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Perspective

The Roles of Synoviolin in Crosstalk Between Endoplasmic Reticulum Stress-Induced Apoptosis and p53 Pathway

Satoshi Yamasaki[1]
Naoko Yagishita[1]
Kusuki Nishioka[2]
Toshihiro Nakajima[1,*]

[1]Department of Genome Science; [2]Rheumatology, Immunology and Genetics Program; Institute of Medical Science; St. Marianna University School of Medicine; Kawasaki, Japan

*Correspondence to: Toshihiro Nakajima; Department of Genome Science; Institute of Medical Science; St. Marianna University School of Medicine; 2-16-1 Sugao Miyamae-ku; Kawasaki, Kanagawa 216-8512 Japan; Tel.: +81.44.977.8111 ext. 4113; Fax: +81.44.977.9772; Email: nakashit@marianna-u.ac.jp

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KEY WORDS

apoptosis, E3 ubiquitin ligase, rheumatoid arthritis, cancer, UPR, ERAD, hrd1

ABBREVIATIONS

GRP	glucose-regulated protein
eIF2α	eukaryotic translation initiation factor 2α
PERK	PKR-like ER kinase
CHOP	C/EBP homologues protein
XBP1	X box binding protein 1
ATF6	activating transcription factor 6
TRAF2	TNF receptor-associated factor 2
PUMA	p53 upregulated modulator of apoptosis
Cop1	constitutive photomorphogenesis protein 1
Parc	Parkin-like cytoplasmic protein,

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ABSTRACT

Endopalsmic reticulum (ER) is specialized organelle to maintain the integrity of secreted and membranous proteins. ER also senses so-called "ER stress", which is a result of various internal and external stresses, and triggers apoptosis when the diverse attempts to accommodate with the stress are in fail. The impairment these ER functions has been implicated in several human diseases, in which aberrant ER stress induced apoptosis is observed. We discuss about another disease model related with ER mediated apoptosis based on the recent studies about Synoviolin, an E3 ubiquitin ligase inherently utilized for ER associated degradation (ERAD). In addition to its canonical role in ERAD, Synoviolin targets tumor suppressor gene p53 for proteasomal degradation, suggesting the crosstalk between ERAD and p53 mediated apoptotic pathway under ER stress. Together with the anti-apoptotic property of Synoviolin previously elucidated by both in vitro and in vivo analyses, its new function in p53 regulation may provide a new insight into the pathomechanism of proliferative diseases such as cancer or rheumatoid arthritis.

SYNOVIOLIN IN ER STRESS

Secreted and membranous proteins are modified in endoplasmic reticulum (ER) and each one of them is highly quality controlled by folding of newly synthesized proteins with ER resident chaperones (e.g., calnexin, calreticulin, GRP78, GRP94, protein disulfide isomerase).[1] If the influx of nascent protein is more than the folding capacity of ER, nascent peptide chains (unfolded proteins) accumulate in ER.[2-3] Similarly, glucose deprivation, DNA damage, inhibition of N-linked glycosylation or increase in protein synthesis can also perturb the proper post-translational modifications of nascent proteins.[3] The unfolded proteins produced under these conditions in the ER cause inverse effect on physiological homeostasis or protein integrity, a plight called the ER stress that is implicated with variety kinds of human diseases. (For a review see refs. 2,4–7.)

It is demonstrated that ER can sense the stress by several ER resident molecules (e.g., IRE1, PERK, ATF6).[2-3] They also initiate the unfolded protein response (UPR) to adapt various internal and external stresses for maintenance of protein integrity.[1-4] The ER stress induce phosphorylation of eIF2 α through the activation of the PERK, which results in attenuation of global translation to reduce the influx of proteins into ER and unfolded proteins.[8] On the other hand, PERK-eIF2α kinase axis upregulates expression of pro-apoptotic protein, CHOP, via activation of transcriptional factor ATF4.[9] ATF6, an ER resident transcriptional factor, is cleaved and translocates into nucleus to promote a group of stress inducible proteins including chaperones (e.g., Grp78, Grp97, protein disulphide isomerase) and transcription factors (XBP1).[10-12] ATF6 was also proved to induce the transcription of CHOP.[13] An ER resident enzyme, IRE1, possesses dual catalytic domains as serine-threonine kinase and endoribonuclease, activates XBP1 by generating its splicing variant (active form), which also contributes to transcription of chaperons and other molecule important for UPR and ERAD.[2,12] IRE1 is also involved in polyglutamine-induced cell death by activating ASK 1 through formation of an IRE1-TRAF2-ASK1 complex.[14] It is worthy to note that these molecules involved in UPR pathway have potential to carry out both prevention and promotion of apoptosis.

