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Critical Review

ER Stress Response, Peroxisome Proliferation, Mitochondrial Unfolded Protein Response and Golgi Stress Response

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Running Title: ORGANELLE AUTOREGULATION

Keywords mitochondrial retrograde signaling; ATF6; IRE1; XBP1; unfolded protein response; PPAR; PEX
ABBREVIATIONS

ER, endoplasmic reticulum; ERAD, ER-associated degradation; AARE, amino acid response element; ERSE, ER stress response element; UPRE, unfolded protein response element; PEX, peroxin; ORE, oleate response element; UPR, unfolded protein response; MURE, mitochondrial unfolded protein response element
Summary

The endoplasmic reticulum (ER) response has been thought a cytoprotective mechanism to cope with accumulation of unfolded proteins in the ER. Recent progress has made a quantum leap revealing that ER stress response can be regarded as an autoregulatory system adjusting the ER capacity to cellular demand. This Copernican change raised a novel fundamental question in cell biology: how do cells regulate the capacity of each organelle in accordance with cellular needs? Though this fundamental question has not been fully addressed yet, research about each organelle has been advancing. The proliferation of the peroxisome is regulated by the PPARα pathway, whereas the abundance of mitochondria appears to be regulated by mitochondrial retrograde signaling and the mitochondrial unfolded protein response. The functional capacity of the Golgi apparatus may be regulated by the mechanism of the Golgi stress response. These observations strongly suggest the existence of an elaborate network of organelle autoregulation in eukaryotic cells.
INTRODUCTION

Eukaryotic cells contain a set of organelles that are specialized in specific cellular functions. The abundance of each organelle appears to be tightly and dynamically regulated in accordance with cellular demand. For instance, secretory cells such as plasma cells contain enormous amounts of the endoplasmic reticulum (ER), almost filling the cytoplasm, while exercise-conditioned skeletal muscle contains enlarged mitochondria [1]. Since most of the genes involved in organelle biogenesis reside in the nuclear genome, inter-organelle signaling between the nucleus and the organelle appears to regulate the autoregulation of the organelle abundance (Figure 1). It is highly possible that each organelle has sensor molecules that monitor whether the capacity is sufficient to satisfy various cellular demands. If the demand exceeds the capacity, an emergency signal is transmitted to the nucleus, and activates the transcription of relevant genes involved in the biogenesis of the organelle, leading to upregulation of the capacity and the abundance. However, the underlying
mechanism of the organelles’ autoregulation has not been fully clarified.

This short review will briefly summarize the recent progress of research on the autoregulation of the abundance of organelles, including the ER, peroxisomes, mitochondria and Golgi apparatus.

**ER STRESS RESPONSE**

The ER is an organelle in which secretory and membrane proteins are synthesized, and proteins correctly folded by ER chaperones are transported to the Golgi apparatus [2]. Unfolded or misfolded proteins are retained in the ER and degraded by ER-associated degradation (ERAD) [3, 4]. If unfolded proteins build up in the ER, eukaryotic cells upregulate the expression of ER chaperones and components of ERAD machinery to enhance the capacity of folding and degradation of unfolded proteins, through the cytoprotective mechanism called the ER stress response or unfolded protein response [5-8].

Mammalian cells developed an elaborate mechanism of the ER
stress response, which utilizes three sensor molecules monitoring the accumulation of unfolded proteins in the ER (ER stress) (Figure 2). PERK, a sensor-kinase localized in the ER membrane, phosphorylates the $\alpha$ subunit of eukaryotic initiation factor of translation (eIF2$\alpha$) in response to ER stress, leading to translational attenuation and then preventing further accumulation of unfolded proteins [9, 10]. PERK also induces the expression of a transcription factor, ATF4, which binds to an enhancer element called AARE (amino acid response element) and is responsible for induction of antioxidative enzymes as well as proteins related to translation [11, 12].

ATF6 is a sensor-transcription factor embedded in the ER membrane [13]. Upon ER stress, ATF6 is transported to the Golgi apparatus and sequentially cleaved by proteases called S1P and S2P [14-16]. A cytoplasmic portion of ATF6 released from the Golgi apparatus translocates into the nucleus, binds to an enhancer element called ERSE (ER stress response element; the consensus sequence is
CCAAT(N9)CCACG) and activates transcription of ER chaperone genes as well as ERAD genes [17-20].

