Integrated Stress Response Activation Discovered to Be the Predominant Response to Mitochondrial Dysfunction: A Therapeutic Target Advancement

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Our bodies continually encounter genetic and developmental stresses, activating stress-responsive signaling pathways to promote proteostasis. However, when these stresses persist and signaling pathways malfunction, they contribute to pathogenesis. The lack of specific therapeutic targets has spurred interest in defining the molecular mechanisms regulating cellular proteostasis in response to pathological stress. The Unfolded Protein Response governs cellular physiology in reaction to endoplasmic reticulum stress. Similarly, the Integrated Stress Response also corrects pathogenesis, selectively phosphorylating eIF2-alpha kinases to activate transcription factors. Nonetheless, the ISR's role in mitigating etiology remains unknown. Post-validation of our gene-set profiling approach using known UPR targets, we monitored the expression of genesets regulated downstream of signaling pathways with perturb-seq datasets from K562 cells CRISPRi-depleted of mitochondrial proteostasis factors. We observed ISR activation predominantly in response to broad-scale mitochondrial disruption, identifying promising therapeutic targets: IARS2, PRELID3B, SLC25A42, TIMM23B, and TOMM22. Gene Ontology revealed roles in mitochondrial protein processing and targeting among ISR target genes. These findings highlight the ISR as the primary stress-responsive pathway activated by mitochondrial proteotoxic stress, presenting a unique opportunity to target it for correcting mitochondrial dysfunction in diseases like diabetes, linked to beta-cell anomalies due to mitochondrial dysfunction. This novel gene-set profiling approach holds promise for identifying therapeutic targets and biomarkers across the proteome, advancing efforts to mitigate cancer, metabolic disorders, and neurodegenerative diseases.

Awards Won:

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