Nitric Oxide and Endoplasmic Reticulum Stress

Tomomi Gotoh, Masataka Mori

Abstract—Nitric oxide (NO) is a multifunctional biomolecule involved in a variety of physiological and pathological processes, including regulation of blood vessel dilatation and anti-arteriosclerotic effects. However, a large amount of NO is toxic to the host and causes several diseases such as apoptosis, septic shock, and diabetes mellitus. Inducible-form NO synthase is induced in inflammatory diseases, including insulitis and arteriosclerosis. Endoplasmic reticulum (ER) stress pathway was first identified as a cellular response pathway induced by the accumulation of unfolded proteins in ER to preserve ER functions. Later it was found that ER stress pathway is also activated by various cellular stresses to protect cells, but when stresses are severe, apoptosis is induced to remove damaged cells. It is reported that NO and reactive oxygen species disturb ER functions, then ER stress-mediated apoptosis pathway is activated. CHOP/GADD153, which belongs to C/EBP transcription factor family, is induced in this process and mediates apoptosis. ER stress pathway induced by NO can be involved in the pathogenesis of various vascular diseases. (Arterioscler Thromb Vasc Biol. 2006;26:1439-1446.)

Key Words: apoptosis ■ Ca^{2+} ■ endoplasmic reticulum stress ■ nitric oxide

Nitric oxide (NO) is an important multifunctional biomolecule involved in a variety of physiological and pathological processes, including regulation of blood vessel dilatation and immune response, and function as a neurotransmitter. NO is synthesized from arginine by NO synthase (NOS). There are 3 types of NOS isoforms, neuronal NOS (nNOS, also called NOS I), inducible NOS (iNOS, NOS II), and endothelial NOS (eNOS, NOS III). nNOS and eNOS are constitutively expressed; therefore, they are also called cNOS. cNOS are low-output NOS, and their activities are dependent on calmodulin and cytosolic Ca^{2+} concentration. iNOS is high-output NOS and induced by lipo polysaccharide (LPS) and some kinds of cytokines such as interferon-γ. The activity of iNOS is not dependent on calmodulin or cytosolic Ca^{2+} and is mainly regulated in transcription level. The availability of intracellular arginine is also a rate-limiting factor of all types of NOS. The activity of NOS also requires additional cofactors such as heme, FAD, NADPH, and tetrahydrobiopterin. The supplies of these cofactors also regulate NOS activity. In cardiovascular system, NO is mainly synthesized from eNOS in endothelial cells. Endothelial cells respond to hemodynamic shear stress with an acute NO release. NO produced from eNOS induces vascular smooth muscle relaxation, inhibits adhesion and aggregation of platelets, and inhibits proliferation of smooth muscle cells. Therefore, NO produced by eNOS prevents vascular diseases, such as hypertension, arteriosclerosis, heart failure, and myocardial infarction. Those cardiovascular diseases are associated with impaired endothelium NO release. It was reported that the blood pressure was significantly increased in...
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ersomal ER is the site of synthesis and folding of proteins, designated for assembly of newly synthesized proteins. Proteins must be folded into proper conformation and properly modified in ER. Unfolded or misfolded proteins cannot be delivered to Golgi apparatus. Accumulation of these abnormal proteins in ER disturbs ER function and cell survival can be threatened. ER also serves as a cellular Ca\(^{2+}\) store and plays an important role in Ca\(^{2+}\) homeostasis by pumping Ca\(^{2+}\) into ER lumen via sarcoplasmic/endoplasmic reticulum Ca\(^{2+}\)-ATPase (SERCA) and by releasing Ca\(^{2+}\) from the ER by the inositol 1, 4, 5-trisphosphate (inositol triphosphate [IP\(_3\)] receptor and/or ryanodine receptor [RyR]).22,25 High concentration of Ca\(^{2+}\) in ER is also necessary for ER functions, such as folding and disulfide bond formation of newly synthesized proteins, because functions of several ER chaperones, such as calreticulin, calnexin, and protein disulfide isomerase, depend on high concentration of Ca\(^{2+}\). Therefore, disruption of Ca\(^{2+}\) homeostasis in ER disturbs ER function.22 As mentioned later, it is reported that excess NO disturbs Ca\(^{2+}\) homeostasis.22 Proper function of the ER is essential to cell survival and disturbance of its function induces cellular damage and results in apoptosis.