IRE1 is a sensor-RNase located in the ER membrane [21-24]. Upon sensing ER stress, IRE1 converts pre-mRNA of XBP1 into mature mRNA by the mechanism of cytoplasmic mRNA splicing, leading to translation of active transcription factor pXBP1(S) [25, 26]. pXBP1(S) activates transcription of ER chaperone and ERAD genes as a homodimer or a heterodimer with ATF6, whereas pXBP1(U), a protein translated from XBP1 pre-mRNA, enhances degradation of pXBP1(S) [17, 18, 27-30].

These response pathways operate not simultaneously but sequentially [18]. In the early phase of the ER stress response, the PERK pathway attenuates translation to facilitate folding of unfolded proteins, without inducing expression of ER chaperones. If unfolded proteins still persist, the ATF6 pathway increases the expression of ER chaperones to enhance the folding of unfolded proteins. If the ATF6 pathway cannot manage unfolded proteins, the expression of ERAD components is induced.
by the IRE1 pathway, leading to degradation of unfolded proteins. If these pathways cannot deal with the ER stress, compromised cells are disposed of by apoptotic cell death.

ER stress-induced apoptosis seems to be regulated by multiple pathways. The CHOP pathway has been analyzed extensively. CHOP is a transcription factor whose transcription is induced by ATF4 in response to ER stress, and which in turn activates the transcription of pro-apoptotic factor Bim [31]. ER stress-induced apoptosis is regulated by other pathways, including the IRE1-TRAF2-ASK1 pathway, the caspase-12 pathway and c-Abl [8].

The biological significance of ER stress response has been obscure since the physiological situations in which unfolded proteins accumulate in the ER were not known. ER stress can be artificially evoked either by treating cells with chemicals preventing protein folding such as tunicamycin and thapsigargin, or by expression of genetically mutated secretory proteins that cannot be folded correctly. However,
organisms seldom ingest such substances, and it is not conceivable that
the ER stress response has been developed to cope with genetic
mutations of secretory proteins.

The answer came from the unexpected finding that XBP1, a key
transcription factor essential for the ER stress response, is a regulator of
the ER abundance in secretory cells, including plasma cells, pancreatic
acinar cells and salivary gland cells [25, 26, 32, 33]. For instance,
precursors of plasma cells (pre-B cells) have a trace amount of ER,
whereas plasma cells secreting large amount of immunoglobulins have
extensively developed ER to support production of immunoglobulin.

Interestingly, XBP1 is indispensable for expansion of the ER, and the ER
stress response is highly activated in plasma cells and other secretory cells,
resulting in the induction of large amounts of ER chaperones as well as
ERAD components. These observations suggest that the production of
large amounts of immunoglobulin activates the ER stress response,
leading to enhanced expression of ER chaperones and ERAD components
as well as ER expansion. In other words, the ER stress response is a mechanism to adjust the capacity of ER functions, including protein folding and ERAD, to cellular demand.

PEROXISOME PROLIFERATION

The peroxisome is an organelle where diverse biochemical reactions including β-oxidation of fatty acids and the detoxification of hydrogen peroxide occur [1]. The abundance of the peroxisome is dynamically regulated by the metabolic status in cells [34]. In budding yeast Saccharomyces cerevisiae, fatty acids such as oleate increase the peroxisomes [35], while methanol induces proliferation of this organelle in methylotrophic yeast Pichia pastoris [36], suggesting that cells tightly regulate the abundance of peroxisomes in accordance with cellular demand. In mammalian cells, the abundance of peroxisomes is enhanced by long chain fatty acids as well as hypolipidemic compounds such as clofibrate, phthalate esters used as plasticizers such as
di(2-ethylhexyl) phthalate, and halogenated hydrocarbon solvents [34].

Though it is still controversial whether the peroxisome proliferates by fission or budding from the ER, many peroxisomal proteins, including peroxins (PEXs), contain a peroxisomal targeting signal instead of a signal sequence, and can be imported to the peroxisome post-translationally, independent of the ER function [37, 38].

The mechanism of peroxisome proliferation in response to fatty acids has been extensively studied in S. cerevisiae (Figure 3) [1, 35, 39-41]. Fatty acids bind and activate Zinc finger-type transcription factors Oaf1p and Pip2p/Oaf2p, which belong to the nuclear hormone receptor superfamily. A heterodimer of Oaf1p and Pip2p binds to an enhancer element called ORE (oleate response element: consensus sequence is CGGN_{15-18}CCG) and induces transcription of genes involved in peroxisome function, leading to peroxisome proliferation. The target genes of Oaf1-Pip2p include β-oxidation enzymes such as Pox1p (acyl CoA oxidase, which is a rate limiting enzyme of the β-oxidation pathway) and enzymes
that degrade hydrogen peroxide, such as Cta1p (catalase A). Though most of the peroxins that are involved in peroxisome biogenesis are not induced by fatty acids, peroxins such as Pex11p/Pmp27p and Pex25p, which are involved in peroxisome proliferation, are regulated by the OAF1-PIP2 pathway [42-54]. Interestingly, the promoter of PIP2 contains ORE, and its expression is induced by fatty acids, whereas the expression of Oaf1p is constitutive [54].

