J. Biochem. 2012;151(3):217–219 doi:10.1093/jb/mvr143

JB THE JOURNAL OF BIOCHEMISTRY

JB Commentary

CHOP is a multifunctional transcription factor in the ER stress response

Received November 30, 2011; accepted December 19, 2011; published online December 30, 2011

Hideki Nishitoh*

Cell Signaling, Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

*Hideki Nishitoh, Cell Signaling, Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan. Tel: +81-3-5841-4858, Fax: +81-3-5841-4798, email: hnishitoh@mol.f.u-tokyo.ac.jp

The accumulation of unfolded proteins in the endoplasmic reticulum (ER) induces ER stress. To restore ER homeostasis, cells possess a highly specific ER quality-control system called the unfold protein response (UPR). In the case of prolonged ER stress or UPR malfunction, apoptosis signalling is activated. This ER stress-induced apoptosis has been implicated in the pathogenesis of several conformational diseases. CCAAT-enhancer-binding protein homologous protein (CHOP) is induced by ER stress and mediates apoptosis. Recent studies by the Gotoh group have shown that the CHOP pathway is also involved in ER stress-induced cytokine production in macrophages. The multifunctional roles of CHOP in the ER stress response are discussed below.

Keywords: apoptosis/CHOP/inflammation/ER stress/UPR.

Abbreviations: ATF6, activating transcription factor 6; BiP, immunoglobulin-binding protein; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; C/EBP, CCAAT-enhancer-binding protein; CHOP, C/EBP homologous protein; ER, endoplasmic reticulum; ERAD, ER-associated degradation; ERO1α, ER oxidoreductin 1α; IP3R1, inositol 1,4,5-trisphosphate receptor 1; IRE1, inositol-requiring enzyme 1; LPS, lipopolysaccharide; PDI, protein disulfide isomerase; PERK, PKR-like ER kinase; PKR, protein kinase RNA; UPR, unfold protein response.

Endoplasmic reticulum (ER) stress is triggered by many physiological and pathophysiological conditions, including glucose starvation, the misglycosylation of glycoproteins, calcium deprivation from the ER lumen, elevated protein synthesis and secretion and a failure in protein folding, transport or degradation (*1*). In response to such conditions, cells react to ER dysfunction through an adaptive pathway known as the ER stress response [also known as the unfolded protein response (UPR)] that is mediated by three types of ER transmembrane receptors: protein kinase RNA-like ER kinase (PERK), activating transcription factor 6 (ATF6) and inositol-requiring enzyme 1 (IRE1) (Fig. 1). Under non-stressed conditions, all three of the ER stress receptors are maintained in an inactive state through their association with the ER chaperone immunoglobulin heavy-chain-binding protein (BiP; also known as GRP78). When unfolded proteins accumulate, BiP dissociates from the receptors, leading to their activation and triggering the ER stress response (*2*). The ER stress response consists of three major pathways: (i) translational attenuation to modulate ER protein synthesis via the PERK-induced phosphorylation of eIF2α; (ii) gene expression to induce ER luminal chaperones, such as BiP/GRP78 and GRP94, and other components to increase the capacity for protein folding; and (iii) ER-associated degradation to remove unfolded proteins from the ER. However, if ER stress persists or is aggravated, ER stress signalling appears to switch from pro-survival to pro-apoptosis (*3*–*5*). ER stress-induced apoptosis is also mediated by the three receptors mentioned above and has recently been implicated in various conformational diseases, including neurodegenerative diseases, ischaemic diseases and diabetes mellitus (*5*, *6*).

The transcription factor CCAAT-enhancer-binding protein homologous protein (CHOP) was first reported as a molecule involved in ER stress-induced apoptosis (*4*, *7*). CHOP expression is low under non-stressed conditions, but its expression markedly increases in response to ER stress through IRE1-, PERK- and ATF6-dependent transcriptional induction. The activation of ATF4, which is induced by the PERK-mediated phosphorylation of eIF2α, is thought to play a dominant role in the induction of CHOP in response to ER stress (*8*). The overexpression of CHOP promotes apoptosis in several cell lines, whereas CHOP-deficient cells are resistant to ER stress-induced apoptosis (*4*, *7*). Therefore, CHOP plays an important role in the induction of apoptosis. $CHOP^{-/-}$ mouse experiments reveal that CHOP-mediated apoptosis contributes to the pathogenesis of a number of ER stress-related diseases (*9*). However, exactly how CHOP mediates ER stress-induced apoptosis remains controversial. The down-regulation of Bcl-2 and the induction of the BH3-only pro-apoptotic proteins Bim, Puma and Bax as well as DR5, a member of the death-receptor protein family, are considered to contribute to CHOP-mediated apoptosis (*4*, *7*, *10*, *11*). Interestingly, CHOP also induces the depletion of cellular glutathione and increases the production of reactive oxygen species in the ER (*4*, *7*). CHOP transcriptionally induces ERO1α, which catalyses the reoxidation of PDI, resulting in the production of hydrogen peroxide (*12*, *13*) Thus, ERO1α may be an important mediator of apoptosis downstream of CHOP. The cellular calcium signalling

