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Journal club

THE BIOLOGICAL MEANING OF THE UPR

My interest in cell biology started when I was exposed to the cell death field in the late 1990s and the idea of an endoplasmic reticulum (ER)-selective cell death mechanism was emerging. Early in 2000, Nakagawa *et al.* shed light on this when they discovered that caspase 12 is an ER-located protease that is exclusively activated by ER stress. This study showed that caspase 12-deficient neurons were resistant to amyloid-β toxicity, which inspired me to investigate the link between protein misfolding and ER stress.

At the time, the unfolded protein response (UPR) in mammals was known to be activated by three stress sensors, including the ER-located kinase and endoribonuclease IRE1α (inositol-requiring protein 1α), the substrate of which was unknown. The years 2001 and 2002 were revolutionary, and within a few months the laboratories of David Ron, Randal Kaufman and Kazutoshi Mori identified X box-binding protein 1 (XBP1) as the target of the RNase activity of IRE1α in mammals. The publication by Calfon *et al.*, from the Ron group, is my favourite in the field. The authors addressed the most relevant aspects of IRE1α biology in just four figures. Beyond the experimental design, how the story is told and how they filled the gaps is almost like an 'odyssey'. First, a genetic screen in *Caenorhabditis elegans* identified XBP-1 as a regulator of the UPR. Second, the authors reported that mammalian XBP1 expression is induced by ER stress in an IRE1α-dependent manner. Finally, they showed that IRE1α spliced out a 26-nucleotide intron of the *XBP1* mRNA to generate an active transcription factor with a longer half-life. I use this paper to teach cell biology because the authors also reconstituted the system *in vitro*, which emphasizes the importance of biochemistry.

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In addition to delineating an unusual mechanism of stress signalling, this study 'connected the dots' in the literature to suggest the physiological relevance of the UPR. Calfon *et al.* highlight the finding by Laurie Glimcher's group, a few months earlier in 2001, that XBP1-deficient B cells fail to produce immunoglobulin and develop the secretory apparatus. XBP1 was discovered a decade before by the same group in an immunological setting, but its function was never linked to protein folding stress. Thanks to these papers, the idea that highly secretory cells depend on the UPR for their function is now common knowledge. These studies transformed the field and inspired a generation of scientists, as evidenced by the expanding literature on the UPR in cell physiology and disease.

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ORIGINAL RESEARCH PAPERS Nakagawa T. *et al.* Caspase-12 mediates endoplasmic-reticulum-specific apoptosis and cytotoxicity by amyloid-β. *Nature* **403**, 98–103 (2000) | Calfon M. *et al.* IRE1 couples endoplasmic reticulum load to secretory capacity by processing the *XBP-1* mRNA. *Nature* **415**, 92–96 (2002) | Reimold A. M. *et al.* Plasma cell differentiation requires the transcription factor XBP-1. *Nature* **412**, 300–307 (2001)