Budding yeast has another regulatory pathway for peroxisome proliferation called retrograde regulation (also called mitochondrial retrograde signaling: see below) (Figure 3) [55, 56]. CIT2, which encodes the peroxisomal glyoxylate cycle enzyme citrate synthase 2, is transcriptionally activated in response to oleate. Transcriptional induction of CIT2 is regulated by three proteins: RTG1, RTG2 and RTG3. RTG1 and RTG3 encode basic helix-loop-helix transcription factors, while RTG2 is a cytoplasmic protein that shows no homology to known proteins (see the section about mitochondrial retrograde signaling). In the absence of
oleate, RTG3 is hyperphosphorylated and RTG1 and RTG3 are localized in the cytoplasm. In response to oleate, RTG3 becomes partially dephosphorylated, and a heterodimer of RTG1 and RTG3 is transported to the nucleus and activates transcription of CIT2 by directly binding to an enhancer element called an R box (consensus sequence is GTCAC) in the CIT2 promoter. RTG2 is required for dephosphorylation and activation of RTG3, and may be involving in sensing of oleate. Though RTG genes are also required for transcriptional induction of POX1 and CTA1, regulation by RTGs appears to be indirect, since RTG1 and RTG3 do not bind to the ORE or the promoters of POX1 and CTA1 [57]. Interestingly, the RTG pathway is also activated by mitochondrial dysfunction such as ρ0 petites blockade of the tricarboxylic acid cycle [58], indicating the crosstalk of autoregulatory systems between the peroxisome and the mitochondria.

The OAF1-PIP2 pathway is considerably conserved in mammalian cells [39, 59]. When long chain fatty acids bind to the ligand binding domain of PPARα (mammalian Zinc finger type transcription factor
belonging to the nuclear hormone receptor superfamily), PPARα becomes activated, forms a heterodimer with a nuclear hormone receptor, RXR, and binds to an enhancer element called PPRE (peroxisome proliferator-response element: the consensus sequence is AGGTCA(N)AGGTCA). PPARα induces expression of peroxisomal proteins including lipid metabolizing enzymes as well as PEX11α [60], leading to proliferation of the peroxisome [61, 62]. Chemicals that induce peroxisome proliferation such as clofibrate (peroxisome proliferators) are thought to directly bind and activate PPARα.

When the number of the peroxisome is excessive as compared for cellular demand, the abundance of the organelle is reduced by the mechanism of selective degradation called pexophagy. Pexophagy utilizes a non-selective autophagy system as well as pexophagy-specific pathways to form pexophagosomes engulfing the organelles and to degrade them in lysosomes. The mechanism of pexophagy has been well analyzed in methylotrophic yeasts Hansenula polymorpha and P. pastoris
In P. pastoris, two modes of pexophagy, macropexophagy and micropexophagy, have been reported. Macropexophagy is restricted to mature peroxisomes, leaving immature peroxisomal vesicles intact. This selectivity relies on two proteins involved in peroxisome biogenesis. Pex3p, a peroxin that is absent from the mature peroxisome and degraded by the proteasome, prevents pexophagy of the immature peroxisome, whereas Pex14p, a potential docking protein for initial factors of pexophagy such as Atg11p, facilitates pexophagy of the mature peroxisome.

Autophagy specific to the mitochondria (mitophagy) and ER (ER-phagy) has been reported. Mitophagy is induced by nutrient deprivation in mammalian cells [63], while it is also involved in elimination of aged and dysfunctional mitochondria since mitochondria are prone to reactive oxygen species [64]. Nutrient starvation triggers the delivery of the ER to the vacuole via autophagy [65]. In addition, ER stress increases the expression of ATG8, a crucial component required for autophagosome formation, and induces ER-phagy in yeast [66-68]. Deletion of ATG8
prevents ER-containing autophagosomes and impairs the ability of the
cells to survive ER stress. In mammalian cells, autophagy is activated in
response to ER stress, and protects cells from ER stress [69-72]. These
organelle-specific type of autophagy may be responsible for
downregulation of excessive amounts of these organelles, as well as
disposal of malfunctioning organelles.