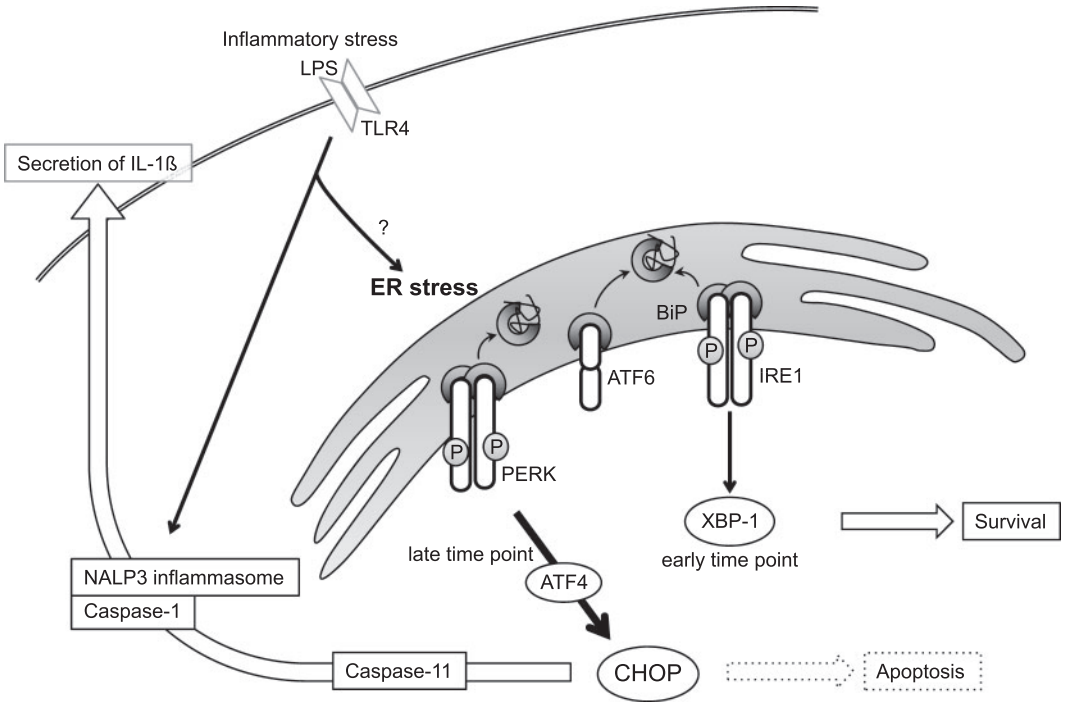

Fig. 1 Schematic representation of the role of the ER stress-CHOP pathway in inflammatory stress responses. The treatment of macrophages with LPS specifically activates the IRE1-XBP-1 pathway at an early time point and inhibits apoptosis. At a later time point, the PERK-ATF4 pathway induces CHOP expression. CHOP mediates the secretion of IL-1β through the caspase-11-induced activation of caspase-1.

pathway has also been implicated in ER stress-induced and CHOP-mediated apoptosis (*14*). The CHOP-induced expression of ERO1α activates the ER calcium release channel IP3R1 (*15*). Cytoplasmic calcium released from the ER triggers apoptosis by the activation of CaMKII, eventually leading to the activation of downstream apoptosis pathways. The ERO1α–IP3R1–CaMKII pathway may be a main axis in CHOP-mediated apoptosis.

The UPR is known to be involved in the pathogenesis of inflammation (*e.g.* atherosclerosis) (*16*). Recent publications have indicated that CHOP is a key molecule not only in apoptosis but also in inflammatory responses. The treatment of mice with lipopolysaccharide (LPS) activates the UPR and induces the expression of CHOP mRNA in the lung via yet unknown mechanism (*17*). LPS-induced CHOP is crucial for the induction of caspase-11 (*18*) that plays an important role in the processing of pro-IL-1β through caspase-1 activation (Fig. 1) (*19*). Moreover, LPS-induced secretion of IL-1β is attenuated in $CHOP^{-/-}$ mice (*18*). These findings suggest that the ER stress-CHOP pathway plays a crucial role in the pathogenesis of inflammation through the induction of caspase-11. However, it remains unclear how toll-like receptor 4, the plasma membrane receptor of LPS, mediates the pro-survival ER stress response, but not the pro-apoptosis response (Fig. 1). In their report in *J Biochem*, Nakayama *et al.* (*20*) provide new insight into the molecular mechanism by which LPS inhibits the CHOP-mediated proapoptosis signal. In macrophages, the induction of CHOP by LPS is delayed compared with that by thapsigargin that triggers ER stress by depleting ER luminal calcium stores. Moreover, LPS specifically activates the IRE1-XBP-1 pathway, but not the PERK-ATF4 pathway, at early time points. Because the PERK-ATF4 pathway is thought to be dominant in the induction of CHOP in response to ER stress, the time course-dependent, specific activation of IRE1 may affect cell fate whether the UPR mediates the inflammatory response or apoptosis in LPS-treated macrophages. Further investigation of this mechanism may help in the development of therapeutic approaches for inflammatory diseases and conformational diseases.