The UPR is closely related with another homeostatic mechanisms in ER known as ER associated degradation (ERAD), a system for disposal of the unfolded proteins.[15-18] The ERAD requires three steps, substrate transportation from the ER to the cytoplasm (dislocation), ubiquitination by specific ubiquitin ligases and proteolysis by proteasome in cytoplasm.[18] There are several ubiquitine ligase are reported involved in ERAD, and

Synoviolin is one of these ER-resident E3 ubiquitin ligases.[19-22] Synoviolin was introduced as a mammalian homolog of Hrd1p/Der3p that is inherent ubiquitin ligase for ERAD system. Misfolded carboxypeptide yscY (CPY*) and 3-hydroxy-3-methylglutaryl-coenzymeA reductase (HMGR), a key enzyme of the mevalonate pathway in yeast are known substrate for Synoviolin.[23-24] In mammal, Synoviolin seems to play more complicated roles, because it is essential for embryogenesis and suggested to be a pathogenic factor for arthritis.[19,25] The *synoviolin* homozygous knock out mouse is embryonic lethal due to severe anemia brought about by enhanced apoptosis in the liver where the embryonic erythrogenesis takes place. Since UPR, such as the induction of chaperon proteins, is not impaired in the knock out mice, the sole disruption of ERAD system in the mice can cause ER stress-induced apoptosis when the protein synthesis rapidly increases to build up fetal erythrogenesis in the liver.[25] The heterozygous knock out mouse can survive and show no phenotype in appearance, however, the mouse shows remarkable resistance to experimental arthritis model, which is induced by immunization of type II collagen (collagen induced arthritis: CIA).[19,25] Histological analyses demonstrate that the hyperplasia of the synovial tissue is suppressed in the mouse, which is usually observed in the CIA-induced wild type mice. Interestingly, enhanced apoptosis is detected in the synovial tissue of the CIA-induced heterozygous knock out mouse, indicating an important role of Synoviolin in antagonizing the apoptotic pathway. Contrary to this, Synoviolin overexpressing mouse exhibits overgrowth of synovial tissue that resembles rheumatoid arthritis (RA), a common chronic inflammatory joint disease in human.[19] In addition, the evidences that Synoviolin prevents ER stress induced apoptosis in cultured cells support the idea that Synoviolin is an anti-apoptotic factor in mammals probably due to protecting the cells from ER stress.[19,21] Based on these data, we proposed one pathogenic status with Synoviolin overexpression as "Hyper-ERAD", which might allow excess elimination of unfolded proteins and provide the cell with ER stress free condition.[19,26] It is estimated that 30 to 40% of the newly synthesized proteins failed to be folded properly in ER, which means most of the cells are facing at risk of ER stress unless enough ERAD constitutively clears these constantly produced unfolded proteins.[27] Since the positive correlation is known between ERAD and the production of secretory proteins, hyper-ERAD may allow the cell to over-produce secretary proteins.[28] A cell equipped with hyper-ERAD could be very refractory to ER stress, because unfolded proteins can be promptly eliminated by the equipped system even if the protein synthesis is upregulated or the environment becomes stressful for ER. When the cells become free from unfolded proteins, it is possible that UPR triggered translational attenuation or apoptosis signal are shut down. These phenotypes that might be resulted from hyper-ERAD (e.g., increased protein production, anti-apoptotic) are similar to the hallmarks of the proliferating diseases including neoplasm and arthritis.

p53 REGULATION BY SYNOVIOLIN

The mechanisms for the ER stress-induced apoptosis remain enigmatic, however, recent reports have succeeded to illustrate some pathways in the ER stress induced apoptosis (reviewed in refs. 29–32). ER resident caspase (caspase-12 in mouse and probably caspase-4 in human) is suggested to be activated in ER stress-induced apoptosis, even though their roles in human are still under debate.[33,34] One of the most characterized pathways in ER