MITOCHONDRIAL RETROGRADE SIGNALING

The mitochondria is an organelle producing ATP from acetyl CoA
in the TCA cycle and the respiratory chain [73]. It has been reported that
the mass of mammalian mitochondria is increased in cells that have
defects in the respiratory chain [74], in adipose tissue upon cold shock [75],
or exercise-conditioned skeletal muscle [1], suggesting that the
mitochondria has an autoregulatory system to adjust its function for cellular
demand, in order to keep ATP levels constant [76]. Though transcription
factors and co-activators such as Tfam, NRF1, NRF2, SP1, YY1, CREB,
MEF2 and PGC-1 alpha are reported to be involved in the transcriptional induction of genes responsible for mitochondrial function and biogenesis, the mitochondrial biosynthetic program appears to be regulated by multiple transcriptional regulatory pathways, including the mitochondrial retrograde signaling and mitochondrial unfolded protein response.

When the function of the mitochondria is compromised and the cellular ATP levels drop, eukaryotic cells activate the mitochondrial retrograde signaling and upregulate the transcription of nuclear genes involved in mitochondrial function to restore the ATP levels [56, 77]. Mitochondrial retrograde signaling is observed in yeast as well as in mammals, though the underlying mechanism appears not to be highly conserved [78].

RTG3 and RTG1 are key transcription factors regulating mitochondrial retrograde signaling in budding yeast (Figure 3) [55, 58, 79-86]. In normal conditions, RTG3 is hyperphosphorylated and localized in the cytoplasm. A cytoplasmic protein, Mks1p, is a negative regulator of
RTG3 that enhances RTG3 phosphorylation. RTG2 is a cytoplasmic protein that contains an ATP-binding domain and thought to monitor cellular ATP levels. Upon a decrease of mitochondrial respiratory capacity, RTG2 promotes dephosphorylation of RTG3, leading to translocation of an RTG3-RTG1 heterodimer to the nucleus. Grr1p, another positive regulator, contains an F-box motif and mediates ubiquitination and degradation of Mks1p. Ubiquitination of Mks1p by Grr1p is blocked by negative regulators, such as 14-3-3 proteins called Bmh1p and Bmh2p. RTG3-RTG1 binds to an enhancer element called the R box (consensus sequence is GTCAC) and activates transcription of CIT2, DLD3, CIT1, ACO1, IDH1 and IDH2. CIT2 encodes a peroxisomal citrate synthase that helps produce citrate from carbon source such as fatty acids, acetate and ethanol via the glyoxylate cycle (Figure 3). DLD3 encodes a cytoplasmic D-lactate dehydrogenase, and may be involved in regeneration of NAD$^+$ due to the buildup of NADH in respiration-deficient cells. CIT1, ACO1, IDH1 and IDH2 encode enzymes involved in the first three steps of the TCA cycle.
Mitochondrial retrograde signaling (also referred to as mitochondrial stress signaling) has been less studied in mammalian cells [78]. Mitochondrial dysfunction caused by partial depletion of mitochondrial DNA or treatment with mitochondria-specific inhibitors such as CCCP induces stress signaling that is associated with increased cytoplasmic free Ca$^{2+}$ and upregulation of a number of genes involved in Ca$^{2+}$ transport and storage, including Ryanodine receptor, calreticulin and calsequestrin, though the link to mitochondrial autoregulation remains obscure.

