



A Busy Cell – Endoplasmic Reticulum Stress in the Pancreatic β -cell

Henrik Ortsäter, Åke Sjöholm

► To cite this version:

Henrik Ortsäter, Åke Sjöholm. A Busy Cell – Endoplasmic Reticulum Stress in the Pancreatic β -cell. *Molecular and Cellular Endocrinology*, 2007, 277 (1-2), pp.1. <10.1016/j.mce.2007.06.006>. <hal-00531938>

HAL Id: hal-00531938

<https://hal.science/hal-00531938v1>

Submitted on 4 Nov 2010

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



HAL Authorization

Accepted Manuscript

Title: A Busy Cell – Endoplasmic Reticulum Stress in the Pancreatic β -cell

Authors: Henrik Ortsäter, Åke Sjöholm

PII: S0303-7207(07)00255-9
DOI: doi:10.1016/j.mce.2007.06.006
Reference: MCE 6676

To appear in: *Molecular and Cellular Endocrinology*

Received date: 14-3-2007
Revised date: 28-6-2007
Accepted date: 30-6-2007

Please cite this article as: Ortsäter, H., Sjöholm, Å., A Busy Cell – Endoplasmic Reticulum Stress in the Pancreatic β -cell, *Molecular and Cellular Endocrinology* (2007), doi:10.1016/j.mce.2007.06.006

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



A Busy Cell – Endoplasmic Reticulum Stress in the Pancreatic β -cell

Henrik Ortsäter and Åke Sjöholm

Karolinska Institutet, Diabetes Research Center, Stockholm South Hospital, SE-118 83
Stockholm, Sweden

E-mail henrik.ortsater@sodersjukhuset.se

The pancreatic β -cell senses nutrients, neurotransmitters and hormones in the circulating blood. The unique function of the cell is to integrate all these ambient signals into an appropriate insulin secretory rate in order to maintain glucose homeostasis. A prerequisite for adequate insulin secretion is proper biosynthesis of the hormone. The rate of biosynthesis needs to be regulated in order to compensate for rapid fluctuations in the secretory rate. The synthesis of insulin includes transcription of its gene to mRNA, translation of mRNA into preproinsulin, and processing of preproinsulin via proinsulin into mature insulin. It also involves the induction of additional components of the secretory pathway to support processing, transport and exocytosis of insulin granules. The endoplasmic reticulum (ER) is the cell organelle playing a paramount role in these processes. A functional ER is crucial to all eukaryotic cells, but especially important in a professional hormone-secreting cell like the β -cell.

In eukaryotic cells, the ER provides a contained environment for the synthesis and modification of membrane proteins and proteins destined for secretion. These co- and post-translational modifications are important for the subsequent folding and assembly of proteins (Helenius 1994). To assist the folding process, the ER contains high levels of protein chaperones including the glucose-regulated proteins calnexin, calreticulin, protein disulphide isomerase and Erp72 (Gething et al. 1992; Ruddon et al. 1997). Disruptions in the ER protein processing system by pathogens, mutations or specific lesions in the protein folding machinery have been implicated in the progression of several human diseases, including neurodegenerative disorders (Lindholm et al. 2006), cystic fibrosis (Vij et al. 2006) and diabetes (Özcan et al. 2004).

This essay will describe the phenomenon of ER stress in pancreatic β -cells with special focus on its involvement in the regulation of β -cell survival and death. The involvement of some ER stress components in the regulation of insulin biosynthesis and secretion will be discussed, along with a short description of the ER stress response (also known as the unfolded protein response). For more in-depth reviews on general ER stress, there are several excellent papers (Boyce et al. 2006) (Wu et al. 2006).

Agents or conditions that compromise protein folding capacity, or evoke an overload of newly synthesized polypeptides, cause an accumulation of unfolded or misfolded proteins in the ER. This event activates three distinct pathways, each controlled by a specific protein: PERK, IRE1 and ATF6 (Boyce and Yuan 2006), respectively. Activation of PERK promotes the phosphorylation and inhibition of the translation initiation factor, eIF2 α (Prostko et al. 1993). The resulting attenuation of general protein synthesis prevents further overloading of the ER folding machinery. IRE1 is a protein that, upon its activation, renders endonuclease activity (Calton et al. 2002). One target for activated IRE1 is the mRNA encoding the X-box-binding protein 1 (XBP-1). This mRNA is alternatively spliced by IRE1 such that it can now be translated into a functional transcription factor. ATF6 is by itself a transcription factor but is

retained in the ER membrane under non-stressed conditions. However, upon ER-stress ATF6 is released from the ER membrane and transported to the Golgi apparatus where it is cleaved into a functional transcription factor (Haze et al. 1999). Activation of IRE1 and ATF6 promotes the expression of ER chaperones, thereby increasing the capacity of the ER to properly fold the accumulated polypeptides. These ER chaperones also function as part of the quality control system that targets misfolded proteins for degradation (Plempner et al. 1997). Thus, the ER stress response normally serves to alleviate ER stress by inhibiting general protein translation, increasing folding capacity and promoting degradation of misfolded proteins (Figure 1).