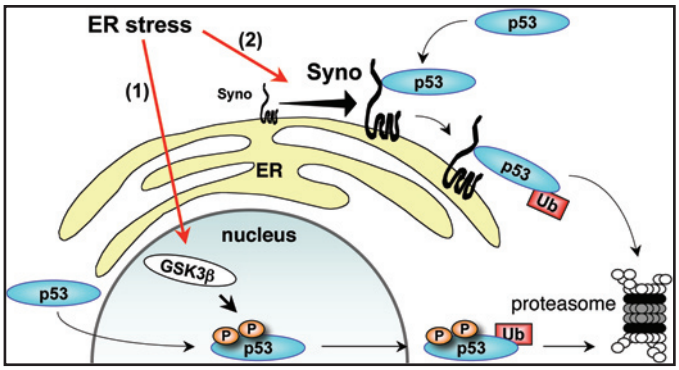

Figure 1. p53 regulatory pathway under ER stress. (1) Nuclear GSK3β, which is probably activated by ER resident kinase(s) after ER stress, phosphorylates p53 at serine 315 and 376. The phosphorylated p53 is ubiquitinated, exported to cytoplasm and degraded by proteasome. (2) ER stress induces Synoviolin expression by IRE and/or ATF6. Cytoplasmic p53 is trapped and ubiquitinated for proteasomal degradation by ER stress-induced Synoviolin (Syno) at ER before translocating into nucleus.

stress-induced apoptosis is carried out through BCL2 family proteins. The first report related with this pathway demonstrated the protective effect of BCL2 overexpression or Bax and Bak deficiency against ER stress-induced apoptosis.[35-37] Furthermore, BCL2 is inhibited by CHOP, which is transcriptionally induced by PERK-eIF2α-ATF4 pathway and post-translationaly activated by kinase pathway originated from IRE1-TRAF2 complex on ER after ER stress.[9,13,38] The other members of the BH3-only BCL-2 family proteins, PUMA and Noxa, have been identified as the pro-apoptotic molecules induced by ER stress.[39,40] Consistent with these facts, the activation of p53 is also observed in the ER stress, because both PUMA and Noxa are the evident transcriptional targets of p53.[40-42] However, the ER stress induced p53 activation is not straight forward, namely a mild or a short time ER stress tends to inhibit p53 dependent apoptosis and a severe or a long time stress promote it.[40,43,44]

The findings from Koromilas and our lab provide the evidence for striking mechanism in p53 regulation at ER (Fig. 1).[43-45] Qu et al. proved that ER stress inhibits p53 dependent apoptosis. The critical step for p53 suppression is accomplished by phosphorylation of p53 at serine 315 and 376 by glycogen synthase kinase-3β (GSK3 β).[43,44] The mechanism how the kinase is activated after ER stress remains unclear, but the C-terminus phosphorylation of p53 by the kinase exhibits remarkable inhibitory effect on nuclear localization and stabilization of p53 in cooperation with Hdm2, one of the most important negative regulators for p53.[46] On the other hand, we introduced Synoviolin as a potent negative regulator of p53.[45] Synoviolin can cytoplasmically capture p53 on ER and degrade it by ubiquitin-proteasome system. Synoviolin is totally independent of known p53 regulating ubiquitin ligases such as Hmd2, Pirh2, Cop1 or Parc in this process.[45,46] The importance of Synoviolin is underlined by the fact that the steady state level of p53 protein is strictly regulated by Synoviolin, because the half life of p53 protein is markedly prolonged in human cell line by siRNA for *synoviolin* as well as in the embryonic fibroblasts from *synoviolin* knock out mouse.[45] Since Synoviolin is known to be upregulated by IRE or ATF6, it can be said that the ER stress also indirectly dampen p53 through an ER resident ubiquitin ligase, Synoviolin.[21] Both GSK3 β and Synoviolin pathways invite the same consequences of p53, cytoplasmic localization and degradation in there, which might

