Supplemental table S1:

Mediators of UPR	Target Genes	Protein Name	Regulation	Cellular process	Author
ATF6	HSP90B1	heat shock protein 90kDa β (Grp94), member 1	Transcription	chaperone protein	Yoshida H et al., [21]
	HSPA5	heat shock 70kDa protein 5 (glucose-regulated protein, 78kDa)	Transcription	chaperone protein	Min Hong, et al., [16]
	DDIT3	DNA-damage-inducible transcript 3	Transcription	inhibits the dna-binding activity of c/ebp and lap by forming heterodimers that cannot bind dna.	Manthey KC. et al., [9]
	SREBF1	sterol regulatory element binding transcription factor 1	Binding and inhibition	transcription factor activity	Lingfang Zeng et al., [13]
	SREBF2	sterol regulatory element binding transcription factor 2	Binding and inhibition	transcription factor activity	Lingfang Zeng et al., [13]
	CANX	calnexin	Transcription	the quality control apparatus of the er by the retention of incorrectly folded proteins	Sørensen S et al., [8]

	UBA1	ubiquitin-like modifier activating enzyme 1	Transcription	protein ubiquitination	Manthey KC. et al., [9]
	EDEM1	ER degradation enhancer, mannosidase alpha-like 1	Transcription	targets misfolded glycoproteins for degradation in an n-glycan-independent manner	Hori O, et al., [11]
	XBP1	X-box binding protein 1	Transcription	transcription factor activity	Yoshida H et al., [21]
ATF4	CCL2	chemokine (C-C motif) ligand 2	Transcription	inflammatory cytokine	Gargalovic PS et al., [6]
	IL8	interleukin 8	Transcription	inflammatory cytokine	Gargalovic PS et al., [6]
	IGFBP1	insulin-like growth factor binding protein 1	Transcription	a secreted protein that modulates IGF bioavailability	Marchand A, et al., [7]
	HSPA5	heat shock 70kDa protein 5 (glucose-regulated protein, 78kDa)	Transcription	chaperone protein	Wu HL, et al., [3]
	HSP90B1	heat shock protein 90kDa β (Grp94), member 1	Transcription	chaperone protein	Wu HL, et al., [3]
	ATF3	activating transcription factor 3	Transcription	transcription factor activity	Jiang HY et al., [10, 15]

	DDIT3	DNA-damage-inducible transcript 3	Transcription	inhibits the dna-binding activity of c/ebp and lap by forming heterodimers that cannot bind dna.	Lawrence MC, et al., [4]
	XBP1	X-box binding protein 1	Transcription	transcription factor activity	Jiang HY, et al., [10]
	VEGFA	vascular endothelial growth factor A	Transcription	growth factor family, pro-angiogenic factor	Roybal CN et al., [14]
	SLC3A2	solute carrier family 3 (activators of dibasic and neutral amino acid transport), member 2	Transcription	Amino acid transport	Averous J Et al., [17]
	ASNS	asparagine synthetase (glutamine-hydrolyzing)	Transcription	response to nutrient deprivation	Siu F Et al., [20]
	YARS	tyrosyl-tRNA synthetase	Transcription	Tyrosine-tRNA ligase activity	Averous J Et al., [17]
	HERPUD1	homocysteine-inducible, endoplasmic reticulum stress-inducible, ubiquitin-like domain member 1	Transcription	Endoplasmic reticulum unfolded protein response	Ma Y, Hendershot LM., [22]
XBP1	IL8	interleukin 8	Transcription	inflammatory cytokine	Iourgenko V et al., [19]
	DNAJB9	DnaJ (Hsp40) homolog, subfamily B, member 9	Transcription	Protein processing in endoplasmic reticulum	Lee AH et al., [18]

