Published in final edited form as:

Cell Tissue Res. 2016 January ; 363(1): 159–167. doi:10.1007/s00441-015-2124-9.

Stress signaling in mammalian oocytes and embryos: A basis for intervention and improvement of outcomes

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Abstract

Oocytes and early stage embryos are highly sensitive to variation in diverse exogenous factors such as temperature, osmolarity, oxygen, nutrient restriction, pH, shear stress, toxins, amino acid availability, and lipids. It is becoming increasingly apparent that many such factors negatively affect the endoplasmic reticulum, protein synthesis and protein processing, initiating ER stress and unfolded protein responses. As a result, ER stress signaling serves as a common mediator of cellular responses to diverse stressors. In oocytes and embryos, this leads to developmental arrest and epigenetic changes. Recent studies have revealed that preventing ER stress or inhibiting ER stress signaling can preserve or even enhance oocyte and embryo developmental potential. This chapter reviews ER stress signaling, how it arises, how it affects oocytes and embryos, and how its occurrence can be managed or prevented.

Keywords

ER stress; autophagy; unfolded protein response; preimplantation embryo; epigenetic

Introduction

Developing gametes and embryos may be confronted with a wide range of environmental stressors. This applies even to mammalian embryos developing in the protected environment of the maternal reproductive tract. Potential types of stress include thermal, osmotic, oxidative, hypoxia, hyperoxia, nutrient restriction, pH, shear stress, toxins, lipids, cytokines, and endocrine factors. It is becoming apparent that the cellular responses to most of these stressors converge at the endoplasmic reticulum, with the induction of the unfolded protein response (UPR) and ER stress signaling (ERSS) response.

It has also become apparent in recent years that insults to gametes and early embryos lead to numerous long-term adverse effects on fetal and post-natal phenotype, and thereby contribute to adult diseases and disorders. Understanding the mechanisms that underlie such effects has become a key objective in reproductive and developmental biology.

This chapter provides a basic review of UPR and ERSS, the evidence that these responses in the gamete and early embryo contribute to adverse developmental outcomes, and the evidence that adverse outcomes may be ameliorated by managing ERSS. Additionally, the chapter will delve into potential mechanisms that mediate epigenetic changes downstream of ERSS.

ER Stress signaling and downstream consequences

Cells possess a variety of pathways that enable them to respond to different kinds of stress. Specific mechanisms exist to enable cells to compensate for changes in temperature, pH, oxygen availability, nutrient availability, and other factors.

Interestingly, many kinds of stress directly impact the ability of the cell to synthesize, fold, transport, and post-translationally modify proteins, so that the UPR is activated, providing one means of sensing stress. Other forms of stress may instead or additionally alter ER characteristics (e.g., calcium content, lipid oxidation, reactive oxygen species concentration) and may activate ERSS. Indeed ERSS often accompanies other stress responses, particularly oxidative stress response (Xu, et al., 2012, Yoon, et al., 2014).

The canonical response to unfolded protein accumulating in the ER is the reduced association of glucose regulated protein GRP78 (a.k.a., BIP or HSPA5) with the three transmembrane regulators: EIF2A kinase 3 (PERK), activating transcription factor 6 (ATF6), and endoplasmic reticulum-to-nucleus signaling (ERN1, a.k.a. IRE1) resulting from transfer of GRP78 to the unfolded proteins (Fig. 1). A complex series of events then occurs, the outcome of which depends on the severity and duration of the stress. The initial responses include inhibition of mRNA translation, splicing and production of activated forms of transcription factors, and up-regulation of proteins that facilitate recovery (e.g., chaperones, and ER associated degradation—ERAD—proteins). The effects of less severe stress can be overcome by promoting removal of unfolded protein to the cytoplasm for degradation and activation of autophagy to enable damaged cellular components to be eliminated. More severe stress or prolonged stress initiates mRNA splicing events, transcriptional activation of additional signaling pathways (e.g., JNK/JUN, p53) that promote apoptosis, and activation of caspase-12, which also promotes apoptosis (Nakagawa, et al., 2000).

