Endocrinología, Diabetes y Nutrición

7 - DEFINING THE ROLE OF EPIGENETIC ELEMENT *PPARGC1A* IN THYROID CANCER DEDIFFERENTIATION

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Resumen

Despite most differentiated thyroid cancer (DTC) patients having an initial good prognosis, some patients become resistant to radioiodide treatment. Having effective markers or long-term therapies available would be key for these patient's management. Many of these patients present dedifferentiated tumours, having lost some or most of their thyrocyte-specific features. As DTC tumours typically present low levels of genetic alterations, epigenetics has emerged as a field to be explored in this disease, but its role in thyroid cancer dedifferentiation is poorly understood. Our aim is to study the epigenetic mechanisms underlying DTC dedifferentiation to identify new prognostic biomarkers as well as potential therapeutic targets. We have identified a set of epigenetic-related genes whose expression correlates with thyroid differentiation levels in publicly available datasets, by correlating DTC tumour differentiation to epigenetic-associated genes. Tumour differentiation was defined using the Thyroid Differentiation Score (TDS). We have selected *PPARGC1A*, an epigenetic and metabolic master regulator, as our main candidate to be a prognostic biomarker in DTC. Its expression consistently correlated with TDS in patient samples and multiple in vitro models, suggesting its role in maintaining thyroid differentiation. Moreover, *PPARGC1A* expression was also associated with other clinical prognostic markers, such as risk of recurrence. Modifying the expression of our candidate in vitro resulted in a change in TDS gene expression, thus affecting the level of differentiation of the models. Furthermore, *PPARGC1A* overexpression showed changes in metabolic state, offering a potential mechanistic link between metabolism and dedifferentiation. In conclusion, we have identified *PPARGC1A* as a candidate epigenetic factor that may help to better understand DTC dedifferentiation, with potential utility as prognostic biomarker and therapeutic target for advanced thyroid carcinomas.