	DNAJC3	DnaJ (Hsp40) homolog, subfamily C, member 3	Transcription	Protein processing in endoplasmic reticulum	Lee AH et al., [18]
	DNAJB11	DnaJ (Hsp40) homolog, subfamily B, member 11	Transcription	Protein processing in endoplasmic reticulum	Lee AH et al., [18]
	UBA1	ubiquitin-like modifier activating enzyme 1	Transcription	protein ubiquitination	Manthey KC. et al., [9]
	DDIT3	DNA-damage-inducible transcript 3	Transcription	inhibits the dna-binding activity of c/ebp and lap by forming heterodimers that cannot bind dna.	Manthey KC. et al., [9]
	FOXO1	forkhead box O1	Binding and inhibition	transcription factor activity	Zhou Y et al., [1]
	BHLHA15	basic helix-loop-helix family, member a15	Transcription	transcription factor activity	Acosta-Alvear D et al., [5]
	HSPA5	heat shock 70kDa protein 5 (glucose-regulated protein, 78kDa)	Transcription	chaperone protein	Wu HL, et al., [3]
	SERP1	stress-associated endoplasmic reticulum protein 1	Transcription	Endoplasmic reticulum unfolded protein response	Lee AH et al., [18]
DDIT3	CEBPB	CCAAT/enhancer binding protein (C/EBP), β	Binding and inhibition	transcription factor activity	Tang QQ et al., [12]
	BCL2	B-cell CLL/lymphoma 2	Transcription	Protein processing in	Sanson M et al., [2]

				endoplasmic reticulum	
	ERO1a	endoplasmic oxidoreductin-1-like protein	Transcription	Protein processing in endoplasmic reticulum	Stefan J. Marciniak et al [17]
	DDIT3	DNA-damage-inducible transcript 3	Transcription	transcription factor activity	Stefan J. Marciniak et al [17]
	WFS1	Wolfram syndrome 1	Transcription	regulation of cellular calcium homeostasis	Stefan J. Marciniak et al [17]

Supplementary information:

Methods for Connexios ER stress module: Details of the data that were manually curated from peer-reviewed literature and included in the ER stress network module are below.

ER machinery involved in protein import, folding and maturation:

A major fraction of the proteome consists of molecules that are destined for the extracellular space or to be inserted into membrane to mediate cell-cell communication thus ultimately regulating overall tissue physiology. Hence the entire process of protein synthesis and folding must be tightly controlled. ER is responsible for the synthesis and proper folding of glycosylated as well as non-glycosylated proteins. Functions of most of these proteins depend on their 3D structure. Hence ER can be considered as a gate keeper wherein newly synthesized proteins enter, get properly folded and modified and are translocated to their respective destinies.

a) Synthesis and translocation of nascent proteins to ER: A signal sequence emerging from the ribosome is recognized by the signal recognition particle and the ribosome-SRP complex with the nascent polypeptide chain is targeted to the ER membrane by interaction with the heterotrimeric SRP receptor. The translocation of nascent polypeptide chain is mediated across the ER membrane by multimolecular machinery termed *translocon* which comprises Sec16p complex, translocating chain associated membrane protein (TRAM), translocon associated protein complex (TRAP complex), small ribosome associated membrane protein 4 (RAMP4) and the signal

peptidase protein, oligosaccharyltransferase (OST). During translocation, N-linked oligosaccharides are attached to the asparagines consensus site to synthesize N-linked glycoproteins [23]. Mutual interplay between folding chaperones and glycosylation machinery ensures proper synthesis of nascent glycoproteins.

b) Folding and misfolding of nascent proteins: As a distinct cellular component, the ER lumen provides a unique protein folding environment for the nascent polypeptide. The oxidizing condition in the ER than the cytoplasm (with a redox potential of -230 mV versus -150 mV) allow the formation of disulfide bonds. In addition the ER resident chaperones and calcium plays a vital role in the protein folding process. One of the driving forces for protein folding is the search for a conformation with a free energy lower than that of the previous state, and has been hypothesized that chaperones play a vital role in the folding process through a number of transition states. A topological landscape representing different energy levels for protein folding has been suggested which has been reviewed elsewhere [24]. ER resident molecular chaperones assist the folding of unfolded and partially folded polypeptide chains utilizing their ATPase domains and also protect the polypeptide from misfolding, thus preventing aggregation. These molecular chaperones ensures proper disulfide bond formation as well as peptidyl prolyl cis-trans isomerisation which in turn requires a mixture of oxidizing and reducing equivalents, usually oxidized and reduced glutathione as well as the enzymatic activity of oxidoreductases and isomerases. Broad categories of chaperones in ER include the classical chaperones, lectin chaperones and some chaperone associated proteins called chaperonins.