With respect to oocytes and early embryos, one key component of ERSS that may conflict with correct execution of the developmental program is the inhibition of translation, as this will impede the normal temporal pattern of mRNA recruitment and translation that supports early embryogenesis prior to transcriptional activation of the embryonic genome. A second consideration is the enhanced susceptibility of early embryos to certain forms of stress owing to the absence of some of the homeostatic mechanisms that exist in somatic cells (Kolajova, et al., 2001, Steeves and Baltz, 2005, Tartia, et al., 2009, Zhao, et al., 1995). A third consideration is capacity for multiple aspects of in vitro oocyte or embryo handling or culture to activate ERSS, discussed in the next section.

Effects of ER stress activators on development

The ultimate result of ERSS activation is a choice between either of two fates—cellular recovery and survival or apoptosis and embryo demise (Fig. 1, green vs. red boxes). With mild or short-lived stress, early ERSS events may provide the capacity for the cell to recover, for example by inhibiting protein translation and any further accumulation of unfolded proteins, increasing expression of chaperones, and increasing expression of ERAD components to clear the unfolded protein. Activation of autophagy allows the removal of damaged proteins or cell structures, and factors that activate autophagy can inhibit cell death upon ERSS activation (Kapuy, et al., 2014, Song, et al., 2012, Tirupathi Pichiah, et al., 2011).

An inhibition of cell division may promote cell survival. Cells may arrest either in G1 or G2 (Thomas, et al., 2013). G2 arrest is mediated downstream of PERK activation, through CHK1 activation, a potent cell cycle inhibitor also known for its activation in response to DNA damage (Malzer, et al., 2010, Thomas, et al., 2013). Cell cycle arrest in G1 occurs secondarily following activation of PERK, which can diminish synthesis of cyclin D1 (Brewer and Diehl, 2000, Thomas, et al., 2013). Induction of p53 activity also contributes to G1 arrest.

Under conditions of severe or prolonged stress, the ERSS pathway leads to the activation of JNK/JUN signaling, degradation of anti-apoptosis factors in the cell, and activation of DNA damage inducible transcript (DDIT3, a.k.a. C/EBP homologous protein, CHOP), which activates pro-apoptotic genes, and inhibits anti-apoptotic genes such as BCL1 (Li, et al., 2014b). Apoptosis in oocytes and embryos can be inhibited by ERSS inhibitors (Kim, et al., 2012, Zhang, et al., 2012a, Zhang, et al., 2012b). Damage to the mitochondria and activation of caspase 12 also contribute to activation of cellular apoptosis.

Beyond the outcome of the choice between survival and apoptosis, activation of ERSS in oocytes and embryos can lead to a range of adverse effects, so that even if the embryos survive, they may display significant developmental defects or abnormalities (Fig. 2). One mechanism for this outcome involves changes to key epigenetic information. This can arise due to the activities of histone deacetylases, histone methylation states, DNA methylation states, and diverse changes in gene expression. For example, increased expression of histone deacetylase 3 (HDAC3) is mediated by XBP1 (Martin, et al., 2014). Activation of XBP1 can also increase expression of histone H3 lysine 4 (H3K4) methyltransferase SET7/9 (Chen, et al., 2014b), and thereby modify histone methylation and gene function. Conversely, HDAC4 can help sequester ATF4 in the cytoplasm and be protective, but is required for ERSS mediated apoptosis (Zhang, et al., 2014). The chromatin regulator SIRT1, which has HDAC activity, can inhibit ERSS (Li, et al., 2014a). HDAC inhibitors are effective inhibitors of ERSS-mediated apoptosis (Fessler, et al., 2013, Zhang, et al., 2011). HDAC1 suppresses the GRP78 gene, and is released from the GRP78 promoter upon ERSS (Baumeister, et al., 2009). HDAC inhibitors induce the GRP78 gene but not other ERSS genes (Baumeister, et al., 2009).

