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THE UNIVERSITY OF BRITISH COLUMBIA

THE ELEVENTH D. HAROLD COPP LECTURE

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Unfolded Protein Response in Health and Disease

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LSC #1, Life Sciences Institute, UBC

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The unfolded protein response is an intracellular signaling pathway that adjusts the abundance and protein folding capacity of the endoplasmic reticulum according to need. The most conserved branch of the pathway mediated by the ER-resident transmembrane kinase/endoribonuclease Ire1, was first discovered in *Saccharomyces cerevisiae*. It mediates signal transduction via a non-conventional mRNA splicing mechanism that was since found conserved in all metazoan cells investigated. In response to accumulation of unfolded proteins in the ER, mRNA splicing results in the production of a transcription factor (Hac1 in yeast and XBP1 in metazoan cells) that up-regulates UPR target genes, which in turn enhance protein folding in the ER to reestablish homeostasis. If homeostasis cannot be restored, cells commit to apoptosis. The UPR therefore makes life death decisions for the cell, which connects it to numerous human diseases, including inherited protein folding diseases, neurodegeneration, diabetes, and cancer. In addition to the highly specific endonucleolytic activity of Ire1 for HAC1/XBP1 mRNA, a more pleiotropic activity of Ire1, first discovered in *Drosophila* and then found in mammalian cells, initiates degradation of a set of ER-bound mRNAs, thereby reducing the load of proteins entering the ER lumen by a process termed RIDD for regulated Ire1-dependent mRNA decay. By contrast to other cells studied, *Schizosaccharomyces pombe* encodes no Hac1 homolog, displays no transcriptional upregulation of UPR target genes, and uses RIDD as the sole mechanism to balance protein folding capacity with protein folding load. A single mRNA encoding the major ER chaperone BiP escapes decay after Ire1 cleavage in its 3'UTR. Truncated BiP mRNA is stable despite its lack of a poly-A tail and is actively translated. Mechanistic aspects and evolutionary considerations will be discussed. Phase transitions are not confined to cell membranes and are emerging as a general principle driving cellular organisation.

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