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Pancreatic Neuroendocrine Tumors Require Homeostatic Signaling from the Unfolded Protein Response.

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The unfolded protein response (UPR) is an intracellular signaling pathway largely controlled by two ER transmembrane kinases—IRE1alpha and PERK—that communicate the protein folding status of the endoplasmic reticulum (ER) to the nucleus to maintain ER homeostasis. Hypoxia, nutrient deprivation, proteasome dysfunction, sustained demands on the secretory pathway or somatic mutations in its client proteins—conditions often encountered by cancer cells—can lead to the accumulation of misfolded proteins in the ER and cause “ER stress.” Under *remediable* levels of ER stress, the UPR activates transcriptional and translational changes that promote adaptation (Homeostatic UPR). But when confronted with *irremediable* levels of ER stress, these adaptive measures fail, and the UPR instead switches strategies to trigger cell death (Terminal UPR).

For the reasons mentioned above, ER stress is documented in many solid cancers, but whether ongoing UPR signaling is beneficial or detrimental to tumor growth remains hotly debated. Given their high secretory activity, we predicted that pancreatic neuroendocrine tumors (PanNETs) would be one neoplasm that is particularly sensitive to protein folding stress. Not only do PanNETs universally hypersecrete one more peptide hormone(s), but the endocrine cells of the pancreas from which these tumors derive are the cells in the body most impacted by genetic loss of the UPR in mice and humans. For the over 1,500 Americans diagnosed with a PanNET each year, surgery is the only potentially curative treatment. Unfortunately, the five year survival is extremely low for the ~25% of patients who develop metastatic disease. Hence, new targets are desperately needed for patients with advanced PanNETs.

We find that the UPR is strongly unregulated in human PanNETs, and that these neoplasms are heavily reliant on elevated levels of Homeostatic UPR signaling to avoid the toxic effects of protein folding stress *in vivo*. Moreover, we discovered that targeted interventions to either reduce Homeostatic UPR outputs or alternatively trigger the Terminal UPR have potent antitumor effects in at least 2 distinct preclinical PanNET models. Inhibiting IRE1alpha or PERK leads to hyperactivation of the opposing arm and pushes it into a Terminal UPR, resulting in the observed anti-PanNET effects *in vivo*. Together, these findings suggest that the UPR is a promising target in PanNETs and related neoplasms.

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