The usefulness of CDH1 methylation as a gastric cancer peritoneal metastasis biomarker

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Gastric cancer (GC) remains one of the most prevalent malignant diseases worldwide, being considered the second leading cause of global cancer deaths, affecting close to one million people per year (1). Although some recent advances in molecular biology, surgery, chemotherapy, and radiotherapy have been made, the poor prognosis and high mortality rate continue to make gastric cancer an attractive target of active clinical and basic scientific research (2).

Due to GC heterogeneity, some classifications have been proposed over the years, based on histopathology, clinical aspects, and endoscopic characteristics (3-5). However, the most widely used is the one proposed by Laurén (4), which classifies GC into intestinal and diffuse types, according to structural characteristics of the tumors. Some studies point out differences in the clinicopathological characteristics between these two types, indicating that they are a result of distinct molecular pathways (6).

The etiology of GC is considered multifactorial as many inherited and environmental factors, like diet, lifestyle, genetic and socioeconomic factors, play a role in its carcinogenesis. However, it is clear that the major etiologic risk factor for GC is *Helicobacter pylori* (*H. pylori*), which is responsible for more than 80% of cases (7).

A number of studies provide evidences that both genetic and epigenetic alterations play critical roles in GC. Although the role of genetic alterations has long been recognized, in the last decade epigenetic modifications have also been considered as an important factor in GC pathway (7).

Accumulating evidence indicates that aberrant promoter methylation is one of the most common molecular alterations in GC, being considered as a sensitive and very promising biomarker in early diagnosis of tumors (8).

A number of tumor-suppressor and tumor-related genes, including *APC*, *CDH1*, *MHL1*, *CDKN2A*, *CDKN2B* and *RUNX3* are commonly methylated in GC (6), suggesting the potential clinical value of DNA methylation as a marker for risk prediction and prognosis (9). Among those, *CDH1* deserves special attention as is widely reported as silenced in GC, mainly of the diffuse type, especially by promoter methylation (10-12).

CDH1, a suppressor gene located on chromosome 16q22.1 and member of the APC pathway, codifies for the E-cadherin protein and belongs to a family of cell surface glycoproteins that mediates the cell-cell adhesion playing an important role in the maintenance of the tissue architecture (13,14). The inactivation of E-cadherin results in a decreased cell adhesion, an increased cell motility and abnormal polarity, which favors the infiltrative ability and promotes tumor metastasis (8,15,16).

Various degrees of methylation in the *CDH1* promoter CpG islands and the consequent loss of E-cadherin expression were reported in GC (8,17), including the Hereditary Diffuse Gastric Cancer (HDGC) as 25-40% of the cases are caused by heterozygous silence of E-cadherin (12,18).

The main consequence of *CDH1* inactivation is the loss of cell-cell adhesion which is correlated with an infiltrative

and metastatic ability in GC (12,19). *CDH1* inactivation is so strongly correlated with GC prognosis and survival that patients with E-cadherin-positive gastric cancers showed statistically significant prolonged 3- and 5-year survival rates, compared to patients with E-cadherin-negative tumors (20).

Frequently, GC is diagnosed in advanced stage where the surgical resection is the only option for treatment (21). Considering this information and the high level of metastasis, including in the peritoneum, the identification of biomarkers for early detection and/or presence of GC metastasis is a very important task for its prevention and treatment (22).

Peritoneal metastasis is an important event in the GC prognosis as it may be responsible for resistance to various chemotherapeutic drugs and causes ascites and intestinal obstruction. This type of metastasis has a difficult identification as it may occurs in cases with negative cytological examination (23,24). The methylation pattern of several genes was evaluated in peritoneal washes in order to identify possible biomarkers of abdomen metastasis. The methylation observed in the peritoneum fluid (PF) was successful in the detection of occult neoplastic cells on the peritoneum, and that its use along with a cytological examination might increase the positive detection of cancer cells in PF (24).

Recently, Yu *et al.* (25) published an important paper in this subject, reporting that alterations in the methylation pattern of *CDH1* in preoperative peritoneal washes were significant correlated with abdomen metastasis and poor prognosis, suggesting that this marker could be used for the diagnosis of tumor invasion, metastasis and progression of GC.

In conclusion, even with few studies focusing the search for peritoneal metastasis biomarkers which can be predictive of poor prognosis, we can speculate that studies in this field are extremely important as they have great utility for the medical community and consequently for the patients' survival.