Activation of ER stress-induced apoptosis pathway is reported in various diseases including vascular diseases. The processes of protein maturation in ER are complex and easily disturbed by various cellular stresses.22,25 Hypoglycemia disturbs modification of protein, hypoxia and ischemia-reperfusion disturb redox-dependent protein folding process.27 Disturbance of cytosolic Ca\(^{2+}\) homeostasis also disturbs Ca\(^{2+}\) homeostasis and Ca\(^{2+}\)-dependent protein folding processes in ER. Therefore, ER stress pathway is activated in ischemic diseases. Activation of ER stress pathway is reported also in the cardiac myocytes of heart failure patients and cardiac hypertrophy model mice.28 Disturbance of redox regulation or increased production of reactive oxygen species (ROS) may be involved in the activation of ER stress pathway in these diseases. In ER, many cysteines are oxidized to form S-S bonds, but the electrons generated in this reaction are transferred to molecular oxygen. Therefore, these reactions do not increase reducing capacity of the cell. In addition, S-S bonds of misfolded proteins needs to be reduced before retro-translocation to cytosol. Therefore, ER consumes large amount of reducing capacity, and ER functions depend on intracellular redox states.25 It is thought that oxidative stress is both ER stress inducer and accelerator. Accumulation of cholesterol in macrophages also activates ER stress pathway, because increase of cholesterol content in ER membrane disturbs ER function.29 Therefore, ER stress pathway is activated in foam cells in atherosclerotic lesions. It is reported that activation of ER stress pathway in macrophages induces both apoptosis and secretion of tumor necrosis factor (TNF\(\alpha\) and IL-6.30 Induction of iNOS in macrophages is also reported in atherosclerotic lesions.10 Therefore, NO produced from iNOS can be also the activator of ER stress pathway in foam cells. In atherosclerotic lesions, cytokines secreted from foam cell accelerates the process of arteriosclerosis, and apoptosis of foam cells are detected in the advanced stage of atherosclerosis. Therefore, ER stress pathway is thought to be involved in the pathogenesis of atherosclerosis.

When ER function is disturbed, and unfolded or misfolded proteins are accumulated in ER, ER stress response pathway is activated to recover or maintain ER functions (Figure 2).22,25,26 There are 3 ER stress sensors (Ire1, ATF6 and PERK) on ER membrane.31–33 In unstressed condition, ER chaperone BiP binds to the ER luminal domain of 3 ER stress

Figure 1. Excess NO shows various cytotoxic effects to the host.

eNOS knockout mice. In contrast, septic shock, cerebral infarction, diabetes mellitus, and neurodegenerative disorders are thought to be associated with NO overproduction.5-9 Expression of eNOS in endothelial cells is decreased in advanced atherosclerotic lesion. In contrast, iNOS and nNOS are not detected in normal vessels, but widespread production of these isoforms is found in early and advanced atherosclerotic lesions associated with macrophages, endothelial cells, and intimal cells.10 It is presumed that large amount of NO produced in atherosclerotic lesions is related to cell death in these tissues. NO has several cytotoxic effects, including reactions with proteins and nucleic acids, and causes apoptosis (Figure 1).9,11

