Título: ***STAT*3 POLYMORPHISM AND *Helicobacter pylori* CagA STRAINS WITH HIGHER NUMBER OF EPIYA-C SEGMENTS INDEPENDENTLY INCREASE THE RISK OF GASTRIC CANCER**

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Resumo:

Background: Because to date there is no available study on *STAT3* polymorphism and gastric cancer in Western populations and taking into account that *Helicobacter pylori* CagA EPIYA-C segment deregulates SHP-2/ERK-JAK/STAT3 pathways, we evaluated whether the two variables are independently associated with gastric cancer.
Methods: We included 1048 subjects: *H. pylori*-positive patients with gastric carcinoma (n = 232) and with gastritis (n = 275) and 541 blood donors. Data were analyzed using logistic regression model.
Results: The rs744166 polymorphic G allele (p = 0.01; OR = 1.76; 95%CI = 1.44 – 2.70), and CagA-positive (OR = 12.80; 95%CI = 5.58 – 19.86) status were independently associated with gastric cancer in comparison with blood donors. The rs744166 polymorphism (p = 0.001; OR = 1.64; 95%CI = 1.16 – 2.31) and infection with *H. pylori* CagA-positve strains possessing higher number of EPIYA-C segments (p = 0.001; OR = 2.28; 95%CI = 1.41 – 3.68) were independently associated with gastric cancer in comparison with gastritis. The association was stronger when host and bacterium genotypes were combined (p < 0.001; OR = 3.01; 95%CI = 2.29 – 3.98). When stimulated with LPS (lipopolysaccharide) or Pam3cys, peripheral mononuclear cells of healthy carriers of the rs744166 GG and AG genotypes expressed higher levels of *STAT*3 mRNA than those carrying AA genotype (p = 0.04 for both). The nuclear expression of phospho-STAT3 protein was significantly higher in the antral gastric tissue of carriers of rs744166 GG genotype than in carriers of AG and AA genotypes.
Conclusions: Our study provides evidence that *STAT*3 rs744166 G allele and infection with CagA-positive *H. pylori* with higher number of EPIYA-C segments are independent risk factors for gastric cancer. The odds ratio of having gastric cancer was greater when bacterium and host high risk genotypes were combined.

Key words: Gastric cancer, *STAT*3 gene polymorphism, *STAT*3 rs744166, *Helicobacter pylori*, CagA, EPIYA-C segments.

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