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The Cancer Control Challenge:
Better Understanding It to Better Face It

ANALYSIS OF THE CO-EXPRESSION OF THE CDH17 AND CDX2 GENES IN PATIENTS DIAGNOSED WITH GASTRIC CANCER IN THE STATE OF PARÁ

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Introduction: Gastric cancer (GC) is still one of the main causes of mortality in the world and represents a major challenge for public health. Given its heterogeneity, it is necessary to identify therapeutic and diagnostic biomarkers. The *CDH17* protein is frequently co-expressed with *CDX2*, a transcription factor that is essential for the development and maintenance of the intestinal epithelium. In normal tissues, *CDH17* and *CDX2* are restricted to the intestine and are absent in healthy gastric epithelium. However, in the GC, *CDX2* acts by regulating the transcription of intestinal genes, including *CDH17*, and contributes to the phenotypic reprogramming of gastric cells. Given the importance of cadherins in cell morphogenesis and differentiation, it is believed that *CDH17* may mediate the effects of *CDX2* in inducing an intestinal phenotype, contributing to carcinogenesis. In this context, *CDX2* and *CDH17* are potential diagnostic and therapeutic targets in gastric cancer. **Objectives:** To evaluate the expression of the *CDH17* and *CDX2* genes in patients with gastric adenocarcinoma in the state of Pará. **Methods:** This study was approved by the Research Ethics Committee (CAAE nº 47580121.9.0000.5634). 79 samples of GC tissue and adjacent tissue (ADJ) were collected for total RNA sequencing. The readings were processed with FastQC and Trimmomatic, aligned with Salmon and normalized in TPM. Comparative analyses of gene expression were carried out using the Wilcoxon test, considering $p < 0.05$ to be significant. Statistical analyses and the generation of expression graphs were carried out using R software. Gene-gene interaction was investigated using the STRING platform. **Results:** Differential expression (DE) analyses considering the intestinal and diffuse subtypes of GC, as well as H. pylori infection status (negative or positive), revealed a statistically significant DE for the *CDH17* ($p = 0.00414$) and *CDX2* ($p = 0.02167$) genes between GC and ADJ tissues, with higher expression in tumors. In relation to H. pylori status, there was a significant difference in *CDH17* expression ($p = 0.01755$), which was higher in negative individuals. *CDX2* had a tendency towards increased expression in negative individuals, but it was not statistically significant ($p = 0.05766$). Network analysis using the STRING platform showed a functional association between *CDH17* and *CDX2* through co-expression. **Conclusion:** The *CDH17* and *CDX2* genes are more expressed in tumor tissue when compared to adjacent tissue, indicating their potential as a

biomarker in GC. Although the inflammation caused by H. pylori favors intestinal metaplasia, an important factor for the activation of these genes, the expression of *CDH17* shows significant variation according to *H. pylori* infection status, being higher in negative individuals. On the other hand, *CDX2* showed no statistically significant difference, only a trend. This apparent contradiction may be explained by the reduction in *H. pylori* colonization in advanced stages of gastric cancer, when intestinal reprogramming mediated by *CDX2* and *CDH17* is already established. Finally, the functional analysis reinforces the interaction between the two genes, suggesting the co-expression and a collaborative role in gastric tumorigenesis.

Keywords: Gastric cancer; *CDH17*; *CDX2*; biomarkers.