The main targets of NO in proteins are the sulfhydryl group\(^1\) and iron (Fe) of active sites, especially Fe\(^{2+}\) in heme.13 In the nucleus, NO has been shown to cause mutations of genes14,15 and inhibition of DNA repair enzymes,16,17 and to mediate DNA strand breaks.18 NO-induced apoptosis is generally considered to be mediated by DNA damage or mitochondrial damage; however, the cascade of the cell death caused by NO has not been fully clarified.9 Recently it is reported that the endoplasmic reticulum (ER) stress pathway involving CHOP/GADD153 is important in NO-induced apoptosis in some cell types.19–23 It is reported that disturbance of Ca\(^{2+}\) homeostasis is involved in the mechanisms of NO-induced ER stress pathway activation.19,22 ER stress pathway was first identified as a cellular response pathway induced by the accumulation of unfolded proteins in ER to preserve ER functions.24–26 Later it was found that ER stress pathway is also activated by various cellular stresses, but when stresses are severe, apoptosis is induced to remove damaged cells. In this review, the relationship between the pathological roles of NO and ER stress pathway is discussed.

ER Stress Pathway

ER is the site of synthesis and folding of proteins, designated for secretion, cell membrane, Golgi apparatus, and lysosomes.22,25 ER has several important functions involving glycosylation, formation of disulfide bonds, folding, and assembly of newly synthesized proteins. Proteins must be folded into proper conformation and properly modified in ER. Unfolded or misfolded proteins cannot be delivered to Golgi apparatus. Accumulation of these abnormal proteins in ER disturbs ER function and cell survival can be threatened. ER
When unfolded or misfolded proteins are accumulated in ER, BiP dissociates from ER stress sensors, then binds to those abnormal proteins. Dissociation of BiP induces the activation of ER stress sensors. Ire1 and PERK are activated by dimer formation and then are autophosphorylated. ATF6 inactive form (p90ATF6) is transported to Golgi, and is activated by a 2-step cleavage by Site-1 protease (S1P) and Site-2 protease (S2P), then ATF6 active form (p50ATF6) is produced. p50ATF6 active form is transported to nucleus, and functions as transcriptional activator for ER stress-related genes. Four distinct ER stress response phases have been identified. The first one involves translational attenuation to reduce the load of newly synthesized proteins through phosphorylation of eIF2 by activated PERK. When eIF2 is phosphorylated by activated PERK, the binding of the initiator Met-tRNA to the ribosome is blocked. Then the frequency of the adenine-uracil-guanine initiation codon recognition is reduced, and the general translation is attenuated. However, translation of the transcription factor ATF4 is upregulated by eIF2α phosphorylation, because of its small upstream open-reading frames within the 5′ untranslated region, called upstream open-reading frame bypass scanning system. ATF4 is a transcriptional factor, which belongs to CREB/ATF family. ATF4 induces dephosphorylation of eIF2 through induction of GADD34 (regulatory subunit of protein phosphatase) and activation of protein phosphatase 1 (PP1c). PP1c catalyzes the dephosphorylation of eIF-2α. The first stage of ER stress response is terminated by re-binding of BiP to PERK and dephosphorylation of eIF-2α.

Protein folding in the ER is facilitated by ER chaperone proteins such as BiP and GRP94 and by the enzymes such as protein disulfide isomerase and peptidyl-prolyl isomerase. Under ER stress conditions, p50ATF6 binds to the cis-acting ER stress response element (ERSE) of ER stress-related genes including BiP and XBP1, then the transcription of those genes are activated. A small fragment of XBP1 mRNA is spliced out by Ire1 active form, then XBP1 active form is produced. XBP-1 active form binds to ERSE to increase the transcription of ER stress-related genes such as BiP and XBP1 itself, and shows a higher transcriptional enhancer activity than ATF6. Each ER stress response phases is described in detail.

As mentioned, the first stage of ER stress response is translational attenuation through phosphorylation of eIF2α by activated PERK. When eIF2α is phosphorylated by activated PERK, the binding of the initiator Met-tRNA to the ribosome is blocked. Then the frequency of the adenine-uracil-guanine initiation codon recognition is reduced, and the general translation is attenuated. However, translation of the transcription factor ATF4 is upregulated by eIF2α phosphorylation, because of its small upstream open-reading frames within the 5′ untranslated region, called upstream open-reading frame bypass scanning system. ATF4 is a transcriptional factor, which belongs to CREB/ATF family. ATF4 induces dephosphorylation of eIF2α through induction of GADD34 (regulatory subunit of protein phosphatase) and activation of protein phosphatase 1 (PP1c). PP1c catalyzes the dephosphorylation of eIF-2α. The first stage of ER stress response is terminated by re-binding of BiP to PERK and dephosphorylation of eIF-2α.

