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• REVIEW •

Endoplasmic reticulum stress-induced apoptosis in the development of reproduction

Kang-sheng LIU[1], Zheng-hang PENG[2], Weng-jun CHENG[3], Chun-fan DAI[4], Hua TONG[5]

1. Department of Clinical Laboratory, State Key Laboratory of Reproductive Medicine Nanjing Maternity and Child Health Care Hospital Affiliated to Nanjing Medical University, Nanjing 210029, China.

2. School of Public Health, Nanjing Medical University, Nanjing 210029, China.

3. Department of Maternity and Child Health Care, School of Public Health, Anhui Medical University, Hefei 230032, China

4. Department of Obstetrical, Nanjing Maternity and Child Health Care Hospital, Nanjing 210009, China

5. Department of Scientific Research and Education, Nanjing Maternity and Child Health Care Hospital, Nanjing 210009, China

Proteins synthesized in the endoplasmic reticulum (ER) are properly folded with the assistance of ER chaperones. Accumulation of misfolded protein in the ER triggers an adaptive ER stress (ERS) response termed the unfolded protein response. Recent interest has focused on the possibility that the accumulation of misfolded proteins can also contribute to reproductive response, including preimplantation embryos, testicular germ cell, placenta, and unexplained intrauterine growth restriction (IUGR). The major ERS pathway constituents are present at all stages of preimplantation development and that the activation of ERS pathways can be induced at the 8-cell, morula and blastocyst stage. This review mainly introduced the research progress of ERS induced apoptosis of reproductive cells, providing a new direction for the research of reproductive disease therapy.

Key words: endoplasmic reticulum (ER); unfolded protein response; placenta diseases; testicular germ cell; intrauterine growth restriction (IUGR)

The endoplasmic reticulum (ER) is a vital organelle that plays an important role in the regulation of cellular homeostasis and communication[1,2]. At the same time, the ER is the cellular organelle where proteins and lipids are synthesized and modified. Many protein

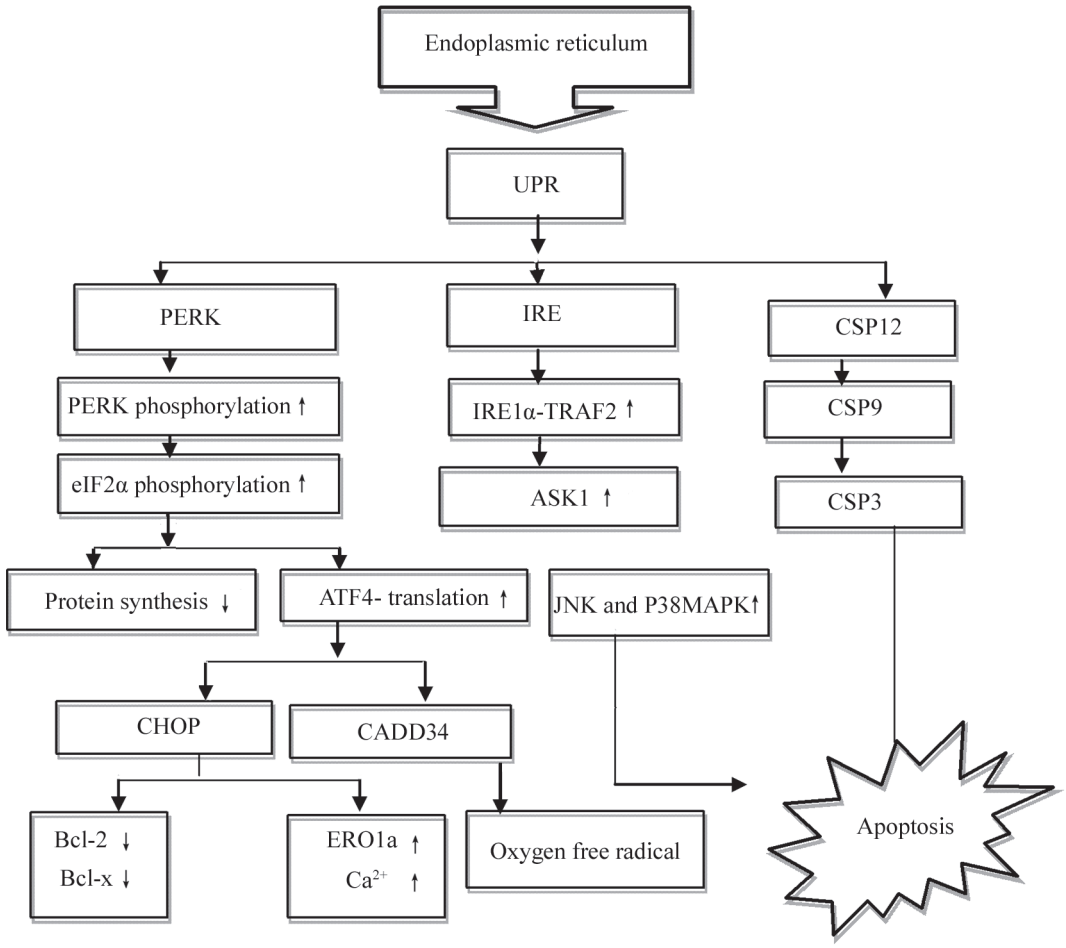
Corresponding author: Hua TONG; Tel/Fax: +86-25-52226777; E-mail: Thua8@163.com