In the area of diabetes research, ER stress has attracted growing interest since it has been shown that markers of ER stress are up-regulated in both human islets from type 2 diabetes patients (Huang et al. 2007; Laybutt et al. 2007) and in islets from animal models of obesity and diabetes (Özcan, Cao et al. 2004). ER stress in human islets might at least partly be explained by high expression rates of human islet amyloid polypeptide (IAPP) as has been demonstrated by over expression of human IAPP in transgenic rats (Huang, Lin et al. 2007). In accordance with a prosurvival function of the ER stress response, several studies have indicated a necessity of especially PERK signaling for preserved β -cell function. Deletion of PERK results in progressive destruction of β -cells in both humans and mice (Delepine et al. 2000; Harding et al. 2001). In humans, mutations in the PERK gene gives rise to Wolcott-Rallison syndrome, a rare form of monogenic diabetes that manifests as an infantile-onset, insulin-requiring diabetes (Delepine, Nicolino et al. 2000). In *perk*^{-/-} mice, there is a progressive loss of β -cells and diabetes evolves within the first few weeks after birth (Harding, Zeng et al. 2001). Even more severe β -cell dysfunction is seen in mice with a homozygous serine 51 alanine point mutation in their eIF2 α gene (Scheuner et al. 2001). Such mice are resistant to eIF2 α phosphorylation and inhibition of general protein synthesis. Mice heterozygous for the same mutation have a normal phenotype under a normal diet but develop obesity and diabetes on a high fat diet (Scheuner et al. 2005). The profound glucose intolerance in these mice results from reduced insulin secretion accompanied by abnormal distension of the ER lumen, defective trafficking of proinsulin and a reduced number of insulin granules. Hence, the inability to activate PERK signaling and phosphorylation of eIF2 α in pancreatic β -cells results in reduced function and death of the cell. Thus, specific inhibition of eIF2 α dephosphorylation could be a way of improving β -cell function. Indeed, when screening for compounds that promote cell survival in PC12 cells under conditions of ER stress, salubrinal was identified as a specific inhibitor of eIF2 α dephosphorylation (Boyce et al. 2005). Despite these effects in PC12 cells, in pancreatic β -cells salubrinal was found to be cytotoxic by itself, and potentiated fatty acid induced ER stress and apoptosis (Cnop et al. 2007). This shows that pancreatic β -cells are very susceptible to any perturbation of ER homeostasis and that the ER stress response is two-faced, promoting both cell survival and death. The molecular basis for this dual action of the ER stress response will be an important research task in the future. An important lesson can be learnt from studies in mouse embryonic fibroblasts (Rutkowski et al. 2006), where an adaptive response to ER stress was found to be dependent on the longer half-life of mRNA encoding molecular chaperones such as BiP/GRP78, GRP94 and calreticulin than those mRNAs that are controlled by the PERK signaling pathway. PERK is considered to be the principle driver of expression of the pro-apoptotic protein CHOP (also known as GADD153 or DDIT3) (Okada et al. 2002). In a recent report, it was suggested that cytokines and palmitate utilize both AP-1 and ATF4 transcription factor to regulate CHOP expression (Pirrot et al. 2007). However, neither AP-1 nor ATF4 used endoplasmic reticulum response elements (ERSE), which is in contrast to the SERCA pump inhibitor cyclopiazonic acid (CPA), which utilized ATF4 and ERSE to regulate