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Figure 3. NO and ER stress-induced apoptosis pathway.

is distinct from ATF6 binding site. Therefore, ATF6 and XBP1 play the key role to enhance the folding activity in the second stage of ER stress response. The remained unfolded or misfolded proteins are degraded in the third stage of ER stress response. In ER, protein quality control system permits only properly folded and modified proteins to translocate to Golgi. The unfolded or misfolded proteins are finally detected by the quality control system in ER, transported from the ER to cytosol, and degraded (ERAD). In the case of glycosylated proteins, ER molecular chaperone calnexin or calreticulin bind with, and prevent, premature proteins to translocate to Golgi, and those proteins are recycled to the re-folding process. Finally, glycoproteins that are not properly folded are transferred to ER-associated degradation system. It is reported that overexpression of EDEM enhances ERAD-mediated degradation. Therefore, it is believed that EDEM function as an acceptor of terminally misfolded glycoproteins that are destined to be degraded. The proteins, which are eventually degraded through ERAD system, are retro-translocated to cytosol by a multi-step process, then are degraded through ubiquitin–proteasome system in cytosol. However, the ERAD pathway downstream of EDEM is not fully clarified. The mechanism of the degradation of nonglycoprotein through ERAD system is almost unknown. On ER stress, expressions of ERAD-related molecules including EDEM are induced through Ire1 signaling and ERAD activity is enhanced. It was reported that XBP1 active form functions as a transcriptional enhancer for EDEM gene in ER stress.

ER Stress-Induced Apoptosis

When ER functions are severely impaired, apoptosis pathway is induced to protect the whole body by eliminating the damaged cells. At least 3 pathways are involved in the ER stress-mediated apoptosis (Figure 3). The first is transcriptional activation of the gene for C/EBP homologous protein (CHOP). The second is activation of the Ire1-TRAF2-ASK1-MAP kinase pathway. The third is activation of ER-associated caspase-12.