HDACs also have activities in the cytoplasm by modifying non-histone proteins. HDAC6 deacetylates the chaperone HSP90, and inhibiting HDAC6 hinders protein re-folding (Sato, et al., 2014a). Other transcription factors such as STAT3 are also regulated by HDACs (Fazi, et al., 2009, Kimura, et al., 2012). Long-term stress and GRP78 mutation can lead to DNA hypomethylation and induction of ERSS genes (Han, et al., 2013). HDACs suppress genes involved in ERSS, and also may suppress genes that are activated as part of the transcriptional response to ERSS. The balance between the two effects appears to be crucial. For example, valproic acid treatment can induce hypomethylation in the *Keap1* gene and suppresses NRF2 activation to inhibit antioxidant protection, leading to cellular demise (Palsamy, et al., 2014), but protects oocytes and embryos from ERSS induced death (Song, et al., 2014).

These observations reveal a complex interplay between stress, ERSS, and epigenetic changes, which can include changes in histone acetylation, histone methylation, and DNA methylation. Additional changes in the activation states of transcription factors also occur, which may lead secondarily to changes in embryonic genome programming. Thus, while treatments with HDAC inhibitors can promote oocyte and embryo survival, the question arises whether epigenetic changes occur as a result of the treatment, and how this might impact long-term phenotype. Clearly stress can alter developmental outcomes and contribute to disease in the adult. How the application of epigenetic drugs will ameliorate these adverse outcomes, or merely replace them with other phenotypic changes, has yet to be determined.

Activation of ERSS in the early embryo may also adversely affect maintenance of pluripotent cell states. ERSS may inhibit maintenance of pluripotency (Blanco-Gelaz, et al., 2010). Developmental pluripotency-associated 5 (Dppa5) suppresses ER stress and enhances pluripotency (Miharada, et al., 2014). Leukemia inhibitory factor (LIF) may also inhibit ERSS as part of its mechanism of maintaining pluripotency (Chen, et al., 2014a). Thus inhibition of ERSS may potentiate the establishment of pluripotent cells experimentally, and the inhibitory effect of ERSS on pluripotency indicates that ERSS during specific windows of development may negatively affect key stem cell populations, again creating a potential for adverse effects of ERSS on developmental phenotypes.

Another recent finding related to stress effects in the oocyte and early embryo relates to changes in mitochondrial content and quality. For example, maternal diabetes exerts many adverse effects on the developing oocyte. One impact is abnormal meiotic spindles and increased aneuploidy (Grindler and Moley, 2013, Wang, et al., 2009). Additionally, mitochondrial DNA content increases, but many of the mitochondria display narrowed inter-membrane space, rupture of the outer membrane, lower electron density, and swelling, and failure of the normal mitochondrial spatial redistributions to occur. These morphological defects are accompanied by lower ATP content, higher variance of ATP content amongst oocytes, reduced citrate, aspartate, and malate indicative of reduced TCA cycle function. These defects may be explicable by damage to oocyte mitochondria accompanied by a failure to eliminate damaged mitochondria, resulting in functional mitochondrial insufficiency and developmental retardation (Wang, et al., 2009). Thus, factors that contribute to ERSS signaling are also associated with numerous defects in oocytes, and these defects may persist in the early embryo, compromising metabolic capability and

possibly adding to the burden of ER stress. Interestingly, mitochondrial defects were also seen in cumulus cells of diabetic female mice, indicating further degradation of oocyte quality (Wang, et al., 2010).