CHOP expression. That CHOP is a mediator of cytotoxicity is evident in the Akita mouse. The Akita mouse serves as an example where a mutated protein can induce ER stress and β -cell apoptosis. One allele of the *Ins2* gene in the Akita mouse harbors a single-point mutation, resulting in a cysteine-tyrosine substitution at position 96 (Wang et al. 1999). This mutation prevents the formation of a disulfide bond so the mutated protein cannot fold properly and gets stuck in the ER, eliciting an ER stress response. Deletion the CHOP gene in Akita mice delays apoptosis induced by ER stress (Oyadomari et al. 2002). The absence of CHOP was also reported to increase resistance to nitric oxide-induced apoptosis in pancreatic β -cells (Oyadomari et al. 2001). The situation is, however, complicated by the fact that exendin-4, a GLP-1 receptor agonist, augments both thapsigargin and tunicamycin induced CHOP expression, but at the same time improves β -cell function and survival following induction of ER stress (Yusta et al. 2006). ER stress has been proposed to mediate the cytotoxic effects induced by saturated fatty acids, like palmitate (Kharroubi et al. 2004; Karasikov et al. 2006). The mechanism for this is not clear, but there might be an involvement of Ca^{2+} influxes, since it was found that the Ca^{2+} channel blocker nifedipine delayed palmitate induced CHOP expression while an opener, Bay K8644, accelerated such process (Choi et al. 2007). Furthermore, diazoxide was recently reported to attenuate fatty acid-induced eIF2 α phosphorylation and CHOP expression and apoptosis in clonal pancreatic β -cells (Ortsäter et al. 2006), indicating that calcium fluxes across the cell membrane are regulating the palmitate induced ER stress response.

If the cytotoxic role of PERK signaling in β -cells remains controversial, the beneficial effect of chaperone activity is clearer. Chemical chaperones can reduce ER stress and restore glucose homeostasis in a mouse model of type 2 diabetes (Özcan et al. 2006). Orally active chemical chaperones, 4-Phenyl butyric acid and taurine-conjugated ursodeoxycholic acid, alleviated ER stress in cells and whole animals. Treatment of obese and diabetic mice with these compounds resulted in normalization of hyperglycemia, restoration of systemic insulin sensitivity, resolution of fatty liver disease, and enhancement of insulin action in liver, muscle, and adipose tissue. The results demonstrate that chemical chaperones enhance the adaptive capacity of the ER and act as potent antidiabetic compounds, with potential clinical utility in the treatment of type 2 diabetes.

Besides being parts of ER stress response, recent data has shown that IRE1 and eIF2 α are also involved in the regulation of insulin biosynthesis. Treating INS-1E or primary β -cells with CPA results in a 40 % decrease in *Ins1* and *Ins2* gene expression after a 2 hour exposure (Pirot et al. 2007), an effect that occurs in parallel with enhanced XBP-1 splicing indicating the involvement of IRE1 signaling. However, IRE1 α phosphorylation is also coupled to enhanced insulin biosynthesis and occurs in response to a transient, 1 hour, exposure to high glucose (Lipson et al. 2006). Inactivation of IRE1 α signaling by siRNA treatment, or inhibition of IRE1 α phosphorylation, hinders insulin biosynthesis. IRE1 activation by high glucose does not accompany XBP-1 splicing or BiP dissociation but up-regulates its target genes, such as WFS1. Thus, IRE1 signaling activated by transient exposure to high glucose uses a unique subset of downstream components that differ from the activation of IRE1 seen during ER stress. In contrast, long term exposure to elevated glucose concentrations is associated with a classical IRE1 signaling response (Figure 2). When it comes to glucose regulation of eIF2 α phosphorylation, it has been shown that the degree of phosphorylation is high at 2 mM glucose, low at 10 mM glucose and at 30 mM glucose it is slightly higher than at 10 mM glucose (Elouil et al. 2007). The fact that glucose can reduce the degree of eIF2 α phosphorylation has been known for some time (Gomez et al. 2004). This is not due to

decreased activity of any eIF2 α kinase (Vander Mierde et al. 2006) rather, by using a series of protein phosphatase inhibitors, this effect was shown to be the result of enhanced activity of ser/thr protein phosphatase-1 (PP1). Hence, glucose activates a PP1-mediated signaling pathway that enhances the overall translation rate in β -cells. Thus, the steady-state level of eIF2 α phosphorylation in β -cells is the net result of a balance between folding-load-induced phosphorylation and PP1-dependent dephosphorylation (Figure 3).

Both a hyperglycemic (Wang et al. 2005) and a hyperlipidemic (Karaskov, Scott et al. 2006; Cnop, Ladriere et al. 2007) environment can induce ER stress in pancreatic islets and β -cells in vitro. What then can be done to help these cells adapt to such metabolically stressful situation? To aid in this process, there is a need to dissect the ER stress response in β -cells in greater detail and gain deeper insight into what molecules that exert regulatory control of the different arms of the ER stress response. In this respect, it will be interesting to dissect which protein phosphatases that can exert feed-back control of PERK and IRE1 signaling.