Conflict of interest
None declared.

References

1. Asada, R., Kanemoto, S., Kondo, S., Saito, A., and Imaizumi, K. (2011) The signalling from endoplasmic reticulum-resident bZIP transcription factors involved in diverse cellular physiology. *J. Biochem.* **149**, 507–518
2. Bertolotti, A., Zhang, Y., Hendershot, L.M., Harding, H.P., and Ron, D. (2000) Dynamic interaction of BiP and ER stress transducers in the unfolded-protein response. *Nat. Cell Biol.* **2**, 326–332
3. Kadowaki, H., Nishitoh, H., and Ichijo, H. (2004) Survival and apoptosis signals in ER stress: the role of protein kinases. *J. Chem. Neuroanat.* **28**, 93–100
4. Kim, I., Xu, W., and Reed, J.C. (2008) Cell death and endoplasmic reticulum stress: disease relevance and therapeutic opportunities. *Nat. Rev. Drug Discov.* **7**, 1013–1030

5. Marciniak, S.J. and Ron, D. (2006) Endoplasmic reticulum stress signaling in disease. *Physiol. Rev.* **86**, 1133–1149
6. Homma, K., Katagiri, K., Nishitoh, H., and Ichijo, H. (2009) Targeting ASK1 in ER stress-related neurodegenerative diseases. *Expert Opin. Ther. Targets* **13**, 653–664
7. Oyadomari, S. and Mori, M. (2004) Roles of CHOP/GADD153 in endoplasmic reticulum stress. *Cell Death Differ.* **11**, 381–389
8. Harding, H.P., Zhang, Y., Bertolotti, A., Zeng, H., and Ron, D. (2000) Perk is essential for translational regulation and cell survival during the unfolded protein response. *Mol. Cell* **5**, 897–904
9. Tabas, I. and Ron, D. (2011) Integrating the mechanisms of apoptosis induced by endoplasmic reticulum stress. *Nat. Cell Biol.* **13**, 184–190
10. Yamaguchi, H. and Wang, H.G. (2004) CHOP is involved in endoplasmic reticulum stress-induced apoptosis by enhancing DR5 expression in human carcinoma cells. *J. Biol. Chem.* **279**, 45495–45502
11. Schneider, P. and Tschopp, J. (2000) Apoptosis induced by death receptors. *Pharm. Acta Helv.* **74**, 281–286
12. Lu, P.D., Jousse, C., Marciniak, S.J., Zhang, Y., Novoa, I., Scheuner, D., Kaufman, R.J., Ron, D., and Harding, H.P. (2004) Cytoprotection by pre-emptive conditional phosphorylation of translation initiation factor 2. *EMBO J.* **23**, 169–179
13. Gross, E., Sevier, C.S., Heldman, N., Vitu, E., Bentzur, M., Kaiser, C.A., Thorpe, C., and Fass, D. (2006) Generating disulfides enzymatically: reaction products and electron acceptors of the endoplasmic reticulum thiol oxidase Ero1p. *Proc. Natl. Acad. Sci. USA* **103**, 299–304
14. Seimon, T.A., Obstfeld, A., Moore, K.J., Golenbock, D.T., and Tabas, I. (2006) Combinatorial pattern recognition receptor signaling alters the balance of life and death in macrophages. *Proc. Natl. Acad. Sci. USA* **103**, 19794–19799
15. Li, G., Mongillo, M., Chin, K.T., Harding, H., Ron, D., Marks, A.R., and Tabas, I. (2009) Role of ERO1-alpha-mediated stimulation of inositol 1,4,5-triphosphate receptor activity in endoplasmic reticulum stress-induced apoptosis. *J. Cell Biol.* **186**, 783–792
16. Woo, C.W., Cui, D., Arellano, J., Dorweiler, B., Harding, H., Fitzgerald, K.A., Ron, D., and Tabas, I. (2009) Adaptive suppression of the ATF4-CHOP branch of the unfolded protein response by toll-like receptor signalling. *Nat. Cell Biol.* **11**, 1473–1480
17. Endo, M., Oyadomari, S., Suga, M., Mori, M., and Gotoh, T. (2005) The ER stress pathway involving CHOP is activated in the lungs of LPS-treated mice. *J. Biochem.* **138**, 501–507
18. Endo, M., Mori, M., Akira, S., and Gotoh, T. (2006) C/EBP homologous protein (CHOP) is crucial for the induction of caspase-11 and the pathogenesis of lipopolysaccharide-induced inflammation. *J. Immunol.* **176**, 6245–6253
19. Kayagaki, N., Warming, S., Lamkanfi, M., Walle, L.V., Louie, S., Dong, J., Newton, K., Qu, Y., Liu, J., Heldens, S., Zhang, J., Lee, W.P., Roose-Girma, M., and Dixit, V.M. (2011) Non-canonical inflammasome activation targets caspase-11. *Nature* **479**, 117–121
20. Nakayama, Y., Endo, M., Tsukano, H., Mori, M., Oike, Y., and Gotoh, T. (2010) Molecular mechanisms of the LPS-induced non-apoptotic ER stress-CHOP pathway. *J. Biochem.* **147**, 471–483