CHOP/GADD153 is expressed at low levels under physiological conditions but is strongly induced at the transcription level in response to ER stress. When cells are subjected to ER stress-inducing stimuli, 3 ER stress sensors including Ire1, ATF6, and PERK, are activated. There are at least 4 ER stress-responsive transcriptional enhancer elements (AARE1, AARE2, ERSE1, and ERSE2) in the transcriptional regulatory region of chop gene. When eIF-2α is phosphorylated by activated PERK and the general translation is attenuated, the translation of ATF4 mRNA is activated as already mentioned. ATF4 binds to the AARE 1 and AARE 2. ATF6 is activated by proteolysis, the released ATF6 active form is translocated to the nucleus and binds to the ER stress response element (ERSE) as a dimer interacting with NF-Y transcription factor. Therefore, it is speculated that the transcription of chop gene is regulated by all 3 ER stress sensor signaling pathways. However, the induction of CHOP by ER stress is nearly completely attenuated in PERK null cells. Therefore, it is speculated that the PERK-ATF4 signaling pathway plays a dominant role in the induction of CHOP over that of the ATF6 and Ire1 signaling pathways. However, to achieve maximal induction of CHOP, the presence of all 3 signaling pathways are required. Under ER stress conditions, the activity of CHOP as a transcriptional activator is enhanced through the phosphorylation of Ser78 and Ser81 of CHOP protein by the p38 MAP kinase. Under ER stress condition, it is reported that p38 MAP kinase is activated through Ire1-TRAF2-ASK1 signaling pathway as mentioned. Therefore, it is speculated there may be a crosstalk between the CHOP pathway and ASK1 pathway. ER stress-induced apoptosis is suppressed both in CHOP-null cells and chop knockout mice. However, the precise mechanisms of CHOP-mediated apoptosis are still to be elucidated. Because CHOP is a transcription factor, there must be a target gene(s), the transcription of which is activated by CHOP, and whose product(s) functions in the apoptosis signal cascade. Wang et al found candidate target genes of the CHOP protein when using representation difference analysis. However, these genes are distinct from known factors involved in the ER stress response and apoptosis. McCullough et al reported that CHOP expression results in downregulation of anti-apoptotic molecule Bcl-2 expression, depletion of cellular glutathione, and exaggerated production of ROS. Marciniak et al reported that CHOP inhibits ER stress-induced attenuation of protein synthesis by dephosphorylation of the eIF-2α through induction of GADD34. They showed that newly protein synthesis, induced by CHOP in ER stress condition, lead to accumulation of high-molecular-weight protein complex in ER and impair ER function. We previously showed that apoptosis signal induced by CHOP is transmitted to mitochondria through the translocation of pro-apoptotic molecule Bax from cytosol to mitochondria. However, the mechanism CHOP induces the translocation of Bax is still unknown. c-Jun N-terminal kinase (JNKs) and p38 MAP kinases are classified as stress-responsive MAP kinase family. JNKs and p38 MAP kinases are activated by various stresses such as ultraviolet radiation, heat shock and osmotic shock, and by inflammatory cytokines such as TNFα, and then control stress adaptation and cell death. Apoptosis signal-regulating kinase 1 (ASK1) belongs to MAPKKK family and activates...
both JNK and p38 pathways by directly phosphorylating and activating MAPK family molecules, SEK1/MKK7 and MKK3/MKK6. ASK1 is activated by the treatment with TNFα or Fas ligand.58,72,73 In the case of activation by TNFα treatment, this activation is regulated by TNF receptor-associated factor 2 (TRAF2). TRAF2 directly interacts with ASK1, and then ASK1 is activated. This activation of ASK1 is redox-dependent.58,72 In unstressed condition, thioredoxin (Trx) directly binds to ASK1, and inhibits kinase activity. Trx is a ubiquitously expressed reduction/oxidation (redox)-regulatory protein, and oxidized Trx cannot bind to ASK1. Treatment with ROS including H2O2 oxidizes Trx, and Trx dissociates from ASK1. It is reported that TNFα treatment or overexpression of TRAF2 leads to the production of ROS. MEFs derived from ASK1 knockout mice are significantly resistant to TNFα-induced apoptosis, and then sustained activation of JNK and p38 is reduced, indicating that ASK1-JNK p38 pathway is required for TNFα-induced apoptosis.58 Under the ER stress condition, activated Ire1, one of the ER stress sensors recruits TRAF2, then ASK1 directly binds to TRAF2 and is activated.57 Oxidative stress activates ER stress–ASK1 pathway. In the case of NO-induced apoptosis, dysfunction of mitochondrial respiration can be the cause of ROS production, as mentioned.74 It is thought that mitochondria pathway is involved in ASK1-mediated apoptosis. Although ER stress-induced cell death is suppressed in ASK1 knockout cells, the precise apoptosis pathway downstream of the activation of JNKs and p38 kinases remains to be clarified.57 Caspase-12 belongs to the ICE (caspase-1) subfamily of caspase cysteine protease family.22,75 ICE subfamily members function as activator of other caspases and cytokines by cleaving them. Caspase family molecules are produced as inactive pro-forms and are activated by cleavage when activating signals including apoptosis-inducing signals are transmitted. The activating signals differ in each caspase family members. Pro-caspase-12 is localized on the cytosolic side of the ER membrane and is activated by ER stress.59 However, the mechanism caspase-12 is activated in ER stress condition has not been confirmed. It was reported that caspase-12 is activated through activation of m-calpain,76 Ire1/TRAF257 and caspase-7.78 In ER stress condition, Ca2+ is released from ER to cytosol, then calpain, which is Ca2+-dependent cysteine protease, is activated. Nakagawa et al reported that activated calpain activates caspase-12 by cleavage.76 Actually, calpain inhibitor inhibits ER stress-induced caspase-12 activation. Rao et al reported that cytosolic caspase-7 is translocated from cytosol to ER in ER stress condition, and caspase-7 activates caspase-12 by cleavage.78 Yoneda et al showed that activated Ire1 recruits TRAF2, which interacts with pro-caspase-12 and promotes its clustering and activation.77 Activated caspase-12 cleaves procaspase-9, and activated caspase-9 activates procaspase-3 by cleavage. Activated caspase-3 activates apoptosis promoting molecules such as DNase. Therefore, this apoptosis pathway is independent on Apaf-1 and cytochrome c release from mitochondria. Caspase-12 knockout cells are partially resistant to ER stress-induced apoptosis.59 However, human caspase-12 gene is nonfunctional (pseudogene).79 Therefore, caspase-12 is not involved in ER stress-induced apoptosis pathway in human cells.