Relationship of ERSS to laboratory procedures for oocytes and embryos

The oocyte and early embryo are very sensitive to a wide range of stressors. This sensitivity creates a particular relevance for understanding the role of ERSS in adverse or unintentional outcomes of procedures related to basic research and clinical procedures involving oocytes and embryos. Relevant stressors include heat stress, low protein and low lipid maternal diet, reduced availability of amino acids, high concentrations of certain kinds of lipid in maternal circulation, and secondary consequences of maternal obesity and diabetes (Cagnone and Sirard, 2014, Edwards and Hansen, 1996, Fleming, et al., 2011, Grindler and Moley, 2013, Jungheim, et al., 2011, Luzzo, et al., 2012, Purcell and Moley, 2011, Wang and Moley, 2010). Effects of these diverse stressors in the oocyte can include disruptions in oocyte imprinting, changes in gene expression, changes in mitochondrial function, and changes in meiotic spindles. By reducing oocyte quality, these changes can ultimately lead to embryo demise or intrauterine growth restriction in fetuses. Exposure of oocytes and embryos to these stressors may negatively affect clinical procedures and research studies.

Excess glucose availability can also impact early embryogenesis (Grindler et al., 2013). Accordingly, maternal diabetes and hyperglycemia are harmful to oocytes and early embryos. Additionally, elevated insulin and maternal insulin resistance can downregulate the embryo IGF1R and attendant glucose uptake, and this downregulation can be harmful to the embryo (Louden, et al., 2008). Reduction in the AMP/ATP ratio can activate AMP kinase (AMPK), which serves as an energy sensor and modulator of cellular metabolism, to inhibit TOR signaling and facilitate survival. Additionally, excess glucose availability can increase oxidative phosphorylation and production of reactive oxygen species harmful to the embryo. Accompanying the effects of high glucose, elevated oxygen availability is also damaging to the oocyte and early embryo, as this encourages production of reactive oxygen species (Orsi and Leese, 2001). Inducers of oxidative stress inhibit early embryogenesis. Reducing glucose and oxygen availability is beneficial for early embryogenesis in vitro. Addition of antioxidants to the environment also improves development, attesting to the role of reactive oxygen species and overall REDOX state of the early embryo in determining developmental potential (Baumann, et al., 2007, Leese, 2012, Nonogaki, et al., 1991, Takahashi, 2012, Takahashi, et al., 2000, Umaoka, et al., 1991, Umaoka, et al., 1992).

Physical changes in the embryo environment such as changes in pH or osmolarity also negatively affect embryo development. ERSS can be activated by these changes, and inhibitors of ERSS can enhance embryo development following osmotic or pH stress. Shear stress can be induced by embryo pipetting (Xie, et al., 2007). Electrical pulses can release calcium from the ER and induce ERSS in some situations, and negative effects of this can be overcome by ERSS inhibitors (Song, et al., 2011).

Interventions to reduce impact of ER Stress Response

As indicated above, recent studies have revealed the importance of ER stress in situations of limited oocyte or embryo developmental potential, and the ability to preserve embryo viability by addressing ERSS. It is worthwhile considering the potential means of addressing specific causes of ERSS in oocytes and embryos.

Chemical inhibitors of ERSS present one approach to preventing embryo demise following ERSS. Different inhibitors impact the ERSS pathways by different routes: antioxidants, chaperones or inducers of GRP78, nitric oxide signaling, TOR inhibition, regulation of ER calcium content, and inhibition of EIF2A phosphorylation. ER stress activated by tunicamycin, or hyperosmolar shock with sorbitol, or other factors such as oxidative stress, and embryo handling inhibit preimplantation development (Basar, et al., 2014, Yoon, et al., 2014, Zhang, et al., 2012b). This can be overcome with the ERSS inhibitor tauroursodeoxycholic acid (TUDCA) (Abraham, et al., 2012, Kim, et al., 2012, Zhang, et al., 2012a). TUDCA is an inhibitor of ERSS-mediated caspase 12 activation and apoptosis, JNK-mediated caspase 2 activation, and p53-dependent pathways, and activates PI3 kinase/AKT signaling (Dionisio et al., 2014). HDAC inhibitors can also alleviate ERSS and enhance preimplantation embryo development (Song, et al., 2014). Inducing autophagy with the TOR inhibitor rapamycin can reduce apoptosis, and enhance early development, whereas inhibiting autophagy compromises development (Song, et al., 2012). Inhibiting ERSS when autophagy is chemically or genetically impaired rescues embryo development (Song, et al., 2012).

