The unfolded protein response: Controlling cell fate decisions under ER stress and beyond

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Protein-folding stress at the endoplasmic reticulum (ER) is a salient feature of specialized secretory cells and is also involved in the pathogenesis of many human diseases. ER stress is buffered by the activation of the unfolded protein response (UPR), a homeostatic signalling network that orchestrates the recovery of ER function, and failure to adapt to ER stress results in apoptosis. Progress in the field has provided insight into the regulatory mechanisms and signalling crosstalk of the three branches of the UPR, which are initiated by the stress sensors protein kinase RNA-like ER kinase (PERK), inositol-requiring protein 1Î ± (IRE1Î ±) and activating transcription factor 6 (ATF6). In addition, novel physiological outcomes of the UPR that are not directly related to protein-folding stress, such as innate immunity, metabolism and cell differentiation, have been revealed.