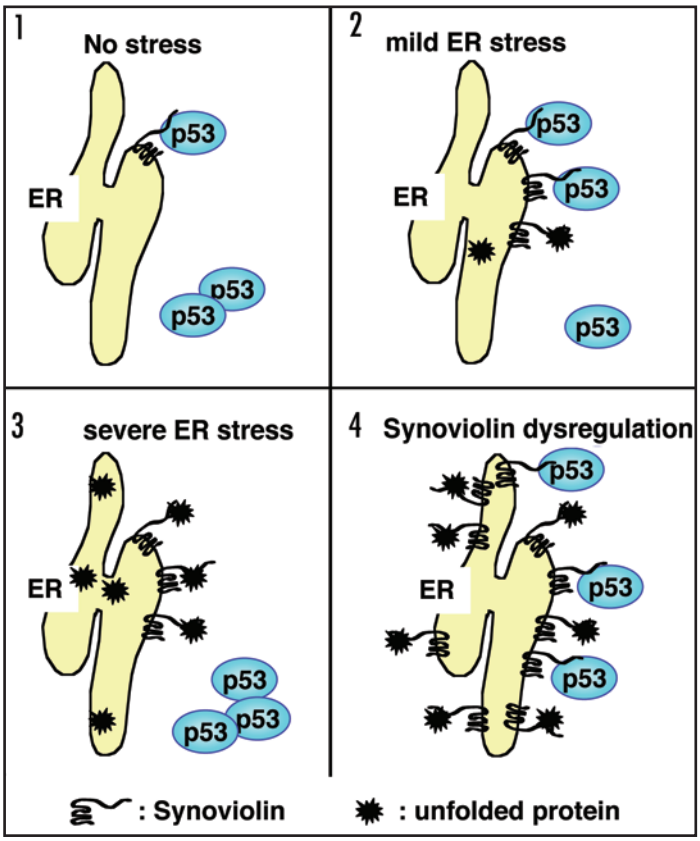

Figure 2. p53 regulatory status according to ER stress. (1) p53 is constitutively downregulated by Synoviolin (Syno) on ER. (2) ER stress induces Synoviolin, which is utilized for trapping p53 for degradation as well as its canonical role in ERAD. (3) Severe or prolonged ER stress produces the excess amount of unfodled proteins that may occupy most of Synoviolin. The trapped p53 are liberated from Synoviolin and translocate into nucleus to function as a transcriptional factor. (4) Neither ER stress nor p53 activation in Synoviolin dys-regulated cells. The aberrantly high expression of Synoviolin due to activation of particular signal pathway (e.g., JNK and ERK) simultaneously degrades p53 and unfolded proteins, which may block both p53 dependent and ER stress-induced apoptosis.

help to gain times for chaperones to refold the unfolded proteins to restore their ER functions before apoptosis is induced in these cells. The aberrant cytoplasmic localization of p53 are described in human cancers, thus the ER stress initiated p53 inhibition by Synoviolin or GSK3 β could be the mechanism how p53 is sequestered in cytoplasm of these cancers.[47,48] The milieu surrounding neoplasm cells also support this idea, namely the stressful external environment may give mild ER stress to tumor cells, and help to inhibit p53 by activating Synoviolin or GSK3 β. Actually, ER stress is demonstrated by the activation of ER stress inducible molecules in human tumor and arthritis.[19,49] On this point of view, blockade of Synoviolin or GSK3 β can be applied for adjuvant therapy for neoplasm therapy or arthritis through p53 activation.

IMPACT OF SYNOVIOLIN DYSREGULATION

There seems to be a transition in function of UPR proteins. IRE1 is one of the most characterized proteins in this aspect, because it renders anti-apoptotic effect by induction of ER chaperons through XBA1 activation, however, IRE1 can be pro-apoptotic by triggering ASK1-JNK pathway.[12,50] The severity or the duration of ER stress seems to determine the down stream pathway of IRE1. It is expected that severely damaged cells by ER stress could produce unfolded proteins that may be harmful to the systemic cells, therefore it is reasonable to change its roles from anti-apoptotic to pro-apoptotic as the cell damage becomes more severe. As mentioned before, the activity of p53 under ER stress also fluctuates according to the level of the stress. It seems that a mild ER stress de-stabilizes p53, but a severe one activates it.[40,43,44] The mechanism that determine the activity of p53 has not been fully figured out experimentally, however, previous data may unravel it by describing in detail the regulation and the function of Synoviolin under ER stress (Fig. 2). In unstressed cell, Synoviolin is thought to regulates steady state levels of p53 by sequestering and ubiquitinating it for proteasomal degradation in cytoplasm, because Synoviolin knocking down by siRNA clearly satbilizes the p53.[45] In the mild ER stress condition, Synoviolin is transcriptionally upregulated by IRE or ATF6 activation and the increased Synoviolin plays its canonical role in ERAD.[19-22] If the expression of Synoviolin is induced more than that is required to eliminate unfolded proteins, the free Synoviolin may capture more p53 than they do in unstressed cell. As a result, a mild ER stress may achieve p53 suppression (Fig. 2B). When a severe or a prolonged ER stress takes place, the unfolded proteins can exceed the capacity of upregulated Synoviolin. The overwhelming unfolded proteins may squelch Synoviolin and let it to liberate p53 for activation (Fig. 2C). This scenario can explain, at least in part, why p53 change its behavior according to the severity of ER stress.

