Pan-Cancer Multi-Omic Analysis of Imprinted Genes Identifies Differential Survival Gene Signatures in Brain and Kidney Cancers

Victor dos Santos Lopes, Leonardo Henrique da Silva, Alan Tardin da Silva, Cristina dos Santos Ferreira, Enrique Medina-Acosta

Imprinted genes exhibit monoallelic expression in a parent-of-origin-dependent manner. In humans, the imprinted gene set includes 125 genes whose monoallelic expression has been experimentally validated in at least on tissue in several subjects and about 60 candidate genes which exhibit patterns consistent with monoallelic expression, and the parental origin of the expression is ambiguous. The known imprinted genes have diverse functions in embryonic, extra-embryonic, fetal, child and adult development. Because the imprinting of genes may occur in several tissues, they exert essential organ development and maintenance functions. Loss-of-imprinting has been reported for some imprinted genes in a few cancer types, where altered gene expression patterns are well documented for either non-imprinted or imprinted genes. Here, we carried out a pan-cancer analysis of a discovery set of 166 imprinted genes to determine the significance of the similarities and differences among the genomic alterations found across diverse tumor types. Because the differential expression of genes is a common feature in cancer, we assessed the differential expression of the imprinted gene set among 33 cancer data sets of 18.397 RNA-Seq individual transcriptomes from The Cancer Genome Atlas (10.535) and the Genotype-Tissue Expression project (7.862). We measured their contribution as a predictor variable of differential survival time of patients, calculating the hazards ratio (HR, 95% confidence interval) based on the Cox Proportional Hazards Model, and using two methods: overall survival (OS) and disease-free survival (DFS). We also examined the extent of copy number variation (CNV) in the gene set and correlated it with gene expression in each cancer type. We identified three significant differential survival imprinted gene signatures - DSIGS (FDR $p < 0.05$). Two in patients with Lower Grade Glioma (LGG) and one in patients with Kidney Clear Cell Carcinoma (KIRC). The two DSIGS identified in LGG associated with poor prognosis according to their overexpression (14-member signature; OS HR(high)=3.7, p(HR)=7.1e-10); DFS HR(high)=2.3, p(HR)=6.4e-07) or under-expression (6-member signature (HR(high)=0.38, p(HR)=6.9e−07; DFS HR(high)=0.39, p(HR)=2.5e-08). In KIRC, we identified a 12-member DSIGS, whose under-expression was associated with poor prognosis (OS HR(high)=0.29, p(HR)=1.2e-12; DFS HR(high)=0.33, p(HR)=2.6e-08). We also identified the genes most affected by CNV and measured their effect. Last, we associated the extent of DNA methylation across each gene with survival. The identified DSIGS serve as potential biomarkers of poor prognosis in LGG or KIRC cancers.

Keyword: Genomic imprinting, cancer, differential survival gene signature, copy number variation

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