chaperones in the ER facilitate the proper folding of individual proteins and the formation of macromolecular complexes. The disruption of ER functions by depletion of ER Ca^{2+} stores, inhibition of asparagine (N)-linked protein glycosylation, disturbance of disulfide bond formation, or viral infection, leads to protein misfolding and subsequent protein aggregation. Over the last decades, it has become clear that the accumulation of misfolded proteins contributes to a number of neurodegenerative, immune, and endocrine pathologies, as well as other age-related illnesses[1]. In large part, the misfolding of proteins takes place during synthesis of free ribosomes in the cytoplasm or of ER ribosomes.

In fact, even under optimal conditions, approximately 30% of all newly synthesized proteins are rapidly degraded, most likely because of improper folding. Accordingly, stresses that perturb the folding of proteins during or soon after synthesis can lead to the accumulation of misfolded proteins and to potential cellular dysfunction and pathological consequences. To avert such outcomes, cells have developed elaborate protein quality-control systems for detecting misfolded proteins and making appropriate adjustments to the machinery responsible for protein synthesis and/or degradation. For experimental purposes, chemicals such as thapsigargin (which depletes Ca^{2+} from ER), tunicamycin (which inhibits protein N-linked glycosylation), and dithiothreitol (which disrupts protein disulfide bonds) are used to induce ER stress (ERS) in cultured cells or animals. There are three distinct signaling pathways that are triggered in response to ERS, initiated by protein kinase activated by ds RNA (PKR)-like ER kinase (PERK), activating transcription factor 6 (ATF6), and inositol-requiring enzyme-1 (IRE1)(Figure 1). IRE1 has at least two different actions. First, the endoribonuclease activity of IRE1 cleaves *XBP*-1 mRNA, converting it into a potent transcriptional activator that, in turn, induces gene expression of proteins involved in protein degradation[3,4]. Second, recent studies from several laboratories have shown that IRE1 links ERS to the activation of c-Jun N-terminal kinase (JNK) signaling pathways. Specifically, IRE1 binds to tumor necrosis factor receptor-associated factor 2 (TRAF2) and through its kinase activity couples ERS to activation of JNK[5]. The activation of JNK by ERS requires the presence of apoptosis signal regulating kinase-1 (ASK1)[6,7]. It has therefore been proposed that ERS induces the formation of IRE1-TRAF2 complex that leads to ASK1-JNK activation[7].

Some studies have reported that the ERS response occurs several physiological and pathological process, including inflammation[8], the immune response[9,10] in SH-SY5Y cells[11], and RNA viruses[5], in the pathogenesis of nonalcoholic fatty liver disease[12].

In addition, some recent researches have suggested that the ERS response is also involved in reproduction. This paper mainly introduced the research progress of ERS-induced apoptosis of reproductive (preimplantation embryos, placenta and in testicular germ) cells, providing important insight into the molecular mechanisms of ERS induced reproductive disease.



