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The Unfolded Protein Response as an Adaptive Cellular Response to Endoplasmic Reticulum Stress

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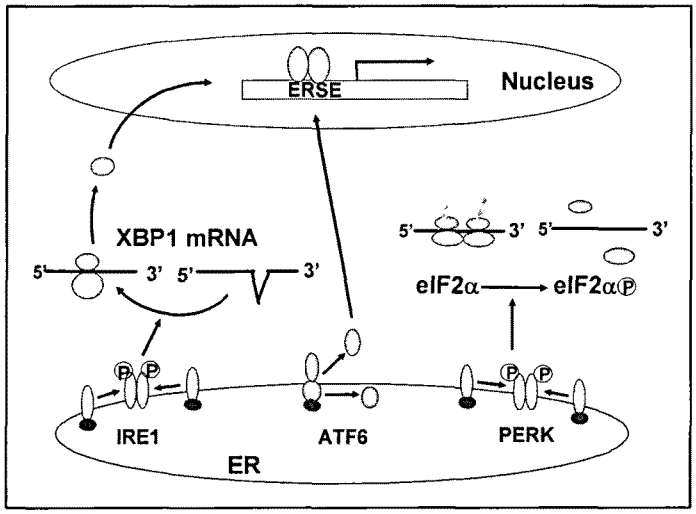
All eukaryotic cells respond to the accumulation of unfolded proteins in the endoplasmic reticulum (ER) by signaling an adaptive pathway termed the unfolded protein response (UPR). The UPR induces the transcription of ER-resident chaperones and folding catalysts and protein degrading complex. The UPR also attenuates translation of general proteins to limit further accumulation of unfolded proteins in the ER. In yeast, a type-I ER transmembrane protein kinase, Ire1p, is the proximal sensor of unfolded proteins in the ER. Ire1p initiates a nonconventional splicing reaction on *HAC1* mRNA. Hac1p is a transcription factor required for induction of the UPR genes. Ire1p requires both protein kinase and site-specific endoribonuclease (RNase) activities to signal the UPR. In mammalian cells, two homologs, IRE1α and IRE1β, are implicated in signaling the UPR. In higher eukaryotic cells, the UPR also induces Site-2 protease (S2P)-mediated cleavage of ER-localized ATF6 to generate an amino-terminal fragment that activates transcription of the UPR genes. We have shown that the endoribonuclease activity of IRE1 is required to splice XBP1 (X-box binding protein) mRNA to generate a new carboxy-terminus, thereby converting it into a potent UPR transcriptional activator. However, ATF6 cleavage was required for IRE1-dependent induction of UPR transcription. Both processing of ATF6 and IRE1-mediated splicing of XBP1 mRNA were required for full activation of the UPR. While ATF6 increases the amount of XBP1 mRNA, IRE1 removes a nonconventional 26-nucleotide intron that increases XBP1 transactivation potential.



<Mammalian에서의 UPR pathway>
소포체에 unfolded proteins이 축적되면 막 단백질인 IRE1, ATF6, PERK이 활성화 되면서 UPR이 시작된다.

References

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