

Influence of ER stress on the hormonal activity of pituitary neuroendocrine tumors (PitNETs)

Cancer cells may experience endoplasmic reticulum (ER) stress due to many factors including hypoxia, nutrient deprivation, or oncogenic pathways dysregulations. As a result cells enhance the unfolded protein response (UPR) to restore normal ER function (via e.g., inhibition of protein translation, degradation of misfolded proteins, or increased chaperons production). This homeostasis may be achieved through the mediation of the three main UPR pathways: PERK pathway (activated by the protein kinase RNA-like ER kinase), IRE1 (Inositol-requiring enzyme 1), or ATF6 (activating transcription factor 6) (1, 2). While the UPR initially promotes cell survival by increasing protein folding and degradation, prolonged ER stress can lead to cell death.

The emerging role of UPR pathways was confirmed in many cancers including invasive breast cancer, colorectal cancer, pancreatic cancer or glioblastoma multiforme (3, 4). Combining standard therapies with UPR inhibitors (such as IRE1, PERK, eIF2A) demonstrated significant efficacy in preclinical cancer models, thus nowadays pathways belonging to UPR are being proposed as potential pharmacological targets in several cancers (1, 5, 6)

PitNETs also known as pituitary adenomas (PAs), are the third most prevalent intracranial tumors, following meningiomas and gliomas. Although predominantly benign, some PitNETs may exhibit invasive and recurrent behavior. They can be classified by the size as microadenomas (10mm in diameter) or macroadenomas (>10mm in diameter) or by the hormonal activity as functioning or non-functioning PitNETs (NF-PitNETs). PitNETs arise from adenohypophysis and may exhibit positive immunohistochemical staining for the hormones secreted by the anterior lobe of the pituitary gland: GH, ACTH, PRL, LH, FSH, TSH or their alpha and beta subunits. Despite the overexpression of hormones within the tissue, biochemical hormonal activity is not always observed (7).

The aim of the current project is to investigate how endoplasmic reticulum stress affects hormone secretion in model rat pituitary adenoma cell lines. To gain an in-depth understanding of the mechanisms by which ER stress affects hormone secretion, NGS (Next Generation Sequencing) at the transcriptome level will be performed, and various molecular biology techniques will be applied.

We strongly believe that apart from exploring pathogenesis of non-functioning PitNETS and establishing the role of ER stress for hormonal secretion, our study will enhance the possibility of use drugs targeting UPR pathways as a potential therapeutics for the PitNETs treatment.

References:

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