ER resident molecular chaperones, oxidoreductases and isomerases: Among the classical chaperones the most predominant ones in the ER are 1) HSP70 (GRP78/BiP), 2) cofactors of the BiP which belong to Hsp40 (ERdj1-5), GrpE families (BAP/Sil1 and Grp170), 3) HSP90 (GRP94), 4) HSP100 (TorsinA). The major lectin chaperones identified in the ER include the calreticulin – calnexin system.

a) Classical chaperones: Bip is one of the most abundant ER chaperones and is closely related to cytosolic HSP70. Bip has an ATPase domain and a peptide binding domain. Affinity of Bip to nascent unfolded proteins depends on the occupancy of ATP in ATPase domain. Thus an unfolded protein regulated by Bip can undergo cycles of binding and release, whose duration depends on the rate at which Bip undergoes ATP exchange and hydrolysis. X-ray crystallographic studies and several *in-vitro* substrate binding studies revealed that Bip substrates include marked hydrophobicity located in the interior of a fully folded protein. Several cofactors which regulate the ATPase activity of Bip have been identified. Erdj3 (DNAJB11), containing J domain

belonging to HSP40 protein family, was found to modulate Bip activity *in-vitro* as well as was found in Bip complex [25]. Recently a mammalian Bip associated protein was identified which belongs to GrpE families, BAP, which encodes 54KDa protein. Highest expression of this protein is identified in secretory organs. ATPase activity of BIP is stimulated by BAP (SIL1), assisting in proper folding of misfolded proteins [26]. Other post translational modifications of Bip include calcium induced autophosphorylation and activation, ADP-ribosylation mediated reduction in activity which might play a vital role in regulating the release of secretory proteins. Grp94/HSP90B1 is another high abundant calcium binding chaperones in the ER. Even though the exact sequential co-ordination of molecular chaperones is not clear in the folding events, it is found that GRP94 binds immunoglobulin during folding after it is released by Bip. Several studies have revealed multimolecular chaperone complexes in ER protein folding and have suggested Bip/Grp94 complex formation with other ER resident chaperones. It is also unclear whether particular sets of chaperones work together on certain classes of proteins or whether the case for each protein is different.

b) Lectin chaperones and glycosylation: Most of the proteins that travel through ER are also targeted for N-linked glycosylation at specific sites. These hydrophilic modifications have significant impact on general protein properties such as stability, solubility, isoelectric point, membrane orientation etc., and also serve as tag for correct protein folding, efficient protein degradation machinery, lysosomal transport and sorting. These hydrophilic N-linked modifications are recognized in ER by lectin chaperones. The two major ER resident lectin chaperones are calnexin and calreticulin. N-linked glycosylation of nascent proteins is characterized by beta-glycosylamide linkage of the glycan, Glc1Man9GlcNAc2 to asparagines residue of the proteins. Initially the glycan is assembled on a polyisoprenyl-pyrophosphate carrier, dolichol pyrophosphate in the cytosolic face [27], which then undergoes an energy independent membrane flip by the activity of a bi-directional flippase into the ER lumen. It is then ultimately transferred to the asparagine residue of the protein located in NXS/T (asparagines-X-serine/threonine) consensus site, by a protein complex located in ER lumen namely Oligosaccharyl transferase (OGT). The glycan which includes three glucose, nine mannose and two N-acetyl glucosamine residues occurs in a flexible branched structures. Subsequent modification of this glycan by ER resident glycanases and transferases, regulate the monoglucosylated N-glycan association with the lectin chaperones calnexin and calreticulin. The first de-glucosylation step, that is cleavage of the outermost alpha1, 2 linked glucose residue by glucosidase 1(G1) occurs as soon as the core glycan has been transferred to the nascent chain. Sequential removal of alpha 1, 3 linked glucose

by glucosidase 2 (GII) at the same time is slower and regulated. Subsequent monoglucosylated glycans interacts with the calcium binding globular domain of calnexin, a 90kDa type 1 membrane protein. Calnexin also consist of long hairpin like structure, termed P domain which is rich in proline residues and recruits thiol oxidoreductase, Erp57 which helps in glycoprotein maturation. Calreticulin which is a soluble lectin chaperone is hypothesized to have a structure similar to calnexin. Both calnexin and calreticulin have high affinity calcium binding site and calcium ion plays a significant structural role in regulating lectin function. Both chaperones bind ATP and like for other chaperones, ATP is hypothesized to regulate the change in conformation of calnexin and calreticulin [28]. Of the various newly synthesized glycoproteins, some interact with only one chaperone while some may interact with both chaperones [29]. These lectin chaperones can be postulated to aid in, suppressing the formation of aggregates, delay folding and promote correct disulfide-bond formation. GII removes the final glucose from the substrates released from lectin chaperones and thereby inhibit substrate rebinding to the lectin chaperones. Properly folded native proteins are directed towards the secretory pathway while nearly native folding intermediates are redirected to the chaperones by the activity of UDP-glucose: glycoprotein glycosyltransferase (UGGT), which transfers single glucose onto non-glycosylated side chains of glycoproteins. UGGT ignores native proteins destined for secretory pathways as well as extensively misfolded polypeptides which are destined for degradation.