Maternal nutrition and maternal health provide another point of control for preventing or minimizing effects of ERSS in embryos. Maternal diabetes, obesity, nutrient intake, lipid can all affect oocyte quality, preimplantation embryo quality, and progeny phenotype. Factors that may create reactive oxygen species (ROS) can induce oxidative stress, and there is an intimate connection between oxidative stress and ERSS. For example, lipid oxidation can induce ERSS, and recovery for ER stress can itself generate ROS (Landau, et al., 2013), and many inducers of ERSS also induce oxidative stress. Inhibition of ERS can reduce ROS in embryos (Yoon, et al., 2014). Oxidative stress can interfere with correct protein folding (Malhotra and Kaufman, 2007). Maternal hyperglycemia as well as in vitro exposure to elevated glucose concentrations can induce ROS formation (Cagnone, et al., 2012, Karja, et al., 2006, Rinaudo, et al., 2006). Maternal insulin resistance is harmful to embryos, due to effect of elevated glucose in eliciting the downregulation of IGF1R and reduced glucose uptake (Louden, et al., 2008). A reduced AMP/ATP ratio activates AMPK, which inhibits TOR. TOR activation during ERSS promotes apoptosis (Kapuy, et al., 2014), so inhibiting TOR during ERSS is beneficial for survival. Amino acid deficiency can activate ERSS by inhibiting protein synthesis, and also activates TOR, providing another link between maternal nutrition and ERSS. TOR is regulated by other sensors of nutrition state. Collectively, these observations indicate that sub-optimal nutrition or impaired health status in the mother can induce ERSS and/or apoptosis in conjunction with ERSS. Hence, improving maternal nutrition and managing other health conditions before and after conception could reduce oxidative stress and ERSS in oocytes and embryos, and enhance reproductive success and success in clinical assisted reproduction procedures. Moreover,

potential transgenerational effects of poor maternal nutrition or health might be mitigated by avoiding meiotic defects, mitochondrial abnormalities and epigenetic changes in the embryo that could persist to the following generation.

Another possible approach to reduce the impact of ERSS in oocytes and early embryos is the use of dietary supplements, including dietary antioxidants. As discussed above, the beneficial effects of antioxidants in vitro on embryogenesis and oocyte quality are well established. Dietary antioxidants may improve reproductive outcomes by protecting oocytes and embryos from stress. Resveratrol, a natural antioxidant, can enhance oocyte quality in diverse mammalian species (Lee, et al., 2010, Liu, et al., 2013, Mukherjee, et al., 2014). In bovine and porcine oocytes, resveratrol activates Sirtuin 1, which in turn promotes mitophagy to eliminate damaged mitochondria, increases mitochondrial number, and improves mitochondrial function (Sato, et al., 2014b, Takeo, et al., 2014). Resveratrol also enhances cumulus cell function, oocyte maturation, decreases ROS in bovine oocytes, and increases glutathione concentration in oocytes (Wang, et al., 2014). Resveratrol treatment also elevates porcine oocyte glutathione levels (Kwak, et al., 2012, Lee, et al., 2010). Interestingly, Sirtuin 1 is a histone deacetylase, which seems contrary to beneficial effects of histone deacetylase inhibitors in suppressing ERSS, suggesting that the balance of activation of different gene sets by antioxidants may be a factor in determining outcome.

Injection of resveratrol to female rats also delays oocyte nest breakdown, inhibits oocyte apoptosis, increases the number of resting follicles and delays reproductive senescence (Kong, et al., 2011). Resveratrol is especially beneficial for improving oocyte quality in older cattle (Takeo, et al., 2013).