ER stress has been implicated in the pathogenesis in human diseases.[2,4-7] Disruption of physiological UPR and/or ERAD or abnormal conformation of proteins have been demonstrated in a variety of human diseases including Alzheimer disease, Parkinson disease, neuronal damage by ischemia, prion disease, cystic fibrosis and diabetes mellitus. The cause of these degenerative changes in the diseases is explained by aberrant ER stress-induced apoptosis in the affected organs. Contrary to this, we would like to propose a novel model for proliferative diseases such as tumor or RA, which is also a hypothesis reply to an interesting question, "what will happen to cells if they are completely free from ER stress?" As previously described, Synoviolin has two functions, one is for ERAD and the other is for p53 blockade. Given that Synvoiolin is aberrantly upregulated in cells as shown in Figure 2D, they could provide the cells an ability to over-secrete and overgrow, because overexpressed Synoviolin will unburden the cells from ER stress by eliminating the unfolded protein even in the hostile milieu surrounding the cells such as hypoxia and/or starvation. In addition, ER stress free cells may be allowed to produce the harmful amount of secretary or membranous protein. Those acquired property will help the cells to proliferate, destruct and invade into surrounding tissues. The overexpressed Synoviolin is also expected to sequester p53 in cytoplasm and degrade it, which may rescues cells that are supposed to commit apoptosis. In this regard, our analyses about *synoviolin* promoter make the hypothesis plausible. The Ets binding site (EBS) is determined to be the crucial site for *synoviolin* transcription in vivo and in vitro, and GABP, a transcription factor known to be down stream of MAP kinases such as JNK and ERK, is proved to be bind to it.[51] The MAP kinase signals are activated in both neoplasm and RA, thus these signal may induce constitutively high expression of Synoviolin in these diseases.[52,53] Similar pathogenic mechanism for neoplasm progression has been actually implicated in a human disease. There is a clinical evidence that XBP-1 is highly upregulated in multiple

myeloma cell, a hematological neoplasm characterized by overproduction of monoclonal immunoglobin or Bence Jones proteins (reviewed in ref. 4). It is important that proteasomal inhibitors have been proved to be effective to this disease, indicating accumulation of unfolded proteins by proteasome blockade affect the proliferation of neoplasmic cells. Our speculation is that the increased unfolded proteins act as an inhibitor for Synoviolin and p53 is released and activated in proteasome inhibitor treated cells. Likewise, the therapy targeting Synoviolin could be a good strategy for the proliferative diseases refractory to the conventional treatment.

CONCLUSION

ER integrates many kinds of stresses and initiates a variety of signalings to adapt to the stresses. Among them, apoptosis pathway has become an important topic for its definite pathogenic potential in human diseases. P53, one of the most important molecules in tumor, has become a novel mediator of ER stress-induced apoptosis. It also can be said that ER regulates p53 pathway, because the ER specific stresses or molecules seem to play some roles in p53 regulation. We discuss about the dual role of Synoviolin on ER, one is the ERAD and the other is p53 inhibition in cytoplasm. In this regard, Synoviolin may upregulate two aspects of proliferative diseases, overproduction of secretory proteins and resistance to apoptosis. Both expression level and its enzyme activity of Synoviolin are required for ERAD and p53 regulation, the blockade of Synoviolin expression or activity may ameliorate the proliferative diseases such as neoplasm and RA. Further research is necessary to answer the important questions about the roles of Synoviolin in ER stress induced apoptosis. Does hyper-ERAD status really exist in human diseases? Can a specific inhibitor against Synoviolin cause p53 activation, and induce apoptosis of target cells? We hope that the continuous attempt to unveil the ER mediated apoptotic pathway will help to develop the new therapeutic approach to the refractory diseases.