c) Disulfide bond formation: The oxidizing environment of ER lumen provides an ideal situation for disulfide bond formation which is critical for the maturation of proteins that pass through the ER. ER resident oxidoreductases which belong to protein disulfide family (PDI) family, with thioredoxin like domain (TLD), catalyze these reactions. They either act as electron acceptors in oxidation reactions or as electron donors for the converse reduction reaction. The maturation of nascent proteins by PDIs is determined by the oxidation state of cysteine in the catalytic domain which is regulated by a membrane associated flavoprotein ERO1p. ERO1p is inturn oxidized by transfer of the electron to other electron acceptors such as oxygen [30]. PDI also functions as chaperone by inhibiting the aggregation of misfolded proteins. Mammalian PDI includes a wide range of proteins and is classified based on the presence of TLD motifs [31]. For maturation of proteins by disulfide bond formation, it is equally important to have disulfide reduction and isomerisation which is mediated by glutathione (L-gamma-glutamyl-Lcysteinyl-glycine) [32].

d) Peptidyl prolyl cis trans isomerisation: cis-trans isomerization of peptidyl proline bonds forms is one of the relevant conformation change occurring during protein folding events. Several refolding experiments have revealed that this conformational change is slow and is one of the rate

limiting steps. Prolyl isomerases (immunophilins) which catalysis this transformation are classified into three families: Cyclophilins family (identified as targets for immunosuppressive drug cyclosporine) and FKBPs (selectively binds FK506 and rapamycin) and a non-immunophilin, phosphorylation dependent prolyl isomerases called Parvulins. Cyclophilins are evolutionarily conserved, ubiquitous proteins which are widely expressed in many tissues. Several forms of cyclophilins with molecular masses ranging from 18 kDa to 150 kDa have been identified. Of them, 20 kDa CypB and 25 kDa CypC is shown to have an N-terminal signal sequence which mediates the ER residency of these proteins. Even though immunofluorescence studies revealed co-localization of CypB with calreticulin and CypC with calreticulin proteins, their exact function in calcium signaling pathways and substrate specificity is yet to be identified. FKBPs are another class of prolyl isomerases which are ubiquitously expressed, ranging in size from 12kDa to 52kDa. FKBP13 is an ER resident prolyl isomerase whose exact function is not yet completely understood. Only a limited number of parvulins are known to date and their ER counterparts have to be identified. [33]

ER associated protein degradation machinery: If the chaperone bound nascent glycoproteins are not folded properly within appropriate time, lectin chaperone bound aggregates of misfolded proteins are cleared from the ER by a process termed ER associated protein degradation (ERAD). For N-linked glycoproteins mannose trimming, by a1, 2-mannosidase I, is considered as the triggering step for transferring the misfolded substrates from calnexin chaperone to another lectin EDEM. These EDEM bound ERAD substrates are translocated into cytoplasm where it undergoes deglycosylation by N-glycanase, are poly-ubiquitinated and degraded by the 26S proteosome. The exact mechanism of how EDEM transfers substrates to cytoplasm is not clear. (Some of the yeast counterparts of EDEM machinery has been identified which has been detailed in reviews by Nishikawa et al, S Gottesman et al [34, 35]). The critical role of Bip in ERAD is identified by the fact that the hydrophobic portions of misfolded proteins are kept in a soluble conformation by the association with Bip. Mutant proteins that escape Bip recognition is shown to accumulate and evade ERAD machinery [36, 37]. Studies in yeast have identified the role of O-mannosylation of misfolded protein, as a major factor which reduces the accumulation independent of BiP function and thereby reducing the load on ER chaperones [38, 39].

