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POST-TRANSLATIONAL MODIFICATION

Sweetening protein quality control

> these studies couple the HBP and ER quality control pathways

The hexosamine biosynthetic pathway (HBP) produces the nucleotide sugar uridine diphosphate-*N*-acetylglucosamine (UDP-GlcNAc). This metabolite is a substrate for *N*-glycosylation, a process important for protein folding within the endoplasmic reticulum (ER), and nutrient-driven *O*-GlcNAcylation. Two studies now report that activation of the HBP following ER stress promotes longevity and cardioprotection, and identify GFAT1 (glutamine fructose 6-phosphate aminotransferase 1), the rate-limiting enzyme of the HBP, as a central node that links the stress response to glucose metabolism and protein homeostasis.

Ischaemia–reperfusion (IR) is known to increase *O*-GlcNAc protein modifications and to activate the unfolded protein response (UPR), which is a cellular response to folding stress in the ER. Using a mouse model for cardiac IR injury, Wang *et al.* investigated the link between the HBP and the UPR, and demonstrated that the increase in *O*-GlcNAc modifications correlated with increased expression of GFAT1 and spliced X-box-binding protein 1 (XBP1s), a transcription factor in the UPR. Furthermore, they showed that GFAT1 is a direct transcriptional target of XBP1s, and that XBP1s induction increased UDP-GlcNAc levels and *O*-GlcNAc modifications. This, together with their finding that several inducers of ER stress lead to XBP1s-dependent HBP activation and *O*-GlcNAc modification, suggests that the UPR is coupled to the HBP under various stress conditions. Finally, the authors report a significant increase in cardiomyocyte cell death in *Xbp1s*-knockout mice compared with control littermates after IR injury; this phenotype was rescued by the expression of XBP1s. The cardioprotective effect was also dependent on GFAT1 and GlcNAc, which highlights the mechanistic link between the UPR, HBP and *O*-GlcNAc protein modification, and their role in cardioprotection from IR injury.

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In the second study, Denzel *et al.* screened for *Caenorhabditis elegans* mutants that were resistant to an inducer of ER stress. They found that animals carrying a *gfat-1* gain-of-function mutation had increased endogenous UDP-GlcNAc levels and an extended lifespan, and they hypothesized that the observed lifespan extension was owing to improved ER protein quality control. Indeed, they found that toxic protein aggregation was decreased in the ER lumen both in mutant animals and following the addition of GlcNAc, which suggests that activity of the HBP improves the clearance of misfolded proteins. Although the authors did not detect UPR activation or changes in UPR-target genes, they showed that expression of SEL-1, a subunit of a ubiquitin ligase that is involved in ER-associated protein degradation (ERAD; a process whereby misfolded ER proteins are targeted for proteasomal degradation), was increased in mutant animals; knockdown of *sel-1* augmented protein aggregation and abolished the longevity of *gfat-1* gain-of-function mutants. In addition, *gfat-1* mutants exhibited increased proteasomal activity, which indicates that improved ER protein homeostasis is linked to greater proteolytic capacity and longevity. Interestingly, the authors showed that another cellular degradation pathway, autophagy, was induced in mutant animals, which leads to an increased lifespan. Thus, activation of the HBP induces distinct quality control pathways to protect cells from the toxic aggregation of misfolded proteins.

Collectively, these studies couple the HBP and ER quality control pathways, and this new link might provide therapeutic targets for improving heart function and decreasing toxic protein aggregation.

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ORIGINAL RESEARCH PAPERS Wang, Z. V. *et al.* Spliced X-box binding protein 1 couples the unfolded protein response to hexosamine biosynthetic pathway. *Cell* **156**, 1179–1192 (2014) | Denzel, M. S. *et al.* Hexosamine pathway metabolites enhance protein quality control and prolong life. *Cell* **156**, 1167–1178 (2014)

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