UPR: unfolded protein response reticulum; PERK: protein kinase RNA-like ER kinase; IRE: inositol-requiring enzyme; CSP: chemosensory protein; TRAF: tumor necrosis factor receptor-associated factor; eIF2α: eukaryotic translation initiation factor 2alpha; ASK: aspartate kinase; ATF: activating transcription factor; JNK: c-Jun N-terminal kinase; CHOP: CCAAT-enhancer-binding protein homologous protein; CADD34: growth arrest and DNA damage-inducible 34; ERO: endoplasmic reticulum oxidoreductase

Figure 1 ERS and unfold protein response signaling pathway

Involvement of ERS response in preimplantation embryos and placenta function

ER stress could involved in granulosa cell apoptosis during goat follicular atresia. Epidermal growth factor (EGF) down-regulates the expression of *ATF*4, *ATF*6 and CCAAT-enhancer-binding protein homologous protein (*CHOP*) mRNA levels, which inhibits goat granulosa cells apoptosis by ERS. The increased ERS in decidual tissue in pregnancy has been shown to be implicated in fetal growth restriction (FGR)[13]. Sustained ERS acts as a

cofactor of oxidative stress in decidual cells from patients with early pregnancy loss[14]. In decidual cells, excessive oxidative stress influences unfolded protein response (UPR) pathways to activate endoplasmic reticulum associated degradation (ERAD) by decreasing valosin containing protein, which is a type II ER-associated protein and a member of the AAA ± ATPase family that facilitates delivery of misfolded proteins to the proteasome, results in cell damage, inhibition of cell growth, and activation of apoptosis[15]. An investigation of Abarham et al.[16] indicated that the major ERS pathway constituents are present at all stages of preimplantation development and that the activation of ERS pathways can be induced at the 8-cell, morula and blastocyst stage[16]. Luo et al.[17] has discovered that the Grp78 promoter is activated in both the trophectoderm and inner cell mass (ICM) of embryos at embryonic day 3.5 via a mechanism requiring the ERS elements. Further studies indicated that mouse embryonic fibroblasts from $Grp78^{+/-}$ mice are capable of responding to ERS. However, $Grp78^{-/-}$ embryos that are completely devoid of GRP78 lead to peri-implantation lethality. These embryos do not hatch from the zona pellucida *in vitro*, fail to grow in culture, and exhibit proliferation defects and a massive increase in apoptosis in the ICM, which is the precursor of embryonic stem cells. inositol requiring enzyme-1α (IRE1α) or XBP1 null mice are unable to produce functional placentas, which is lethal to the embryo, implying that the IRE1α arm of the UPR coping response is essential for placental development and embryonic viability[17]. Furthermore, ERS-induced coping responses in the maternal decidua and placenta may counteract developmental problems during implantation and post-implantation development. The findings of Luo et al.[17] provided the first evidence that GRP78 is essential for embryonic cell growth and pluripotent cell survival.

Maternal exposure to cadmium resulted in activation of PERK, phosphorylation of placental eIF2α, and an increase in CHOP, indicating that UPR signaling is activated in the placenta due to cadmium-induced toxicity[18]. Among UPR constituents, p-eIF2α, GRP94, and CHOP are increased in the placenta from intrauterine growth restriction (IUGR) and preeclampsia, indicating that ERS responses are also inducible under diseased conditions[19]. The function of the placenta is impaired by both loss of ERS response and excessive ERS[20], which indicate that ERS is mediated in placental development. Increased PERK-pEIF2α and ATF6 signaling have been associated with decreased cellular proliferation and may contribute to the impaired placental growth characterising pregnancies with FGR and preeclampsia (PE)+FGR[8] by using *in vivo* imaging analysis and conventional knockout mice, respectively, The research of Iwawaki et al.[20] showed that IRE1α was activated predominantly in the placenta and that loss of IRE1α led to reduction in vascular endothelial growth factor (VEGF)-A and severe dysfunction of the labyrinth in the placenta, a highly developed tissue of blood vessels. In recent years, TM promote the expression of *Grp*78, *Ire*1, *Chop*, *Bax* gene and inhibit the expression of Bcl-2, as well as activate the XBP-1 splicing to induce bovine granular cell (GC) apoptosis. ERS is present in the process of

bovine oocytes *in vitro* maturation (IVM) and embryos *in vitro* culture (IVC), supplementing with 500 μmol/L taurocholate ursodeoxycholic acid (TUDCA) into the occytes maturation medium or embryo culturing medium may inhibit ERS to facilitate the oocytes maturation and embryonic development[21].

