Título: **STAT3 POLYMORPHISM AND Helicobacter pylori CagA STRAINS WITH HIGHER NUMBER OF EPIYA-C SEGMENTS INDEPENDENTLY INCREASE THE RISK OF GASTRIC CANCER**

Autores: Batista, S.A¹, Rocha, G.A¹, Rocha, A.M.C¹, Gomes, A.D¹, Faria Júnior, C.L.L¹, Melo, F.F¹, Fernandes, V.C¹, Almeida, N.B.F¹, Teixeira, K.N¹, Brito, K.S¹, Queiroz, DMM¹

Instituição: ¹Laboratory of Research in Bacteriology, Faculdade de Medicina, Universidade Federal de Minas Gerais. Av. Alfredo Balena, 190 s/216. CEP.: 30130-100. Belo Horizonte, Brazil. Phone +5531 3409 9784, Fax: +5531 3274 2767

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-positive 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 **STAT3** 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 **STAT3** 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, **STAT3** gene polymorphism, **STAT3** rs744166, **Helicobacter pylori**, CagA, EPIYA-C segments.

**Grants:** CAPES, CNPq, FAPEMIG and INCT.