Endocrinología, Diabetes y Nutrición

12 - STUDYING RESISTANCE TO LENVATINIB USING SINGLE CELL RNA SEQUENCING IN THYROID CANCER

H. Rodríguez Lloveras, J. Marcos Ruiz, E. del Fresno Ventura, À. Pérez Hita and M. Jordà Ramos

Institut de Recerca Germans Trias i Pujol, Badalona.

Resumen

Some patients with differentiated thyroid cancer (DTC) are refractory to the standard therapy with radioiodine (RAI-R) and show decreased survival. This leads to disease progression, and the only approved treatment are multikinase inhibitors, lenvatinib being the most widely used. However, patients eventually develop resistance. We aim to study the mechanisms of resistance to lenvatinib to identify biomarkers of response and potential therapeutic targets. We used the TPC-1 cell line to establish a model resistant to lenvatinib by treating the cells with gradually increasing doses. We analysed the transcriptome by single-cell RNA-seq (scRNA-seq) for two controls (parental TPC-1 and TPC-1 treated with DMSO) and two time points along the process of generation of resistant cells (TPC-1 LR5 and TPC-1 LR8,6 cultured with 5 µM and 8,6 µM lenvatinib, respectively). ScRNA-seq data was obtained using 10x Genomics and CellRanger and analysed using Seurat. Results showed that controls and resistant cells clustered separately, indicating that lenvatinib significantly affects the transcriptome. We found no differences between controls, while resistant cells were divided into different clusters. We identified 220 and 551 overexpressed genes (logFC > 1, adj p < 0,05) in TPC-1 LR5 and TPC-1 LR8,6 cells when compared to control cells, respectively, with 74 common genes. The gene ontology analysis showed that overexpressed genes in TPC-1 LR5 were associated with cell adhesion and migration, while overexpressed genes in TPC-1 LR8,6 cells were associated with different metabolic pathways. Results were also validated by bulk RNA-seq and RT-qPCR. Based on these data and publicly available datasets, we selected some candidate genes to further study their role in lenvatinib resistance *in vitro*. In conclusion, we have identified candidate genes involved in lenvatinib resistance with potential as response biomarkers and/or therapeutic targets in RAI-R DTC patients.