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Abstract

This grant was focused on exploring a possible connection between stress responsive-signaling pathways and the molecular architecture of the N-glycoproteome.

Objectives: The molecular architecture of the mature N-glycome is dynamic, with consequences for both normal and pathologic processes. Elucidating cellular mechanisms that modulate the N-linked glycome is, therefore, crucial. The unfolded protein response (UPR) is classically responsible for maintaining proteostasis in the secretory pathway by defining levels of chaperones and quality control proteins. Our goal was to test the hypothesis that the UPR also regulates the composition and architecture of the N-glycoproteome.

Methods: We used stress-independent, small molecule-regulated methods for UPR activation to elucidate whether and how UPR-mediated remodeling of the endoplasmic reticulum proteostasis network regulates N-glycan maturation on two model secreted proteins, the CD2 adhesion domain and the collagen-I C-propeptide. We employed enzymatic digests and mass spectrometry-based glycomics analyses to analyze effects.

Results: We discovered that stress-independent activation of the UPR's XBP1s transcription factor also induces a panel of N-glycan maturation-related enzymes. The downstream consequence is a distinctive shift towards specific hybrid and complex N-glycans on N-glycoproteins produced from XBP1s-activated cells, which we characterized. Pulse-chase studies attributed this shift specifically to altered N-glycan processing, rather than to changes in degradation or secretion rates.

Discussion: Our results are significant because they provide the first mechanistic link between intracellular stress responses classically involved in maintaining proteostasis and the molecular architecture of the extracellular N-glycome. There are important implications for the cellular response to protein misfolding, cancer metastasis, and auto-immunity, which we are now exploring.

List of Publications: Dewal, M.B.; DiChiara, A.S.; Taylor, R.J.; Antonopoulos, A.; Haslam, S.M.; Dell, A.; Shoulders, M.D. "XBP1s Links the Unfolded Protein Response to the Molecular Architecture of Mature N-Glycans" **2015**, submitted.