown to display hypermethylation of *CDH1*, which expresses E-cadherin protein, associated with DNMT1 protein overexpression by EBV infection[12].

The frequency of molecular studies aimed to analyze promoter methylation of tumor suppressor genes (TSG) and global proteomics in gastric carcinogenesis is increasing. Nonetheless, only a few[13] consider important characteristics, such as: the different types of stomach cells, the tumor location and the influence of *H. pylori* and EBV infection.

The molecular differences relating to anatomical and histological tumor areas were recently described[14]. The authors propose a molecular classification of gastric cancer, dividing it into four subtypes: tumors positive for EBV; microsatellite unstable tumors; genomically stable tumors and tumors with chromosomal instability. This classification may be important in future proteomics studies.

A meta-analysis[15] revealed differences based on gender and anatomic location in EBV-positive

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gastric cancer compared with EBV-negative ones, and emphasized the importance of investigating the significance of EBV in GC.Another study analyzed the protein profiles of paired surgical specimens from primary gastric tumor with non-tumor mucosa[16]. Aquino *et al*.[17] showed that the non-tumor surgical margins presented several proteins previously correlated with cancer, but also other overexpressed proteins that may be related to tumor nourishment and metastasis. Lima *et al*.[18] observed that gastric carcinogenesis has different pathways depending on the presence of the *H.pylori* or EBV, suggesting a possible involvement of *H. pylori* with the apoptotic process; and the low expression of c-Myc and Bax in the EBV-positive groups suggests that EBV may inhibit the expression of these proteins.

The molecular and cytological heterogeneity of GC indicate that proteomics interpretations should not be generalized. One must consider individual factors such as: genetics and epigenetics, gender, environmental factors and pathological characteristics. In this context, the analysis of individual tumor tissue may show more straight results when compared with a pool of samples as tissues or liquid biopsies, where specific information of some patients can be missed.

R E S U M O

A frequência de estudos moleculares visando a analisar os promotores de metilação de genes supressores de tumor e proteômica globais na carcinogênese gástrica está aumentando. No entanto, apenas alguns consideraram os diferentes tipos de células do estômago, a localização do tumor e a influência da infecção por *Helicobacter pylori* e pelo vírus Epstein-Barr (EBV). Diferenças moleculares relacionadas com áreas tumorais anatômicas e histológicas também foram recentemente descritas. Os autores propõem uma classificação molecular de câncer gástrico, dividindo-o em quatro subtipos: tumores positivos para o EBV; tumores microssatélite instáveis; tumores genomicamente estáveis e tumores com instabilidade cromossômica.

Descritores: Neoplasias Gástricas. Proteoma. Helicobacter pylori. Herpesvirus Humano 4. Metilação.

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