



37_ Dissecting the (epi)genetic landscapes of Gastric Cancer: on the road to liquid biopsy

J. Carvalho^{1,2}, P. Ferreira^{1,2}, P. Oliveira^{1,2}, G.M. Almeida^{1,2}, H. Pinheiro^{1,2}, S. Rocha^{1,2}, D. Ferreira^{1,2}, A.S. Valente^{1,2}, M. Santos^{1,2,3}, D. Martins^{1,2}, N. Saraiva⁴, N. Bonito⁴, M. Cravo^{5,6}, J. L. Passos-Coelho^{5,6}, F. Carneiro^{1,2,7}, C. Oliveira^{1,2,7}

¹ Expression Regulation in Cancer Group, IPATIMUP, Institute of Molecular Pathology and Immunology of the University of Porto, Portugal; ² Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Portugal; ³ Department of Medical Sciences and Institute of Biomedicine – iBiMED, University of Aveiro, Portugal; ⁴ Instituto Português de Oncologia de Coimbra Francisco Gentil E. P. E, Coimbra, Portugal; ⁵ Hospital Beatriz Angelo, Lisboa, Portugal; ⁶ Faculdade de Medicina de Lisboa, Portugal; ⁷ Medical Faculty of the University of Porto, Porto, Portugal.

Introduction: Gastric cancer (GC) affects ~1 million people a year and kills 75% of patients, being the 3rd deadliest cancer worldwide. Portugal has the highest incidence of GC in Europe, with ~3000 new cases and ~2300 deaths in 2012¹. Surgery is the single curative treatment, though helpful only for early-stage and localized tumors. Most patients (>90%) present with advanced stages (III and IV) at diagnosis and only 4-20% survive after 5 years². For these patients, conventional chemotherapy and radiotherapy are the main treatment options, and the only marker for targeted therapy is HER2 status, which is overexpressed/amplified in less than 20% of GC overall³⁻⁵. Therefore, it is essential to develop early diagnostic and accurate monitoring tools to improve GC patients' clinical outcome. Recently, Next Generation Sequencing (NGS) technology provided the spectrum of somatic alterations in several GC series but its usefulness for decision-making in clinical practice is still scarce⁶⁻⁸.

Objectives: In this study, we aimed at characterizing genetic and epigenetic alterations of two distinct GC molecular subgroups. This global characterization will help us to: 1) predict targetable molecular signatures, which may guide better therapy selection strategies and, 2) highlight specific GC biomarkers with great potential for detecting and monitoring the disease in gastric washes and plasma from GC patients.

Material and Methods: Fifty GC tumor/normal pairs (frozen tissue) either showing Chromosomal Instability (CIN=25), or Microsatellite Instability (MSI=25), were submitted to DNA extraction and analyzed by Whole genome and Methylome sequencing. Data was analyzed by using integrative bioinformatics and validated in independent GC datasets deposited in The Cancer Genome Atlas (TCGA). In parallel, we are prospectively collecting gastric washes and plasma samples from several GC patients at different timepoints: prior/at surgery; after surgery and/or along conventional/targeted treatment cycles and patients' follow-up, which will be further submitted to isolation of circulating nucleic acids and subsequent molecular analysis.



Results: MSI tumors displayed hypermethylated tumor suppressor genes and activating point mutations in oncogenes. CIN tumors displayed gene amplification at oncogenes and drug-resistance genes and hypomethylation at oncogene promoters. The same type of differential mechanisms was found for Chromatin remodeling, and Cell cycle control, but Splicing factors and RNA-binding proteins were affected similarly in both subgroups. Despite differences in mechanisms, genes encoding targetable oncogenic signalling proteins were similarly affected in both subgroups. At this point, we have already collected on average 10 plasma samples from 22 GC patients in a longitudinal manner, that will be used to search for the previously identified GC markers.

Conclusions: These data demonstrate that most tumors present similar tumorigenic pathways independently of the molecular subgroup, and that differences in prognosis and drug response are likely related with the action of modifier proteins. Moreover, we identified MSI and CIN GC signatures that may be integrated in non-invasive strategies to accurately diagnose the onset of GC, monitor treatment of advanced disease and predict risk of recurrence.

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