

***Imperial Prize and Japan Academy Prize to:***

Kazutoshi MORI  
Professor, Graduate School of Science,  
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for “Discovery and Elucidation of the Unfolded  
Protein Response”

***Outline of the work:***

Proteins must adopt correct tertiary and quaternary structures to fulfill their functions based on the genetic code. Secretory proteins such as hormones and transmembrane proteins such as hormone receptors are synthesized on ribosomes bound to the endoplasmic reticulum (ER). Further, these proteins are folded in the ER, which contains abundant molecular chaperones that assist in correct protein folding. Only correctly folded molecules are allowed to exit the ER, move along the secretory pathway, and reach their final destination.

In 1988, it was reported that, when unfolded/misfolded proteins accumulate in the ER, an ER stress signal is transmitted to the nucleus to induce the transcription of genes encoding ER-resident molecular chaperones (termed ER chaperones hereafter), resulting in the refolding of unfolded/misfolded proteins that have accumulated in the ER. This homeostatic response is termed the unfolded protein response (UPR).

Prof. Kazutoshi Mori began analyzing the mechanism of UPR in 1989. It is a transcriptional induction program coupled with intracellular signaling from the ER to the nucleus. Using budding yeast, he first identified IRE1 as an ER stress sensor and HAC1 as a UPR-specific transcription factor and then discovered a unique mechanism by which ER stress sensing by IRE1 results in production of HAC1 through IRE1-dependent splicing of *HAC1* mRNA.

Prof. Mori further analyzed the mechanism of the mammalian UPR and clarified that the IRE1-HAC1 pathway is conserved in the form of the IRE1-XBP1 pathway and that the novel ATF6 pathway is functional in mammals. He revealed that ATF6 is a major regulator of the transcriptional induction of ER chaperones in response to ER stress and that deletion of the *ATF6* gene causes embryonic lethality at a very early developmental stage in mice and medaka fish.

Therefore, Prof. Mori demonstrated the great importance of protein folding in cells and the body and redefined our image of the ER from a static to a dynamic organelle. His initiative with regard to elucidating the molecular mechanism of UPR paved a way for curing various diseases in which ER stress is involved in their development and progression, such as diabetes, obesity, Alzheimer's disease, Parkinson's diseases, arteriosclerosis, and cancer.

**List of Publications**

1. Mori, K., Sant, A., Kohno, K., Normington, K., Gething, MJ, and Sambrook, JF: A 22 bp *cis*-acting element is necessary and sufficient for the induction of the yeast *KAR2* (BiP) gene by unfolded proteins. *EMBO J.*, 11; 2583-2593, 1992.

2. Mori, K, Ma, W, Gething, MJ, and Sambrook, J: A transmembrane protein with a *cdc2<sup>+</sup>*/CDC28-related kinase activity is required for signaling from the ER to the nucleus. *Cell*, 74; 743–756, 1993.
3. Mori, K, Kawahara, T, Yoshida, H, Yanagi, H, and Yura, T: Signalling from endoplasmic reticulum to nucleus: transcription factor with a basic-leucine zipper motif is required for the unfolded protein-response pathway. *Genes Cells*, 1; 803–817, 1996.
4. Kawahara, T, Yanagi, H, Yura, T, and Mori, K: Endoplasmic reticulum stress-induced mRNA splicing permits synthesis of transcription factor Hac1p/Ern4p that activates the unfolded protein response. *Mol. Biol. Cell*, 8; 1845–1862, 1997.
5. Kawahara, T, Yanagi, H, Yura, T, and Mori, K: Unconventional splicing of *HAC1/ERN4* mRNA required for the unfolded protein response: sequence-specific and non-sequential cleavage of the splice sites. *J. Biol. Chem.*, 273; 1802–1807, 1998.
6. Yoshida, H, Haze, K, Yanagi, H, Yura, T, and Mori, K: Identification of the *cis*-acting endoplasmic reticulum stress response element responsible for transcriptional induction of mammalian glucose-regulated proteins; involvement of basic-leucine zipper transcription factors. *J. Biol. Chem.*, 273; 33741–33749, 1998.
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9. Yoshida, H, Okada, T, Haze, K, Yanagi, H, Yura, T, and Mori, K: ATF6 activated by proteolysis directly binds in the presence of NF-Y (CBF) to the *cis*-acting element responsible for the mammalian unfolded protein response. *Mol. Cell. Biol.*, 20; 6755–6767, 2000.
10. Mori, K: Tripartite management of unfolded proteins in the endoplasmic reticulum (review). *Cell*, 101; 451–454, 2000.
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12. Yoshida, H, Okada, T, Haze, K, Yanagi, H, Yura, T, Negishi, M, and Mori, K: Endoplasmic reticulum stress-induced formation of transcription factor complex ERSF including NF-Y (CBF) and activating transcription factors 6 $\alpha$  and 6 $\beta$  that activates the mammalian unfolded protein response. *Mol. Cell. Biol.*, 21; 1239–1248, 2001.
13. Yoshida, H, Matsui, T, Yamamoto, A, Okada, T, and Mori, K: XBP1 mRNA is induced by ATF6 and spliced by IRE1 in response to ER stress to produce a highly active transcription factor. *Cell*, 107; 881–891, 2001.
14. Yoshida, H, Matsui, T, Hosokawa, N, Kaufman, RJ, Nagata, K, and Mori, K: A time-dependent phase shift in the mammalian unfolded protein response. *Dev. Cell*, 4; 265–271, 2003.
15. Nadanaka, S, Yoshida, H, Kano, F, Murata, M, and Mori, K: Activation of mammalian unfolded protein response is compatible with the quality control system operating in the endoplasmic reticulum. *Mol. Biol. Cell*, 15; 2537–2548, 2004.
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19. Ishikawa, T, Okada, T, Ishikawa-Fujiwara, T, Todo, T, Kamei, Y, Shigenobu, S, Tanaka, M, Saito, TL, Yoshimura, J, Morishita, S, Toyoda, A, Sakaki, Y, Taniguchi, Y, Takeda, S, and Mori, K: ATF6 $\alpha$ / $\beta$ -mediated adjustment of ER chaperone levels is essential for development of the notochord in medaka fish. *Mol. Biol. Cell*, 24; 1387–1395, 2013.
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