

Helicobacter pylori and EBV in gastric carcinomas

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Mechanisms of gastric carcinogenesis are still not yet understood. Studies have linked genetic and epigenetic factors or microbiological agents to gastric cancer, but they didn't look for these events together. Dr. Ferrasi from Brazil verified the methylation profile, microsatellite instability (MSI), Helicobacter pylori status and Epstein Barr virus infection in gastric cancer samples. Intestinal and diffuse adenocarcinoma showed different methylation profiles and an association was found between methylation and Helicobacter pyloricagA+.

Gastric cancer, one of the most common types of cancer, is associated with high mortality rates. In the last decades, a decrease in the worldwide incidence has been observed with some changes in the therapeutic and diagnostic options. However, the prognosis for this disease still remains poor, mainly when the diagnosis is performed at advanced stages. The therapy most effective is still surgical resection and in a significant number of cases, especially in the advanced stage, it is only palliative. Thus, it is of extreme importance to study the mechanisms that act in gastric carcinogenesis and research possible markers that can assist in earlier diagnosis. <u>Helicobacter pylori</u> (H. pylori) is one of the more important etiological factors in gastric cancer, especially in those who have the cagA gene in their genome. In addition to the accepted role of H. pylori in the pathogenesis of gastric cancer, the Epstein Barr virus (EBV) has been associated with gastric cancer. DNA methylation is an epigenetic modification found in many physiological events, however, when it is aberrant it has been identified as being associated with



inactivation of tumor suppressor genes. Microsatellite instability (MSI) reflects an erroneous form of <u>DNA replication</u> in repetitive microsatellite sequences and has been considered a hallmark of DNA mismatch repair gene inactivation and therefore consequently leads to genetic instability. Some studies have linked DNA hypermethylation and MSI with H. pylori-cagA+ and EBV infection but these data are not conclusive and the studies did not examine both agents at the same time.

A study by Ferrasi et al, has recently been published on January 21, 2010 in World Journal of Gastroenterology, analyzed samples of gastric cancer (diffuse and intestinal type) for both etiological factors and correlated them with genetic (MSI) and epigenetic (methylation) alterations as well as with clinical and epidemiological data. Five genes were analyzed for methylation status: CDH1, COX2, hMLH1, CDKN2A and DAPK. The findings of this research are important as they suggest an association between H. pylori-cagA+ infection and silencing of the CDH1 gene. This gene encodes the E-cadherin protein that is very important in preventing metastasis. Also, the study suggests that intestinal-type and diffuse-type gastric cancer show different methylation profiles in the genes analyzed. In diffuse cases, the global methylation status, especially of CDH1, COX2 and CDKN2A, has the highest frequency in early stage tumors with a tendency to decrease along with tumor progression; while in the intestinal-type, the methylation status for CDH1, COX2, hMLH1 and CDKN2A tended to increase from the earliest to advanced stage. In addition, an important finding in this study was the inverse correlation observed between DAPK methylation and MSI. Although the mechanisms linking MSI to DAPK methylation are not known, this finding may provide a clue towards a better understanding of the association between MSI and better prognosis (already pointed out by other researchers with regard to sporadic colorectal cancer) since DAPK participates in the positive control of apoptosis.

The data presented in this article represent important information about



methylation profiles for intestinal-type and diffuse-type gastric cancer. Also, results show the association between HP-cagA+ and methylation in an important gene involved in metastasis (CDH1), in addition to showing the inverse association between DAPK methylation and MSI, providing new data for elucidating the mechanisms involved in the association of MSI and better prognosis. This will add to the available body of knowledge about gastric cancer carcinogenesis and aid in future research into this important disease.

More information: Ferrasi AC, Pinheiro NA, Rabenhorst SHB, Caballero OL, Rodrigues MAM, Carvalho F, Souza Leite CV, Ferreira MVP, Barros MAP, Pardini MIMC. Helicobacter pylori and EBV in gastric carcinomas: Methylation status and microsatellite instability. World J Gastroenterol 2010; 16(3): 312-319. www.wjgnet.com/1007-9327/16/312.asp

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