As mentioned, there are several signaling pathways in ER stress-induced apoptosis. It is speculated that these pathways function in parallel in ER stress condition, and one of those pathways play the major roles dependent on the kind of cells and ER stress-inducing stresses. Suppression of 1 of 3 ER stress-induced apoptosis pathway could not completely prevent ER stress-induced apoptosis.

**NO-Induced ER Stress**

Excess NO production has been implicated in diseases, such as septic shock, autoimmune diseases, cerebral infarction, and diabetes mellitus, in which NO-mediated apoptosis is often observed.59,11 NO has several cytotoxic effects, including reactions with proteins and nucleic acids, and causes apoptosis. However, the cascade of the cell death has not been fully clarified. It was generally believed that NO induces DNA damage leading to cell death through induction of p53 and activation of poly (ADP-ribose) polymerase (PARP).80,81 In unstressed condition, p53 is rapidly degraded, and the protein level of p53 within cells is very low.82 p53 is induced in response to DNA damage through suppression of rapidly degradation, then upregulated p53 either blocked cellular proliferation by cell cycle arrest at G1 stage or induced programmed cell death in the case of severe DNA damage. Apoptosis induced by p53 accumulation is mediated by mitochondria pathway.80 DNA damage also activates PARP, which results in depletion of NAD+ and ATP; subsequently, necrosis takes place.81 However, we found that NO induces apoptosis even in p53-null microglia cell lines.20 We also found that relatively low concentrations of NO induce apoptosis, at least in some types of cells including pancreatic β cells32 and macrophages,21 even though severe DNA damage is not induced. Depletion of ER Ca2+, and activation of ER stress pathway including ATF6 activation and CHOP induction was also detected in those cells treated with NO.19,21 In addition, pancreatic islets and peritoneal macrophages from chop knockout mice showed resistance to NO-induced apoptosis.19,21 Therefore, we concluded that ER stress pathway is involved in NO-induced apoptosis, at least in some cell types.22