Unfolded protein response (UPR): Three arms of adaptive response identified in response to UPR include: dimerisation and activation of PERK , dimerisation and activation of IRE1 and release and processing of ATF6

a) PERK arm of UPR: Pancreatic eIF2α kinase (PEK) or PKR like eukaryotic initiation factor 2 alpha kinase – PERK (EIF2AK3) is an ER resident transmembrane protein ubiquitously expressed and highly enriched in secretory cells. Relevance of this protein in regulating protein synthesis in response to ER load was identified from a rare human disease Wolcott-Rallison syndrome (Wolcott and Rallison). PERK regulation in response to ER load is identified to be regulated by the changes in ER chaperone activity, especially BiP. BiP is shown to associate with luminal domain of PERK [40, 41]. In response to ER load BiP dissociates from PERK, which is hypothesized to allow clustering of PERK. This results in activation of cytosolic kinase domain of PERK resulting in trans-autophosphorylation and an increase in affinity towards eIF2α [42, 43]. PERK-mediated phosphorylation of eIF2α, reduces its ability to associate with its interacting partner (GTP exchange factor) eIF2B. GTP unbound state of eIF2 α does not initiate methionyl tRNA binding to ribosome [44], thereby halting excess protein load into ER. The transcriptional regulation of PERK arm came to picture through studies conducted in cells from patients with CACH/VMW leukodystrophies. Mutations that cause CACH/VMW disorder appear to interfere with eIF2B GEF activity, which in turn is associated with increased ATF4 transcriptional activity [45, 46]. Stress induced activation of ATF4 is implicated in transcription of key enzymes involved in chaperones, anti-oxidants, amino acid synthesis and transport, regulation of apoptosis and cellular differentiation (Table 1) [47,48,49]. Hence PERK arm activation can be considered as a feedback mechanism that regulate the protein load into ER as well as increase the ER chaperone content which can ensure proper folding as well as prevent aggregation of misfolded proteins.

b) IRE1 arm of UPR: One of the most ancient and evolutionarily conserved arms of ER stress sensors was first identified as a gene for inositol prototrophy [50]. In mammals two IRE1 genes has been identified; IRE1alpha, ubiquitously expressed and IRE1 beta, expressed primarily in intestinal epithelial cells [51, 52, 53]. IRE1 is an integral membrane glycoprotein, with an N-terminal domain resident in ER, which is hypothesized to sense the accumulation of unfolded proteins in the ER lumen and a C –terminal domain facing the cytoplasm. Experimental studies suggest that IRE1 oligomerizes and is trans autophosphorylated upon induction of UPR. Immunoprecipitation studies shows that IRE1 is phosphorylated at the serine residues [54]. Even though the exact mechanism of IRE1 activation is not clear, it is suggested that Bip might play an inhibitory role on the ER luminal domain, which when depleted by the unfolded protein accumulation results in clustering of N-terminal domains of IRE1 [55, 56], resulting in activation and autophosphorylation of the protein. Studies using HAC1 (homology to ATF and CREB)

mRNA as a substrate, by Sidrauski and Walter et al [57], demonstrated the endonuclease activity of IRE1. In mammalian cells XBP1 mRNA has been identified as the endonuclease substrate for IRE1. Spliced mRNA of XBP1 encodes functionally active transcription factor, (a 26 nucleotide length intron located centrally in the open reading frame of transcription factor is removed by IRE1), which transcribes key genes which contain unfolded protein response element in their promoter (Table1).

c) ATF6 arm of UPR: ATF6 is an ER resident type II transmembrane protein. Its DNA binding and transcriptional activation region is located in the N-terminal region which is in the cytoplasm. The luminal domain of ATF6, is bound to BiP and also by calreticulin (through its three glycosylation sites). Upon ER stress, the luminal domain of ATF6 is released from BiP and from calreticulin [58]. ATF6 undergoes site directed proteolysis and allows it to migrate to nucleus where it transcribes classical UPR genes (Table 1). The exact mechanism of activation of proteolytic machinery involved in activation of ATF6 is not clear. Similar to SREBF transcription factor, substilisin related site1 protease and intramembraneous site II metalloprotease have been identified to be involved in ATF6 proteolysis and activation [59]. Two mammalian ATF6 genes has been identified, ATF6α and ATF6β, which are shown to be regulated in similar fashion [60]. N-terminal transactivation domain of ATF6α differs markedly from that of ATF6β and hence the ability of ATF6βto engage with active transcriptional complex is weaker compared to that of ATF6α. Even though the membrane forms of ATF6α and ATF6β are similar, rate of cleavage and the time of generation of cleaved active forms of ATF6α, in response to ER stress precedes that of ATF6β. Pulse chase labeling and siRNA based studies has shown that expression levels and half lives of ATF6β is greater than that of ATF6α isoform and ATF6β acts as a transcriptional repressor of ATF6α [61, 62]. ATF6β which is generated after ATF6α and which is relatively long lived might act as an endogenous inhibitor to modulate ATF6α gene induction in response to ER stress

