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

EVATUATION OF *ANPEP/CD13* AS A BIOMARKER OF GASTRIC PREMALIGNANT LESIONS

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Introduction: Autoimmune atrophic gastritis (AAG) is a condition that compromises the gastric mucosa, leading to atrophy and hypochlorhydria, with a potential increased risk of gastric cancer (GC), especially in the presence of intestinal metaplasia, dysplasia, and *Helicobacter pylori* (Hp) infection. Studies indicate that chronic inflammation, mediated by CD4+ T lymphocytes and alterations in the gastric microbiome, may promote malignancy. The biomarker *ANPEP*/*CD13*, expressed in metaplastic cells, has been associated with the carcinogenic potential of both AAG and Hp-induced gastritis. **Objectives:** This study evaluates *ANPEP*/*CD13* expression by NGS in samples of gastric cancer (GC), tumor-adjacent tissue (ADJ), and metaplasia (MP), aiming to elucidate the mechanisms of malignant transformation in AAG, with particular attention to the role of Hp. **Methods:** A total of 124 GC and 62 ADJ samples from patients who underwent surgical resection, and 20 MP samples obtained via endoscopic biopsy at the João de Barros Barreto University Hospital were analyzed. RNA-seq was conducted in a paired-end manner on the NextSeq® platform (Illumina®, US). The NextSeq® 500 MID Output V2 kit – 150 cycles (Illumina®) was used according to the manufacturer's instructions. Human transcript reads were characterized through alignment and quantification using Salmon v1.5.2, with the coding transcripts from hg v38 (www.ensembl.org) as the reference index and GENCODE v.42 (www.gencodegenes.org) as annotation. The reads were imported from Salmon into RStudio using the Tximport v3.14.0 package. **Results:** *ANPEP* expression was significantly higher in MP samples compared to GC and ADJ samples ($p<0.0001$, Kruskal-Wallis test, adjusted by Benjamini-Hochberg). A trend toward lower survival was observed in patients with high *ANPEP* expression ($p=0.073$, Kaplan-Meier), suggesting a possible association between elevated expression of this gene and poorer prognosis. No significant differences were found between *ANPEP* expression and *H.*

pylori status, tumor staging, location, grade of differentiation, or subtype. These results suggest that *ANPEP* is an important marker of pre-neoplastic lesions, corroborating the literature that highlights this gene as a biomarker of metaplastic cells in Hp-induced gastritis and AAG. Its higher expression in metaplasia reinforces its relevance for early detection and risk stratification in patients with chronic gastritis. The lack of association with Hp may be influenced by false-negative diagnoses due to the coccoid form of the bacterium under hypochlorhydric conditions, as seen in AAG and GC. **Conclusion:** The findings of this study support the importance of *ANPEP* in the early detection of GC risk in patients with chronic gastritis. However, the relationship with AAG and the influence of Hp require further investigation, especially considering the possibility of false-negative results for Hp.

Keywords: Autoimmune atrophic gastritis, Metaplasia, Gastric cancer, *ANPEP/CD13*, Carcinogenesis.