Resveratrol (0.5 μ M) can also protect against oxidative damage in preimplantation embryos (Chan, 2011) and improve porcine and bovine preimplantation embryo development in vitro (Lee, et al., 2010, Salzano, et al., 2014, Wang, et al., 2014). A natural flavonoid, quercetin, can protect embryos from peroxide induced damage (Yu, et al., 2014). Vitamin E may protect oocytes and embryos from lipid stress (Khalil, et al., 2013). Vitamin C can also be beneficial to oocytes and embryos (Gao, et al., 2013, Hammami, et al., 2013, Hu, et al., 2012, Huang, et al., 2011).

Taken together, these observations indicate that naturally occurring compounds when applied in vitro to oocytes and embryos, and when injected into females can enhance oocyte and embryo quality and improve reproductive capacity. These compounds have antioxidant activity, and may exert their benefits by suppressing oxidative stress. However, because of the link between oxidative stress and ERSS, they may also mitigate ERSS and exert benefits by that pathway as well. Further research is needed to ascertain whether sufficient quantities of these compounds can be safely ingested and permeate to the level of the oocyte or embryo within the ovary or reproductive tract.

Precautions in oocyte and embryo handling may also provide a means to improve viability and outcome. The finding that pipetting induces a stress response in early embryos raises concerns that casual embryo handling could contribute to reduced developmental potential. Minimizing physical stress to oocytes and embryos, including shear stress, thermal stress

(heat or cold), osmotic stress, pH stress, and calcium efflux following electrical impulses, remains a key consideration for maximizing outcomes from experimental and clinical procedures.

Conclusions

Decades of research observations have taught us that mammalian oocytes and embryos are sensitive to a broad range of insults. These include insults present in in vitro environments, as well as insults that may be experienced in vivo. While the negative effects of many stressors on oocytes and embryos have been appreciated for many years, a coherent mechanism linking stress to adverse outcomes has only recently emerged. The activation of ERSS in oocytes and embryos by these diverse stressors, and the ability of ERSS to lead to inhibition of mRNA translation, epigenetic changes, reduced cell division, and apoptosis suggest that interventions to minimize ERSS in oocytes and embryos should yield substantial benefits. This prediction has been upheld in initial studies using ERSS inhibitors such as TUDCA. The beneficial effects of antioxidants may likewise link to inhibition of ERSS that can arise along with oxidative stress response. Recent findings that ERSS in the trophoblast and placenta may interfere with positive pregnancy outcome, and that ERSS inhibitors may alleviate these problems indicate that management of ERSS throughout development may be beneficial. Some considerations for future study include what interventions are available for alleviating ERSS, when must these interventions be applied, to what degree can deleterious effects of ERSS be reversed, to what degree might ERSS inhibition become detrimental, for example by preventing the elimination of damaged cells or cellular structures, what is the range of environmental agents that may activate ERSS, and what are the genetic determinants of overall ERSS and its impact on oocyte and early embryos.

Acknowledgments

The work in the author's laboratory is supported in part by grants from the National Institutes of Health, National Institute of Child Health and Development (RO1 HD-075093), and the Office of Research Infrastructure Programs, Division of Comparative Medicine Grants R24 OD-012221), and by MSU AgBioResearch and Michigan State University.

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Figure 1.

Three main branches of the ER stress response. Upon accumulation of unfolded protein within the ER, GRP78 (HSPA5) dissociates from PERK(EIF2AK3), ATF6 and IRE1(ERN1), to bind to the unfolded protein. These three effectors initiate early events that are pro-survival (green box). With prolonged or more severe ER stress, these effectors direct later events that lead to apoptosis (red box). Other events, such as caspase-12 activation contribute to apoptosis (not shown).

Figure 2.

Relationship between stage of development, stressors, multiple stress response pathways, and developmental outcomes. Stressors can act upon oocytes, early embryos, or placenta. ER stress activation can accompany other stress responses. The cellular responses to ER stress can include apoptosis, autophagy, recovery, and epigenetic changes that can lead to developmental abnormalities.