There are some reports concerning the mechanisms how NO activates ER stress pathway. Calreticulin is a Ca2+-binding ER chaperone. Overexpression of calreticulin increased the Ca2+ content of ER and protected cells against NO-mediated apoptosis.19 As already mentioned, maintenance of Ca2+ homeostasis in the ER is essential for protein folding, because some of ER chaperones are Ca2+-dependent proteins.25 NO was reported to inhibit Ca2+-ATPase activity of SERCA by tyrosine nitration within the channel-like domain.83,84 Three subtypes of RyR have been identified, RyR1 (skeletal muscle type), RyR2 (heart type), and RyR3 (brain type). It was reported that the activities of RyR1 and RyR2 are increased by NO through S-nitrosylation.85 Therefore, it is speculated that NO depletes ER Ca2+ either by inhibiting Ca2+ uptake from cytosol through SERCA or by activating Ca2+ release to cytosol through RyR.
Another proposed mechanism for NO and ER stress-mediated apoptosis involves the effects of NO on mitochondria cytochrome c oxidase (complex IV). In physiological concentrations, NO bind to mitochondrial enzyme complex IV and inhibit it in a manner that is reversible and in competition with oxygen.²³³⁷ Four. Cytochrome c oxidase is the terminal enzyme of the mitochondrial respiratory chain. Therefore, increases in NO concentration can prevent the enzyme from using any available oxygen, prevent respiratory chain, even in the condition of enough oxygen supply, and can cause the production of ROS.²⁴ Xu et al reported that there is a disruption in the respiratory chain that is accompanied by a mitochondrial Ca²⁺ flux in NO-generating cells.²³ They also reported that this NO-mediated change in Ca²⁺ flux activates S1P, and activates ATF6 by proteolysis in association with the S2P, the resulting soluble transcription factor ATF6 active form is translocated to the nucleus where it subsequently activates ER stress-responsive genes, such as BiP. Actually, the NO-mediated ER stress response was diminished in rho⁻ cells that are devoid of mitochondrial DNA.²³ As mentioned, folding process of newly synthesizes proteins are redox-dependent. Therefore, excess NO may directly disturb ER function and activate ER stress pathway. The mechanisms NO activate ER stress pathway need to be more investigated.

An excess amount of NO is produced from iNOS. Induction of iNOS is observed mainly in inflammatory diseases including severe infection. In septic shock, excess NO is the cause of hypotension. In addition, excess NO give direct damages to cells as already mentioned. Islet cell death in insulitis induced by NO is thought to be the cause of type 1 diabetes. We can imagine that NO-induced ER stress-mediated apoptosis is involved in the pathogenesis of type 1 diabetes.²² Actually, islet cells from chop knockout mice are resistant to NO-induced apoptosis.¹⁹ It is reported that ER stress pathway is always activated in pancreas islet, probably because of complex maturation process of newly produced large amount of insulin.⁸⁶ Therefore, it is speculated that ER stress-induced apoptosis pathway is easy to be activated in islet cells.¹⁹

A small amount of NO produced by eNOS prevent atherosclerosis, ischemic diseases, and hypertension. However, excess NO production is thought to be involved in the pathogenesis of various vascular diseases including arteriosclerosis, ischemia/reperfusion, and heart failure.²⁵⁸⁷–⁹¹ Induction of iNOS is detected in inflammatory cells and endothelial cells of those lesions. It was reported that ER stress pathway is also involved in the pathogenesis of those cardiovascular diseases.²⁸²⁹⁹² Zhou et al reported that ER stress pathway including CHOP expression is activated in macrophages, which invaded to vascular wall, at all stages of arteriosclerosis.⁹³ Therefore, ER stress pathway activated by NO can be involved in the pathogenesis of arteriosclerosis, even though accumulation of free cholesterol in macrophages is thought to be the main cause of ER stress activation in the lesion of arteriosclerosis at present.⁹⁴ Activation of ER stress pathway by excess NO may be involved in the dysfunction of other vascular cells such as endothelial cells, but those issues remains to be investigated.

Conclusion

NO is a multifunctional biomolecule, and is involved in various vascular diseases. However, the NO-induced ER stress pathway has not been fully investigated. Further studies on the relationship between ER stress and NO will provide a basis for new therapeutic approaches to vascular diseases.

Acknowledgments

We thank our colleagues for valuable suggestions and discussions. We also thank R. Shindo for technical assistance and Y. Inda for secretarial assistance.

Sources of Funding

This work was supported in part by grants-in-aid (14037257 and 17390096 to M.M., 16590233 to T.G.) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan, and grants (to T.G.) from the Inamori Foundation and Mitsubishi Pharma Research Foundation.

Disclosures

None.

References


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Arterioscler Thromb Vasc Biol. 2006;26:1439-1446; originally published online April 27, 2006;
doi: 10.1161/01.ATV.0000223900.67024.15

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