The incidence of type 2 diabetes is rapidly growing globally, reaching epidemic proportions in the Western world (Zimmermann-Belsing et al. 2004). More than 100 million people world wide have diabetes and will suffer a substantially reduced quality of life as a consequence. A sedentary life style, along with an excessive caloric intake, contributes to the development of the disease by imposing a increased functional demand on the β -cell. The frequent ingestion of blood sugar elevating snacks makes the pancreatic β -cell – a busy cell. Hopefully, the knowledge evolving from ongoing and future studies of the ER stress pathways can be harnessed to advantage in the quest for drugs conferring protection of the β -cell from functional exhaustion and demise.

References

- Boyce, M., Bryant, K. F., Jousse, C., Long, K., Harding, H. P., Scheuner, D., Kaufman, R. J., Ma, D., Coen, D. M., Ron, D. and Yuan, J. 2005. A selective inhibitor of eIF2 α dephosphorylation protects cells from ER stress. *Science* 307, 935-9.
- Boyce, M. and Yuan, J. 2006. Cellular response to endoplasmic reticulum stress: a matter of life or death. *Cell Death Differ* 13, 363-373.
- Calfon, M., Zeng, H., Urano, F., Till, J. H., Hubbard, S. R., Harding, H. P., Clark, S. G. and Ron, D. 2002. IRE1 couples endoplasmic reticulum load to secretory capacity by processing the XBP-1 mRNA. *Nature* 415, 92-6.
- Choi, S. E., Kim, H. E., Shin, H. C., Jang, H. J., Lee, K. W., Kim, Y., Kang, S. S., Chun, J. and Kang, Y. 2007. Involvement of Ca²⁺-mediated apoptotic signals in palmitate-induced MIN6N8a beta cell death. *Mol Cell Endocrinol.* (2007), doi:10.1016/j.mce.2007.04.004
- Cnop, M., Ladriere, L., Hekerman, P., Ortis, F., Cardozo, A. K., Dogusan, Z., Flamez, D., Boyce, M., Yuan, J. and Eizirik, D. L. 2007. Selective Inhibition of Eukaryotic Translation Initiation Factor 2 α Dephosphorylation Potentiates Fatty Acid-induced Endoplasmic Reticulum Stress and Causes Pancreatic β -Cell Dysfunction and Apoptosis. *J Biol Chem* 282, 3989-97.
- Delepine, M., Nicolino, M., Barrett, T., Golamaully, M., Lathrop, G. M. and Julier, C. 2000. EIF2AK3, encoding translation initiation factor 2- α kinase 3, is mutated in patients with Wolcott-Rallison syndrome. *Nat Genet* 25, 406-9.
- Elouil, H., Bensellam, M., Guiot, Y., Vander Mierde, D., Pascal, S. M., Schuit, F. C. and Jonas, J. C. 2007. Acute nutrient regulation of the unfolded protein response and integrated stress response in cultured rat pancreatic islets. *Diabetologia* 50, 1442-52.
- Gething, M. J. and Sambrook, J. 1992. Protein folding in the cell. *Nature* 355, 33-45.
- Gomez, E., Powell, M. L., Greenman, I. C. and Herbert, T. P. 2004. Glucose-stimulated protein synthesis in pancreatic β -cells parallels an increase in the availability of the translational ternary complex (eIF2-GTP.Met-tRNAi) and the dephosphorylation of eIF2 α . *J Biol Chem* 279, 53937-46.
- Harding, H. P., Zeng, H., Zhang, Y., Jungries, R., Chung, P., Plesken, H., Sabatini, D. D. and Ron, D. 2001. Diabetes mellitus and exocrine pancreatic dysfunction in perk^{-/-} mice reveals a role for translational control in secretory cell survival. *Mol Cell* 7, 1153-63.
- Haze, K., Yoshida, H., Yanagi, H., Yura, T. and Mori, K. 1999. Mammalian transcription factor ATF6 is synthesized as a transmembrane protein and activated by proteolysis in response to endoplasmic reticulum stress. *Mol Biol Cell* 10, 3787-99.
- Helenius, A. 1994. How N-linked oligosaccharides affect glycoprotein folding in the endoplasmic reticulum. *Mol Biol Cell* 5, 253-65.
- Huang, C. J., Lin, C. Y., Haataja, L., Gurlo, T., Butler, A. E., Rizza, R. A. and Butler, P. C. 2007. High Expression Rates of Human Islet Amyloid Polypeptide Induce Endoplasmic Reticulum Stress-Mediated Beta Cell Apoptosis, a Characteristic of Humans with Type 2 but Not Type 1 Diabetes. *Diabetes* In press
- Karaskov, E., Scott, C., Zhang, L., Teodoro, T., Ravazzola, M. and Volchuk, A. 2006. Chronic palmitate but not oleate exposure induces endoplasmic reticulum stress, which may contribute to INS-1 pancreatic β -cell apoptosis. *Endocrinology* 147, 3398-407.
- Kharroubi, I., Ladriere, L., Cardozo, A. K., Dogusan, Z., Cnop, M. and Eizirik, D. L. 2004. Free fatty acids and cytokines induce pancreatic β -cell apoptosis by different