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References

1. Ellgaard L, Molinari M, Helenius A. Setting the standards: Quality control in the secretory pathway. Science 1999; 286:1882-8.
2. Schroder M, Kaufman RJ. The mammalian unfolded protein response. Annu Rev Biochem 2005; 74:739-89.
3. Rutkowski DT, Kaufman RJ. A trip to the ER: Coping with stress. Trends Cell Biol 2004; 14:20-8.
4. Marciniak SJ, Ron D. Endoplasmic reticulum stress signaling in disease. Physiol Rev 2006; 86:1133-49.
5. Lindholm D, Wootz H, Korhonen L. ER stress and neurodegenerative diseases. Cell Death Differ 2006; 13:385-92.
6. Zhao L, Ackerman SL. Endoplasmic reticulum stress in health and disease. Curr Opin Cell Biol 2006; 18:444-52.
7. Wu J, Kaufman RJ. From acute ER stress to physiological roles of the Unfolded Protein Response. Cell Death Differ 2006; 13:374-84.
8. Harding HP, Zhang Y, Ron D. Protein translation and folding are coupled by an endoplasmic-reticulum-resident kinase. Nature 1999; 397:271-4.
9. Harding HP, Novoa I, Zhang Y, Zeng H, Wek R, Schapira M, Ron D. Regulated translation initiation controls stress-induced gene expression in mammalian cells. Mol Cell 2000; 6:1099-108.
10. Haze K, Yoshida H, Yanagi H, Yura T, Mori K. Mammalian transcription factor ATF6 is synthesized as a transmembrane protein and activated by proteolysis in response to endoplasmic reticulum stress. Mol Biol Cell 1999; 10:3787-99.
11. Yoshida H, Haze K, Yanagi H, Yura T, 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 1998; 273:33741-9.
12. Yoshida H, Matsui T, Yamamoto A, Okada T, 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 2001; 107:881-91.
13. Yoshida H, Okada T, Haze K, Yanagi H, Yura T, Negishi M, Mori K. ATF6 activated by proteolysis binds in the presence of NF-Y (CBF) directly to the cis-acting element responsible for the mammalian unfolded protein response. Mol Cell Biol 2000; 20:6755-67.
14. Nishitoh H, Matsuzawa A, Tobiume K, Saegusa K, Takeda K, Inoue K, Hori S, Kakizuka A, Ichijo H. ASK1 is essential for endoplasmic reticulum stress-induced neuronal cell death triggered by expanded polyglutamine repeats. Genes Dev 2002; 16:1345-55.
15. Hampton RY. ER-associated degradation in protein quality control and cellular regulation. Curr Opin Cell Biol 2002; 14:476-82.
16. Friedlander R, Jarosch E, Urban J, Volkwein C, Sommer T. A regulatory link between ER-associated protein degradation and the unfolded-protein response. Nat Cell Biol 2000; 2:379-84.
17. Travers KJ, Patil CK, Wodicka L, Lockhart DJ, Weissman JS, Walter P. Functional and genomic analyses reveal an essential coordination between the unfolded protein response and ER-associated degradation. Cell 2000; 101:249-58.