Involvement of ERS response in unexplained IUGR

ERS has recently been identified as a major regulator of cell homeostasis through its involvement in post-translational protein modifications and folding, and its capacity to activate the UPR[21]. Further evidence that the degree of ER stress was greater in the IUGR+PE placentas than in the IUGR alone cases was provided by the fact that levels of GRP94 and CHOP were obviously raised in former, but not in the latter[11]. A few studies have estimated the frequency of apoptosis in placentas from complicated pregnancies[22]. By contrast, the research of Ishihara et al.[23] obtained values of approximately 1%, 4% and 8% in the syncytiotrophoblast alone on the basis TUNEL labelling. Even if these differences in absolute values there is general agreement that apoptosis is increased in IUGR placentas, and even more so in those from cases of IUGR+PE. This increase in cell death could also contribute to the smaller placental phenotype, but more importantly may underlie the shedding of trophoblastic microparticles that occurs in preeclampsia but not in IUGR alone[24]. This debris has been implicated in the activation of the maternal endothelial cells that characterise the maternal syndrome[25].

The investigation of Løset et al.[26] recently performed a whole-genome transcriptional profiling on decidual tissue from preeclamptic and normal pregnancies, identifying several up-regulated transcripts involved in ERS in PE. The above analysis indicate that ERS is involved in the pathogenesis of both PE and FGR, but whether the degree of ERS differs between these pregnancy complications is still unknown. Emerging observations indicate that PE and/or FGR may represent more or less severe stages on a continuous spectrum of responses to impaired placentation. Abraham et al.[16] have shown that decidual ERS is increased in pregnancies complicated by FGR and PE+ FGR. In trophoblast-like cell lines, increased levels of pEIF2α were associated with reduced proliferation through suppression of protein synthesis and decreased survival[16]. The net effect of reduced proliferation and cell survival was proposed as a cause for reduced placental growth in pregnancies with FGR and PE+FGR, which are characterised by decreased placental villous tissue volume and surface area[16]. Of relevance, Lian et al.[13] observed that the pEIF2α/EIF2α ratio was negatively correlated with placental weight ratio, with a similar tendency for ATF6, suggesting an association between ATF6 and PERK-pEIF2α signalling and reduced placental weight. And they found that decidua basalis is a source of ERS, and that ERS is increased in pregnancies complicated by FGR and PE+FGR. In PE, Lian et al.[13] found increased levels

of XBP1(U), which may be a protective mechanism against the detrimental effects of ERS.

Recently, the result of Iwawaki et al.[20] reported that the function of a molecule involved in ERS, IRE1α in the placenta is essential for placental development and embryonic viability and that ERS and IRE1α may be involved in other physiological phenomena. A genetic deficiency of UPR transducers has been found to result in prenatal mortality and developmental abnormality. PERK knockout mice show postnatal growth retardation and permanent neonatal diabetes. ATF6 knockout mice show embryonic lethality[27,28]. Some researches suggest that exposure to ERS may result in increased fetal growth retardation, teratogeny, and preterm delivery, although the critical window and underlying molecular mechanism(s) are unclear. In fact, exposure to heavy metals results in various effects, including ERS, oxidative stress, teratogenicity, and apoptosis[17]. The decidua basalis plays a basic role in the separation of the placenta during labor. ERS induced by oxidative stress may be involved in the development of early pregnancy loss with impairment of the decidua function[29]. Lian et al.[13] showed that increased ERS in decidual tissue was involved in FGR and FGR + PE. It will be important to elucidate the relationship between alteration of the decidua function and late pregnancy in future studies. Interestingly, passive cigarette smoke during pregnancy, which was reported to induce an ERS response, increases the mean relative area of spongiotrophoblast cells in the placenta and causes IUGR with a reduction in placental blood flow[30]. Further study demonstrated the formation of a cluster of spongiotrophoblast cells in the labyrinth zone of the placenta of Tun-treated mice. The glycogen content of the fetal liver and placenta from Tun-treated mice was lower than that from control mice. Tun treatment decreased mRNA expression of Slc2a1/glucose transporter (GLUT)-1, which is a major transporter for glucose, but increased placental mRNA levels of Slc2a3/GLUT3. Moreover, maternal exposure to Tun resulted in a decrease in vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, and placental growth factor. The results suggest that excessive and exogenous ERS may induce functional abnormalities in the placenta, at least in part, with altered GLUT and vascular-related gene expression, resulting in low infant birth weight[31].