- mechanisms: role of nuclear factor- κ B and endoplasmic reticulum stress. *Endocrinology* 145, 5087-96.
- Laybutt, D. R., Preston, A. M., Akerfeldt, M. C., Kench, J. G., Busch, A. K., Biankin, A. V. and Biden, T. J. 2007. Endoplasmic reticulum stress contributes to beta cell apoptosis in type 2 diabetes. *Diabetologia*
- Lindholm, D., Wootz, H. and Korhonen, L. 2006. ER stress and neurodegenerative diseases. *Cell Death Differ* 13, 385-92.
- Lipson, K. L., Fonseca, S. G., Ishigaki, S., Nguyen, L. X., Foss, E., Bortell, R., Rossini, A. A. and Urano, F. 2006. Regulation of insulin biosynthesis in pancreatic beta cells by an endoplasmic reticulum-resident protein kinase IRE1. *Cell Metab* 4, 245-54.
- Okada, T., Yoshida, H., Akazawa, R., Negishi, M. and Mori, K. 2002. Distinct roles of activating transcription factor 6 (ATF6) and double-stranded RNA-activated protein kinase-like endoplasmic reticulum kinase (PERK) in transcription during the mammalian unfolded protein response. *Biochem J* 366, 585-94.
- Ortsäter, H., Thörn, K., Sargsyan, E. and Bergsten, P. 2006. Unfolded protein response in fatty acid treated pancreatic β -cells. *Diabetologia* 49, 0100.
- Oyadomari, S., Koizumi, A., Takeda, K., Gotoh, T., Akira, S., Araki, E. and Mori, M. 2002. Targeted disruption of the Chop gene delays endoplasmic reticulum stress-mediated diabetes. *J Clin Invest* 109, 525-32.
- Oyadomari, S., Takeda, K., Takiguchi, M., Gotoh, T., Matsumoto, M., Wada, I., Akira, S., Araki, E. and Mori, M. 2001. Nitric oxide-induced apoptosis in pancreatic beta cells is mediated by the endoplasmic reticulum stress pathway. *Proc Natl Acad Sci U S A* 98, 10845-50.
- Pirot, P., Naamane, N., Libert, F., Magnusson, N. E., Orntoft, T. F., Cardozo, A. K. and Eizirik, D. L. 2007. Global profiling of genes modified by endoplasmic reticulum stress in pancreatic beta cells reveals the early degradation of insulin mRNAs. *Diabetologia* 50, 1006-14.
- Pirot, P., Ortis, F., Cnop, M., Ma, Y., Hendershot, L. M., Eizirik, D. L. and Cardozo, A. K. 2007. Transcriptional regulation of the endoplasmic reticulum stress gene chop in pancreatic insulin-producing cells. *Diabetes* 56, 1069-77.
- Plempner, R. K., Bohmler, S., Bordallo, J., Sommer, T. and Wolf, D. H. 1997. Mutant analysis links the translocon and BiP to retrograde protein transport for ER degradation. *Nature* 388, 891-5.
- Prostko, C. R., Brostrom, M. A. and Brostrom, C. O. 1993. Reversible phosphorylation of eukaryotic initiation factor 2 α in response to endoplasmic reticular signaling. *Mol Cell Biochem* 127-128, 255-65.
- Ruddon, R. W. and Bedows, E. 1997. Assisted protein folding. *J Biol Chem* 272, 3125-8.
- Rutkowski, D. T., Arnold, S. M., Miller, C. N., Wu, J., Li, J., Gunnison, K. M., Mori, K., Sadighi Akha, A. A., Raden, D. and Kaufman, R. J. 2006. Adaptation to ER stress is mediated by differential stabilities of pro-survival and pro-apoptotic mRNAs and proteins. *PLoS Biol* 4, e374.
- Scheuner, D., Mierde, D. V., Song, B., Flamez, D., Creemers, J. W., Tsukamoto, K., Ribick, M., Schuit, F. C. and Kaufman, R. J. 2005. Control of mRNA translation preserves endoplasmic reticulum function in beta cells and maintains glucose homeostasis. *Nat Med* 11, 757-64.
- Scheuner, D., Song, B., McEwen, E., Liu, C., Laybutt, R., Gillespie, P., Saunders, T., Bonner-Weir, S. and Kaufman, R. J. 2001. Translational control is required for the unfolded protein response and in vivo glucose homeostasis. *Mol Cell* 7, 1165-76.
- Vander Mierde, D., Scheuner, D., Quintens, R., Patel, R., Song, B., Tsukamoto, K., Beullens, M., Kaufman, R. J., Bollen, M. and Schuit, F. C. 2006. Glucose Activates a Protein