18. Meusser B, Hirsch C, Jarosch E, Sommer T. ERAD: The long road to destruction. Nat Cell Biol 2005; 7:766-72.
19. Amano T, Yamasaki S, Yagishita N, Tsuchimochi K, Shin H, Kawahara K, Aratani S, Fujita H, Zhang L, Ikeda R, Fujii R, Miura N, Komiya S, Nishioka K, Maruyama I, Fukamizu A, Nakajima T. Synoviolin/Hrd1, an E3 ubiquitin ligase, as a novel pathogenic factor for arthropathy. Genes Dev 2003; 17:2436-49.
20. Bordallo J, Plemper R, Finger A, Wolf DH. Der3p/Hrd1p is required for endoplasmic reticulum-associated degradation of misfolded lumenal and integral membrane proteins. Mol Biol Cell 1998; 9:209-22.
21. Kaneko M, Ishiguro M, Niinuma Y, Uesugi M, Nomura Y. Human HRD1 protects against ER stress-induced apoptosis through ER-associated degradation. FEBS Lett 2002; 532:147-52.
22. Kikkert M, Doolman R, Dai M, Avner R, Hassink G, vanVoorden S, Thanedar S, Roitelman J, Chau V, Wiertz E. Human HRD1 is an E3 ubiquitin ligase involved in degradation of proteins from the endoplasmic reticulum. J Biol Chem 2004; 279:3525-34.
23. Shearer AG, Hampton RY. Structural control of endoplasmic reticulum-associated degradation: Effect of chemical chaperones on 3-hydroxy-3-methylglutaryl-CoA reductase. J Biol Chem 2004; 279:188-96.
24. Shearer AG, Hampton RY. Lipid-mediated, reversible misfolding of a sterol-sensing domain protein. EMBO J 2005; 24:149-59.
25. Yagishita N, Ohneda K, Amano T, Yamasaki S, Sugiura A, Tsuchimochi K, Shin H, Kawahara K, Ohneda O, Ohta T, Tanaka S, Yamamoto M, Maruyama I, Nishioka K, Fukamizu A, Nakajima T. Essential role of synoviolin in embryogenesis. J Biol Chem 2005; 280:7909-16.
26. Yamasaki S, Yagishita N, Tsuchimochi K, Nishioka K, Nakajima T. Rheumatoid arthritis as a hyper-endoplasmic-reticulum-associated degradation disease. Arthritis Res Ther 2005; 7:181-6.
27. Yewdell JW. Not such a dismal science: The economics of protein synthesis, folding, degradation and antigen processing. Trends Cell Biol 2001; 11:294-7.
28. Molinari M, Sitia R. The secretory capacity of a cell depends on the efficiency of endoplasmic reticulum-associated degradation. Curr Top Microbiol Immunol 2005; 300:1-15.
29. Boyce M, Yuan J. Cellular response to endoplasmic reticulum stress: A matter of life or death. Cell Death Differ 2006; 13:363-73.
30. Ferri KF, Kroemer G. Organelle-specific initiation of cell death pathways. Nat Cell Biol 2001; 3:E255-63.
31. Szegezdi E, Logue SE, Gorman AM, Samali A. Mediators of endoplasmic reticulum stress-induced apoptosis. EMBO Rep 2006; 7:880-5.
32. Chunyan X, Bailly-Maitre B, Reed JC. Endoplasmic reticulum stress: Cell life and death decisions. J Clin Invest 2005; 115:2656-64.