Some other researchers observed that lead exposure significantly induced ER apoptosis compared with that of the controls accompanied with increased *caspase*-12 mRNA expression. In lead-exposed groups, trophoblast cells underwent degeneration and fibrin deposition, mitochondria were swollen and decreased in number ER swelling expansion and vacuolization. Lead exposure contributes to placental apoptosis, as well as increased *caspase*-12 mRNA expression, which in turn promoted ER[32].

Involvement of ERS response in testicular germ cell

Some studies demonstrated that some reproductive toxicants, such as mono-(2-ethylhexyl)

phthalate, diethylstilbestrol, bisphenol A, lindane, p,p'-DDE, and fenvalerate, evoked testicular germ cell apoptosis through the Fas/FasL pathway[33]. Mitochondrial signaling is another important apoptotic pathway. Several earlier studies found that mitochondrial signaling pathway was involved in the process of heat-induced germ cell apoptosis in testes[34]. Vaithinathan et al.[35] reported that some reproductive toxicants induced testicular germ cell apoptosis through the mitochondrial pathway. In the recent reports, Ji's result showed that spliced form of XBP-1, the target of the IRE1 pathway, was significantly increased in testes of mice injected with $CdCl_2$. GRP78, an ER chaperone, and CHOP, a downstream target of the PERK pathway, were up-regulated in testes of Cd-treated mice. In addition, acute Cd exposure significantly caused eIF2α and JNK phosphorylation in testes, indicating that the unfolded protein response pathway in testes was activated by Cd. Interestingly, phenylbutyric acid (PBA), an ER chemical chaperone, attenuated Cd-induced ERS and protected against germ cell apoptosis in testes[36].

The further research demonstrated the effects of melatonin on Cd-evoked germ cell apoptosis in testes. Melatonin significantly alleviated Cd-induced testicular germ cell apoptosis. An additional experiment showed that spliced form of XBP-1, the target of the IRE-1 pathway, was significantly increased in testes of mice injected with $CdCl_2$. GRP78, an ER chaperone, and CHOP, a downstream target of the PERK pathway, were up-regulated in testes of Cd-treated mice. Further analysis showed that N-acetylcysteine (NAC) attenuated the Cd-induced up-regulation of testicular GRP78, an important ER molecular chaperone. Moreover, NAC inhibited the Cd induced phosphorylation of testicular eIF2α, a downstream target of PERK pathway. In addition, NAC blocked the Cd-induced activation of testicular XBP-1, indicating that NAC attenuates the Cd-induced ER stress and the UPR. NAC protects against Cd-induced germ cell apoptosis by inhibiting ERS in the testes[37].

Conclusion

ER, one of the major organelles of eukaryotic cells, is an important place for protein folding and modifying. The homeostasis of ER can be broken and ERS will caused by many physiological and pathological factors.

At the same time, an ERS coping response are expressed in reproduction (preimplantation embryos, testicular germ cell), suggesting that ERS as a normal physiological coping mechanism plays a pivotal role in the development of reproduction.

In the presence of ERS, the data provide a theoretical reference to reveal the mechanism of the clinical early embryonic development stagnation, abortion, abnormal placenta treatment, such as: 1) the increased ERS in decidual tissue has been shown to be implicated in FGR in pregnancy; 2) the major ERS pathway constituents are present at all stages of preimplantation development; 3) the reproductive toxicants exposure significantly caused eIF2α and JNK

phosphorylation in testes; 4) the development of novel targeted drugs that inhibit pathological apoptosis and maintain cellular homeostasis.

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