Endocrinología, Diabetes y Nutrición

9 - UNRAVELING THE ROLE OF THE PI3K/MYC AXIS IN FGSLR RESISTANCE IN ACROMEGALY

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Resumen

Introduction: Around 50% of patients with acromegaly are not controlled with first-generation somatostatin receptor ligands (fgSRLs) as first-line therapy, leading to delayed hormonal control and increased comorbidities. Therefore, there is a need to personalize therapeutic decision algorithms to achieve faster disease control. Identifying new therapeutic targets for those patients that do not respond to the current therapeutic options is also essential. To address this, we analysed the transcriptome of fgSRL responder and non-responder patients, focusing on genes upregulated in non-responders.

Methods: We analysed the transcriptome of a cohort of 45 GH-producing pituitary neuroendocrine tumours (PitNETs), both responders and non-responders to fgSRL, through RNA-seq, and validated candidate genes by RT-qPCR. Differential pathway activation was assessed using the HiPathia R package. To explore functional relevance, GH4C1 cells were treated with PI3K and MYC inhibitors (LY294002 and 10058-F4, respectively). Treatment effects were then evaluated by Western Blot, GH secretion ELISA and RT-qPCR.

Results: Non-responder tumours showed significant overactivation of the PI3K pathway and overexpression of MYC ($p < 0.0001$). Higher MYC expression levels were associated with a higher invasiveness. PI3K and MYC were inhibited in GH4C1 cells to further study their role on resistance to fgSRLs. Treated cells showed a shift towards a more responsive phenotype, evidenced by the upregulation of already stablished response markers (RORC, SSTR2). Further studies combining PI3K or MYC inhibitors with fgSRL needs to be performed to evaluate effects on fgSRL resistance.

Conclusions: MYC may be used as a predictor of response to fgSRLs as well as a therapeutic target in combination with fgSRLs to improve response and clinical outcomes in acromegaly.