- Phosphatase-1-Mediated Signaling Pathway to Enhance Overall Translation in Pancreatic β -Cells. *Endocrinology*
- Wang, H., Kouri, G. and Wollheim, C. B. 2005. ER stress and SREBP-1 activation are implicated in β -cell glucolipotoxicity. *J Cell Sci* 118, 3905-15.
- Wang, J., Takeuchi, T., Tanaka, S., Kubo, S. K., Kayo, T., Lu, D., Takata, K., Koizumi, A. and Izumi, T. 1999. A mutation in the insulin 2 gene induces diabetes with severe pancreatic beta-cell dysfunction in the Mody mouse. *J Clin Invest* 103, 27-37.
- Vij, N., Fang, S. and Zeitlin, P. L. 2006. Selective inhibition of endoplasmic reticulum-associated degradation rescues $\Delta F508$ -cystic fibrosis transmembrane regulator and suppresses interleukin-8 levels: therapeutic implications. *J Biol Chem* 281, 17369-78.
- Wu, J. and Kaufman, R. J. 2006. From acute ER stress to physiological roles of the Unfolded Protein Response. *Cell Death Differ* 13, 374-84.
- Yusta, B., Baggio, L. L., Estall, J. L., Koehler, J. A., Holland, D. P., Li, H., Pipeleers, D., Ling, Z. and Drucker, D. J. 2006. GLP-1 receptor activation improves β cell function and survival following induction of endoplasmic reticulum stress. *Cell Metab* 4, 391-406.
- Zimmermann-Belsing, T. and Feldt-Rasmussen, U. 2004. Obesity: the new worldwide epidemic threat to general health and our complete lack of effective treatment. *Endocrinology* 145, 1501-2.
- Özcan, U., Cao, Q., Yilmaz, E., Lee, A. H., Iwakoshi, N. N., Özdelen, E., Tuncman, G., Görgün, C., Glimcher, L. H. and Hotamisligil, G. S. 2004. Endoplasmic reticulum stress links obesity, insulin action, and type 2 diabetes. *Science* 306, 457-61.
- Özcan, U., Yilmaz, E., Özcan, L., Furuhashi, M., Vaillancourt, E., Smith, R. O., Görgün, C. Z. and Hotamisligil, G. S. 2006. Chemical chaperones reduce ER stress and restore glucose homeostasis in a mouse model of type 2 diabetes. *Science* 313, 1137-40.

Figure legends

Figure 1.

Schematic representation of the endoplasmic reticulum stress response. The accumulation of misfolded proteins in the endoplasmic reticulum leads to the release of BiP/GRP78 from ATF6, PERK and IRE1, which allows these three proteins to become active. Activation of PERK promotes the phosphorylation and inhibition of the translation initiation factor, eIF2 α , leading to a reduced translation rate. However, the translation rate of some mRNAs, like ATF4 mRNA, is actually increased during eIF2 α phosphorylation. ATF4 is a transcription factor for GADD34 that activates a negative feedback loop to dephosphorylate eIF2 α and the proapoptotic protein CHOP. IRE1 is a protein that, upon its activation, renders endonuclease activity. A target for activated IRE1 is the mRNA that encodes the X-box-binding protein 1 (XBP-1). This mRNA is alternatively spliced by IRE1 and can now be translated into a functional transcription factor. ATF6 is by itself a transcription factor but is retained in the ER membrane under non-stressed conditions. However, upon ER stress ATF6 is released from the ER membrane and transported to the Golgi apparatus where it is cleaved into a functional transcription factor. Activation of IRE1 and ATF6 promote the expression of ER chaperones and thereby increase the capacity of the ER to properly fold the accumulated polypeptides. These transcription factors also enhance the expression of proteins involved in protein degradation. Figure is inspired by Rutkowski and Kaufman (2004) Trends Cell Biol vol. 14:20-28.

