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1 - DNA METHYLATION PROFILING TO IDENTIFY PREDICTIVE BIOMARKERS AND RESISTANCE PATHWAYS TO LENVATINIB IN RAI-REFRACTORY THYROID CANCER

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Resumen

Lenvatinib (LEN) is a first-line treatment for patients with advanced differentiated thyroid cancer refractory to radioactive iodide (RAI-R DTC). However, most patients eventually develop resistance, highlighting the need for predictive biomarkers and a better understanding of resistance mechanisms. DNA methylation is an epigenetic mark at CpG dinucleotides that has emerged as a valuable biomarker in several diseases, including cancer. We recently identified a DNA methylation signature in primary thyroid tumours that predicts the risk of distant metastases. Here, we aimed to use DNA methylation to identify predictive biomarkers of response to LEN and to uncover resistance-related pathways. We profiled DNA methylation using the Infinium MethylationEPIC array in 21 samples from RAI-R DTC patients treated with LEN, as well as in an *in vitro* LEN-resistant cell model developed in our laboratory. We also analysed the transcriptome of the LEN-resistant model using bulk and single-cell RNA-seq. We integrated these data with clinico-pathological and molecular features. We identified over 32,000 CpGs whose methylation levels significantly correlated with the progression-free survival after LEN treatment. About 2,500 of these CpGs were also differentially methylated between LEN-resistant and LEN-sensitive cells from the in vitro model, supporting the robustness of the results. Moreover, over a hundred of these CpGs were associated with thyroid-specific genes, LEN target receptors and genes involved in pathways previously associated with LEN resistance in other cancer types, such as cytoskeleton organization or RNA methylation. Some of these genes were also differentially expressed in the in vitro model and further validated by RT-qPCR. Our data suggest the role for DNA methylation in LEN resistance, implicating specific pathways in this process and providing predictive biomarkers and therapeutic targets to guide more personalised and effective treatment.