Acknowledgements

References

1. Siegel R, Ward E, Brawley O, et al. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 2011;61:212-36.
2. Zheng L, Wang L, Ajani J, et al. Molecular basis of gastric cancer development and progression. Gastric Cancer 2004;7:61-77.
3. Jass JR, Sobin LH, Watanabe H. The World Health Organization's histologic classification of gastrointestinal tumors. A commentary on the second edition. Cancer 1990;66:2162-7.
4. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. Acta Pathol Microbiol Scand 1965;64:31-49.
5. Mulligan RM. Histogenesis and biologic behavior of gastric carcinoma. Pathol Annu 1972;7:349-415.
6. Yamamoto E, Suzuki H, Takamaru H, et al. Role of DNA methylation in the development of diffuse-type gastric cancer. Digestion 2011;83:241-9.
7. Nagini S. Carcinoma of the stomach: A review of epidemiology, pathogenesis, molecular genetics and chemoprevention. World J Gastrointest Oncol 2012;4:156-69.
8. Yu QM, Wang XB, Luo J, et al. CDH1 methylation in preoperative peritoneal washes is an independent prognostic factor for gastric cancer. J Surg Oncol 2012;106:765-71.
9. Sapari NS, Loh M, Vaithilingam A, et al. Clinical potential of DNA methylation in gastric cancer: a meta-analysis. PLoS One 2012;7:e36275.
10. Borges Bdo N, Santos Eda S, Bastos CE, et al. Promoter polymorphisms and methylation of E-cadherin (CDH1) and KIT in gastric cancer patients from northern Brazil. Anticancer Res 2010;30:2225-33.
11. Leal M, Lima E, Silva P, et al. Promoter hypermethylation of CDH1, FHIT, MTAP and PLAGL1 in gastric adenocarcinoma in individuals from Northern Brazil. World J Gastroenterol 2007;13:2568-74.
12. Nobili S, Bruno L, Landini I, et al. Genomic and genetic alterations influence the progression of gastric cancer. World J Gastroenterol 2011;17:290-9.
13. Gervais ML, Henry PC, Saravanan A, et al. Nuclear E-cadherin and VHL immunoreactivity are prognostic indicators of clear-cell renal cell carcinoma. Lab Invest 2007;87:1252-64.
14. Rodriguez FJ, Lewis-Tuffin LJ, Anastasiadis PZ. E-cadherin's dark side: possible role in tumor progression. Biochim Biophys Acta 2012;1826:23-31.
15. Ghaffari SR, Rafati M, Sabokbar T, et al. A novel

truncating mutation in the E-cadherin gene in the first Iranian family with hereditary diffuse gastric cancer. Eur J Surg Oncol 2010;36:559-62.

16. Mateus AR, Simões-Correia J, Figueiredo J, et al. E-cadherin mutations and cell motility: a genotype-phenotype correlation. Exp Cell Res 2009;315:1393-402.

17. Barber M, Murrell A, Ito Y, et al. Mechanisms and sequelae of E-cadherin silencing in hereditary diffuse gastric cancer. J Pathol 2008;216:295-306.

18. Becker KF, Keller G, Hoefler H. The use of molecular biology in diagnosis and prognosis of gastric cancer. Surg Oncol 2000;9:5-11.

19. Chan AO, Lam SK, Wong BC, et al. Promoter methylation of E-cadherin gene in gastric mucosa associated with Helicobacter pylori infection and in gastric cancer. Gut 2003;52:502-6.

20. Ohno T, Aihara R, Kamiyama Y, et al. Prognostic significance of combined expression of MUC1 and adhesion molecules in advanced gastric cancer. Eur J

Cancer 2006;42:256-63.

21. Yonemura Y, Canbay E, Ishibashi H, et al. Multidisciplinary approach for the treatment of gastric cancer. Transl Gastrointest Cancer 2012;1:178-80.

22. Wong H, Yau T. Targeted therapy in the management of advanced gastric cancer: are we making progress in the era of personalized medicine? Oncologist 2012;17:346-58.

23. Hiraki M, Kitajima Y, Sato S, et al. Aberrant gene methylation in the peritoneal fluid is a risk factor predicting peritoneal recurrence in gastric cancer. World J Gastroenterol 2010;16:330-8.

24. Hiraki M, Kitajima Y, Koga Y, et al. Aberrant gene methylation is a biomarker for the detection of cancer cells in peritoneal wash samples from advanced gastric cancer patients. Ann Surg Oncol 2011;18:3013-9.

25. Yu QM, Wang XB, Luo J, et al. CDH1 methylation in preoperative peritoneal washes is an independent prognostic factor for gastric cancer. J Surg Oncol 2012;106:765-71.