Mitochondrial Differential Survival Gene Signatures in Human Cancer Using High-Throughput RNA Sequencing

Alan Tardin da Silva, Enrique Medina-Acosta

Transcriptome profiling by high-throughput RNA-sequencing (RNA-Seq) is a powerful method to investigate the likely correlation between gene expression, overall survival (OS), and disease-free survival (DFS) in cancer patients. Identifying signatures of differential gene expression that are upregulated or downregulated among cancer patients can be done as a measure of hazard ratio (HR) in the survival of patients expressing high or low discovery levels of gene sets. Most studies reporting the prognostic value of gene expression dealt with nuclear genes, because its high sensitivity to mutations and inefficient repair mechanisms. Mitochondrial genes (MT-genes) are among the highest expressed in human cells and tissues. Here, we investigated whether MT-genes differential expression has a prognostic value in Low Grade Glioma (LGG). We centered the analysis on the mitochondrial-encoded genes involved in the oxidative phosphorylation system (OXPHOS), which comprises over 80 nuclear and 13 mitochondrial protein-coding genes. In most human tissues, the OXPHOS genes are co-expressed, except in the hypothalamus, basal ganglia, and amygdala. We queried The Cancer Genome Atlas (TCGA), the most extensive public data set of RNA-Seq from tumor tissues, using GEPIA2, which includes a dataset from 33 cancer types. In each cancer dataset, we compared the survival contribution of multiple OXPHOS genes in multiple cancer types, estimated using the Mantel-Cox test. The genes were grouped by the positive or negative correlation between high or low expressing individuals and the HR to measure the survival map's effect. The resulting gene were then queried as likely signatures of differential OS or DFS, normalizing or not for the most differential survival gene (MDSG) in each cancer type, and adjusting for multiple tests using the Benjamini-Hochberg method and false discovery rate (FDR; $p \leq 0.05$). We found two five-component signatures. The first signature is *MT-CO1, MT-CO2, MT-ND5, MT-ND6, MT-RNR2*, with prognostic value for OS (HR(high)=0.31, p(HR)=7.7e-09), normalized by the *ISL2* (MDSG) in LGG. The second signature is *MT-ATP8, MT-CO1, MT-CO2, MT-CYB, MT-ND4*, with prognostic values for DFS (HR(high)=0.096, p(HR)=5.7e-07), normalized by the *PTMA* (MDSG) and OS (HR(high)=0.14, p(HR)=4.2e-05), normalized by the *MXD3* (MDSG) in adrenocortical carcinoma. The lack of effect of the remaining MT-genes was not due to lack of expression because all the 13 genes were co-expressed at comparable levels in all cancer types ($R > 0.90$, $p = 0$, Pearson) and normal tissues from the GTEX Consortium as determined by Principal Component Analysis dimensionality reduction (PC1 >90% of variances).

Keywords: mtDNA, Glioma, Adrenocortical carcinoma, OXPHOS genes

Instituição do Programa de IC, IT ou PG: UENF
Fomento da bolsa: FAPERJ