33. Hitomi J, Katayama T, Eguchi Y, Kudo T, Taniguchi M, Koyama Y, Manabe T, Yamagishi S, Bando Y, Imaizumi K, Tsujimoto Y, Tohyama M. Involvement of caspase-4 in endoplasmic reticulum stress-induced apoptosis and Abeta-induced cell death. J Cell Biol 2004; 165:347-56.
34. Nakagawa T, Zhu H, Morishima N, Li E, Xu J, Yankner BA, Yuan J. Caspase-12 mediates endoplasmic-reticulum-specific apoptosis and cytotoxicity by amyloid-beta. Nature 2000; 403:98-103.
35. Scorrano L, Oakes SA, Opferman JT, Cheng EH, Sorcinelli MD, Pozzan T, Korsmeyer SJ. BAX and BAK regulation of endoplasmic reticulum Ca2+: A control point for apoptosis. Science 2003; 300:135-9.
36. Zong WX, Lindsten T, Ross AJ, MacGregor GR, Thompson CB. BH3-only proteins that bind pro-survival Bcl-2 family members fail to induce apoptosis in the absence of Bax and Bak. Genes Dev 2001; 15:1481-6.
37. Zong WX, Li C, Hatzivassiliou G, Lindsten T, Yu QC, Yuan J, Thompson CB. Bax and Bak can localize to the endoplasmic reticulum to initiate apoptosis. J Cell Biol 2003; 162:59-69.
38. McCullough KD, Martindale JL, Klotz LO, Aw TY, Holbrook NJ. Gadd153 sensitizes cells to endoplasmic reticulum stress by downregulating Bcl2 and perturbing the cellular redox state. Mol Cell Biol 2001; 21:1249-59.
39. Reimertz C, Kogel D, Rami A, Chittenden T, Prehn JH. Gene expression during ER stress-induced apoptosis in neurons: Induction of the BH3-only protein Bbc3/PUMA and activation of the mitochondrial apoptosis pathway. J Cell Biol 2003; 162:587-97.
40. Li J, Lee B, Lee1 AS. Endoplasmic reticulum stress-induced apoptosis: Multiple pathways and activation of p53-upregulated modulator of apoptosis (PUMA) and NOXA by p53. J Biol Chem 2006; 281:7260-70.
41. Huang DC, Strasser A. BH3-Only proteins-essential initiators of apoptotic cell death. Cell 2000; 103:839-42.
42. Oda E, Ohki R, Murasawa H, Nemoto J, Shibue T, Yamashita T, Tokino T, Taniguchi T, Tanaka N. Noxa, a BH3-only member of the Bcl-2 family and candidate mediator of p53-induced apoptosis. Science 2000; 288:1053-8.
43. Qu L, Huang S, Baltzis D, Rivas-Estilla AM, Pluquet O, Hatzoglou M, Koumenis C, Taya Y, Yoshimura A, Koromilas AE. Endoplasmic reticulum stress induces p53 cytoplasmic localization and prevents p53-dependent apoptosis by a pathway involving glycogen synthase kinase-3β. Genes Dev 2004; 18:261-77.
44. Pluquet O, Qu L, Baltzis D, Koromilas AE. Endoplasmic reticulum stress accelerates p53 degradation by the cooperative actions of Hdm2 and Glycogen synthase kinase 3β. Mol Cell Biol 2005; 25:9392-405.
45. Yamasaki S, Yagishita N, Sasaki T, Nakazawa M, Kato Y, Yamadera T, Bae E, Toriyama S, Ikeda R, Zhang L, Fujitani K, Yoo E, Tsuchimochi K, Ohta T, Araya N, Fujita H, Aratani S, Eguchi K, Komiya S, Maruyama I, Higashi N, Sato M, Senoo H, Ochi T, Yokoyama S, Amano T, Kim J, Gay S, Fukamizu A, Nishioka K, Tanaka K, Nakajima T. Cytoplasmic destruction of p53 by the endoplasmic reticulum-resident ubiquitin ligase 'Synoviolin'. EMBO J 2007; 26:113-22.
46. Brooks CL, Gu W. p53 ubiquitination: Mdm2 and beyond. Mol Cell 2006; 21:307-315.
47. Moll UM, Ostermeyer AG, Haladay R, Winkfield B, Frazier M, Zambetti G. Cytoplasmic sequestration of wild-type p53 protein impairs the G_1 checkpoint after DNA damage. Mol Cell Biol 1996; 16:1126-37.
48. Schlamp CL, Poulsen GL, Nork TM, Nickells RW. Nuclear exclusion of wild-type p53 in immortalized human retinoblastoma cells. J Natl Cancer Inst 1997; 89:1530-6.
49. Shuda M, Kondoh N, Imazeki N, Tanaka K, Okada T, Mori K, Hada A, Arai M, Wakatsuki T, Matsubara O, Yamamoto N, Yamamoto M. Activation of the *ATF6*, *XBP1* and *grp78* genes in human hepatocellular carcinoma: A possible involvement of the ER stress pathway in hepatocarcinogenesis. J Hepatol 2003; 38:605-14.
50. Urano F, Wang X, Bertolotti A, Zhang Y, Chung P, Harding HP, Ron D. Coupling of stress in the ER to activation of JNK protein kinases by transmembrane protein kinase IRE1. Science 2000; 287:664-6.
51. Tsuchimochi K, Yagishita N, Yamasaki S, Amano T, Kato Y, Kawahara K, Aratani S, Fujita H, Ji F, Sugiura A, Izumi T, Sugamiya A, Maruyama I, Fukamizu A, Komiya S, Nishioka K, Nakajima T. Identification of a crucial site for synoviolin expression. Mol Cell Biol 2005; 25:7344-56.
52. Fang JY, Richardson BC. The MAPK signalling pathways and colorectal cancer. Lancet Oncol 2005; 6:322-27.
53. Meyer LH, Pap T. MAPK signalling in rheumatoid joint destruction: Can we unravel the puzzle? Arthritis Res Ther 2005; 7:177-8.