Temporal Regulation of Unfolded protein Response: As observed with other signaling pathways, the UPR as an internal sensor of the quantity and quality of the protein load emanating from ER, process both feedback positive and negative feed back regulations which are separated in time space. Studies by Du Rose et al, Okada et al has revealed rapid induction of IRE1, PERK and ATF6 in response to multiple ER stress inducers. Immediate impact of these responses seems to be a positive feedback mechanism in regulating the protein load by PERK-EIF2 mediated inhibition of protein synthesis, IRE1- P58IPK mediated selective degradation of ER associated mRNAs [63], and rapid cytosolic proteasomal degradation of nascent polypeptides, phenomena termed as pre-emptive quality control [64].

Transcriptional induction of genes by the UPR arms is slightly delayed when compared to the activation of the ER membrane resident UPR machineries. Probably this might be due to the mechanisms required for nuclear translocation of ER resident transcription factors as well as the co-ordination required with multiple other nuclear transcription factors such as CEBP, NFY etc; to trigger the transcription from ERSE & UPRE promoters [65]. IRE1-XBP1 mediated transcriptional regulation has been shown to be delayed compared to ATF4 and ATF6, might be because XBP1 mRNA is maximally induced in response to ATF6. This transient phase might be a feedback mechanism to increase machineries such as

1. Chaperones & cochaperones to mediate proper protein folding.
2. Degradation machinery to remove misfolded proteins.

Ron et al, using wild type mouse fibroblasts have highlighted the importance of ATF4 & PERK arm of UPR in increasing the supply of amino acids for proteins synthesis and also for glutathione biosynthesis thereby protects the cells against oxidative stress [66]. PERK arm of UPR is shown to activate NRF2, a major transcription factor for antioxidant genes & thereby mediating cellular protection against stress induced apoptosis [67, 68, and 69]. Similarly studies by Sriburi et al & Bommiasamy et al [70] have identified additional role for ATF6 and XBP1 transcription factors in regulating ER membrane biogenesis by increasing phosphatidylcholine biosynthesis. [71]

ER stress and Apoptosis: Prolonged ER stress triggers PERK, ATF6 and IRE1-mediated pro-apoptotic events. Two of the major signaling cascades activated by the UPR to initiate apoptosis are DDIT3, (growth-arrest and DNA damage inducible gene 153) and the JNK pathway. (For a brief review see Eva Szegezdi et al [72]). Overexpression and knockout studies have revealed the role of DDIT3 in ER stress induced apoptosis. Expression of BCL-2, one of the anti-apoptotic genes is reduced by DDIT3 overexpression [73]. Similarly in response to ER stress, IRE1 is shown to from a complex which TRAF 2-ASK1 and triggers the p38MAPK and JNK cascade which are known inducers of apoptosis under stress [74]. The activation of P38MAPK in response to ER stress phosphorylates and increases transcriptional activity of DDIT3 [75]. Synergistic impact of DDIT3 and JNK signaling, on BCL-2 protein ultimately leads to programmed cell death. Sequential cascade of caspase activation mediating ER stress induced cell death has not yet been conclusively established. Similarly increased JNK activity has been reported to reduce PDX1 activity thereby impairing insulin gene transcription in pancreatic beta cells [76, 77].

Another gene directly activated by DDIT3 is GADD34, a member of GADD family of genes that are induced by genotoxic stress and growth arrest signals. GADD34 promotes ER protein biosynthesis by dephosphorylating the eIF2α. GADD34 deficient mice are protected from renal toxicity in response to tunicamycin [78]. In a recent review by Rutkowski and Kaufman [79, 80], GADD34 mechanism of action

has been articulated as a positive feed back mechanism wherein the protein synthesis is revived back once the transient phase of ER stress is reduced. Moreover prolonged, selective inhibition of eIF2α phosphorylation is shown to potentiate fatty acid induced beta cell death [81].Hence it will be interesting to understand the dynamic regulation of GADD34 as a sensor to regulate protein synthesis in multiple phases of ER stress.

Statistical methods:

Microstats package was used to compute m-value as a log ratio of the gene expression data from the BTBR mice as compared to the age and weight-matched B6 and lean BTBR control mice. M-value of >0.3 and p-value of >0.05 was considered significant.

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