Figure 2.

Exposure to high glucose time-dependently activates two phases of IRE1 α signaling. On the short time scale an exposure to an elevated glucose concentration results in phosphorylation of IRE1 α , evoking an enhanced expression of the target gene WFS1 and enhanced rate of insulin synthesis but does not induce alternative splicing of XBP-1. On the other hand, when the exposure time is extended, XBP-1 mRNA is alternatively spliced and insulin biosynthesis rate is decreased below normal levels. The figure is produced from data presented in reference (Lipson, Fonseca et al. 2006).

Figure 3.

The degree of eIF2 α phosphorylation is a balance between ER stress associated phosphorylation and glucose-induced protein phosphatase-1-mediated dephosphorylation. The figure is produced from data presented in reference (Vander Mierde, Scheuner et al. 2006).

Figure 1

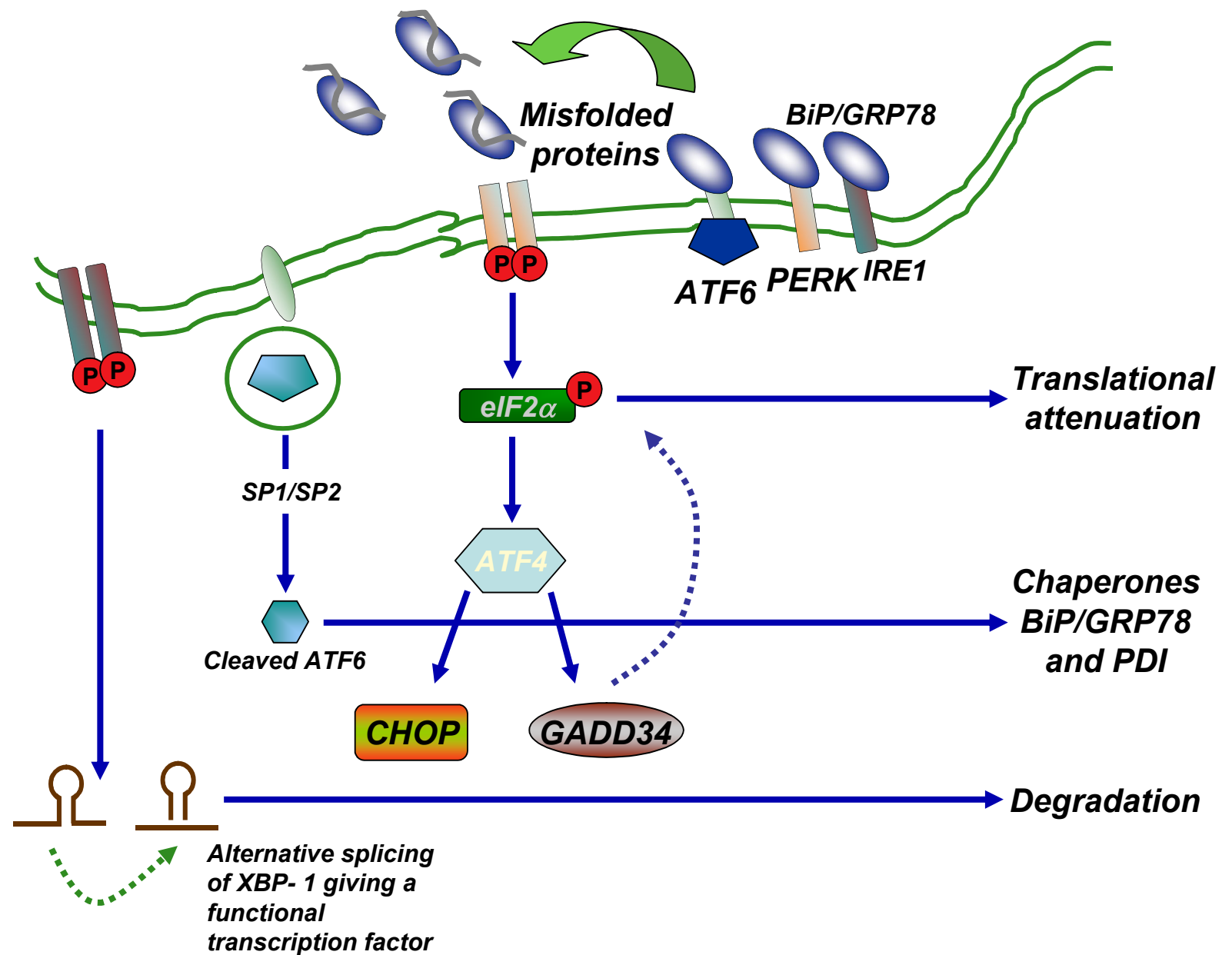


Figure 2

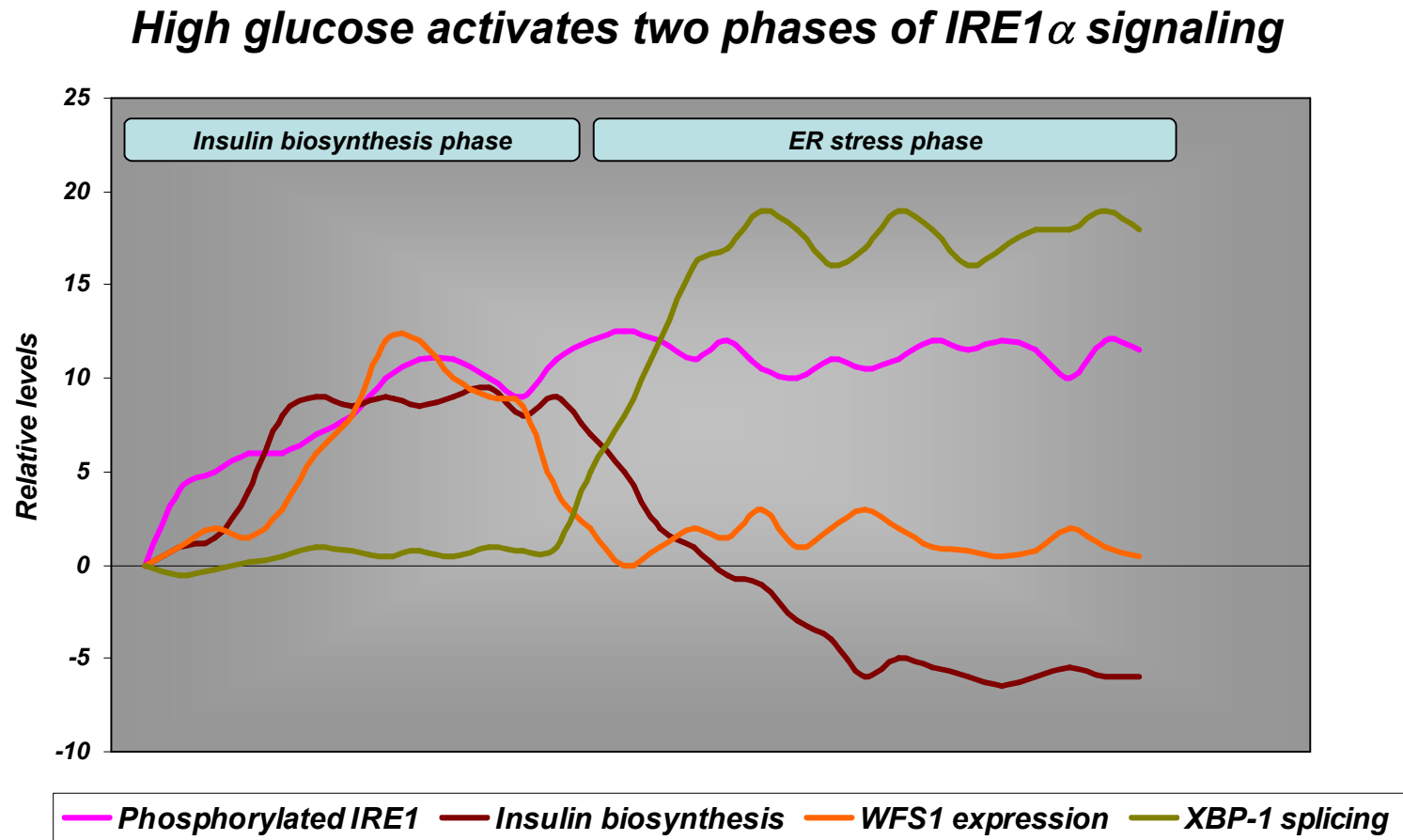


Figure 3

