Estrogen-Related Receptor Alpha Modulates Lactate Dehydrogenase Activity in Thyroid Tumors

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Résumé en anglais
Metabolic modifications of tumor cells are hallmarks of cancer. They exhibit an altered metabolism that allows them to sustain higher proliferation rates in hostile environment outside the cell. In thyroid tumors, the expression of the estrogen-related receptor α (ERRα), a major factor of metabolic adaptation, is closely related to the oxidative metabolism and the proliferative status of the cells. To elucidate the role played by ERRα in the glycolytic adaptation of tumor cells, we focused on the regulation of lactate dehydrogenases A and B (LDHA, LDHB) and the LDHA/LDHB ratio. Our study included tissue samples from 10 classical and 10 oncocytic variants of follicular thyroid tumors and 10 normal thyroid tissues, as well as samples from three human thyroid tumor cell lines: FTC-133, XTC.UC1 and RO82W-1. We identified multiple cis-acting promoter elements for ERRα, in both the LDHA and LDHB genes. The interaction between ERRα and LDH promoters was confirmed by chromatin immunoprecipitation assays and in vitro analysis for LDHB. Using knock-in and knock-out cellular models, we found an inverse correlation between ERRα expression and LDH activity. This suggests that thyroid tumor cells may reprogram their metabolic pathways through the up-regulation of ERRα by a process distinct from that proposed by the recently revisited Warburg hypothesis.

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