**MITCHONDRIAL UNFOLDED PROTEIN RESPONSE**

Mitochondria have an autoregulatory system similar to the ER stress response (Figure 4) [73, 87]. Accumulation of unfolded proteins in the mitochondria induces the mitochondrial unfolded protein response (UPR$^{\text{mt}}$), leading to enhanced expression of mitochondrial chaperones
including HSP70 and HSP60 in Caenorhabditis elegans (hsp-6 and hsp-60, respectively) [87]. Four essential components of UPR\textsuperscript{mt} have been identified in C. elegans: CLPP-1 is a mitochondrial matrix protease that is similar to bacterial protease ClpP. Though bacterial ClpP is associated with AAA-ATPases such as ClpA and ClpX, C. elegans has no obvious ClpA homolog and two homologs of ClpX, though knock down of the two ClpX homologs did not affect UPR\textsuperscript{mt}. The second component is a transcription factor, DVE-1. DVE-1 contains a homeobox, and translocates into the nucleus upon UPR\textsuperscript{mt}. ChIP assays revealed that DVE-1 binds the promoters of hsp-6 and hsp-60. The third component is a ubiquitin-like protein, UBL5. UBL5 binds to DVE-1, and its expression is induced in response to UPR\textsuperscript{mt}. The fourth component is RheB. Rhe1 is a GTPase implicated in signaling via TOR. The current working hypothesis of UPR\textsuperscript{mt} in C. elegans is as follows [87]: unfolded proteins are refolded by mitochondrial chaperones and degraded by mitochondrial proteases such as SPG7. If unfolded proteins overwhelm mitochondrial
chaperones, they are processed by CLPP-1 and the resultant peptides are transported to the cytosol via a mitochondrial inner membrane protein, MDL-1. The peptides released to the cytosol activate DVE-1 and UBL5, and enhance their association. Then DVE-1 enters the nucleus and activates the transcription of mitochondrial chaperone genes. RheB and TOR may be involved in the negative feedback loop of UPR\textsuperscript{mt}.

In mammals, UPR\textsuperscript{mt} induces the expression of mitochondrial chaperones and proteases, including HSP60, HSP10, mtDnaJ and ClpP [73, 88-91]. Promoters of these UPR\textsuperscript{mt} target genes contain a binding site for transcription factors CHOP and C/EBP\(\beta\), flanked by a pair of conserved cis-elements called mitochondrial UPR elements (MUREs). Transcription of CHOP and C/EBP\(\beta\) is induced by UPR\textsuperscript{mt}, possibly by binding of cJUN activated by JNK2 to an AP-1 site of the CHOP promoter. It remains to be clarified whether the UPR\textsuperscript{mt} pathway in C. elegans is conserved in mammals, and whether UPR\textsuperscript{mt} actually regulates the capacity of mitochondria in accordance with cellular demand.
GOLGI STRESS RESPONSE

If the ER stress response enhances the capacity of ER function, large amounts of secretory proteins are transported to the Golgi apparatus, probably causing insufficiency of Golgi function (Golgi stress). It is possible that the mechanism of autoregulation called the Golgi stress response evolved to cope with such a stressful situation. Interestingly the Golgi apparatus is well developed in secretory cells such as a secretory mucous cells of the intestinal Brunner's glands, which require a high level of Golgi function. Brunner's gland cells synthesize a large amount of mucin that contains enormous amounts of O-linked sugar chains. Since O-linked sugar chains are conjugated to secretory proteins in the Golgi apparatus, the demand for Golgi function is thought to be very high in Brunner's cells. Moreover, the Golgi apparatus of prolactin cells and mammary gland cells of female mice is known to develop dynamically in response to increased production of prolactin and milk proteins induced by
the sucking stimulus. These observations strongly suggest the existence of the Golgi stress response to adjust the capacity of the Golgi apparatus to cellular demand in eukaryotic cells. Actually, the expression of genes involved in Golgi function was increased when mammalian as well as yeast cells were treated with monensin or nigericin, chemicals that impair Golgi function. Identification of enhancer elements, transcription factors and sensors responsible for transcriptional induction would reveal the molecular mechanism of the Golgi stress response pathway.

CONCLUDING REMARKS

Though the human body consists of various types of cells such as neurons, muscle cells and lymphocytes, the basic structures of these cells are very similar, and are comprised of organelles including the nucleus, ER, mitochondria, peroxisomes, Golgi apparatus, lysosomes and endosomes. Thus, the capacity of each organelle has to be highly adaptive, in order to support various types of functions in a variety of cells. In other words, the
autoregulation of organelle capacity is a fundamental process for multicellular organisms. Achieving a complete view of the network of organelle autoregulation should be indispensable for understanding the sophisticated homeostatic mechanisms of eukaryotic cells, as well as the diseases related to loss of organellar function [8, 92-94].

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**FIGURE LEGENDS**

Figure 1. Organelle autoregulation. When the functional capacity of an organelle becomes insufficient compared to cellular demand, a regulatory signal is transmitted to the nucleus, where transcription of relevant genes involved in function of the organelle is activated, resulting in augmentation of the functional capacity.
Figure 2. ER stress response. When ER functions such as folding and ERAD become insufficient in mammalian cells, the program of transcriptional induction is activated through three response pathways, leading to enhancement of the capacity of ER function or the apoptotic removal of the compromised cell.

Figure 3. Peroxisome proliferation and mitochondrial retrograde signaling in yeast. Excessive amounts of fatty acids induce peroxisome proliferation to increase the capacity of processing fatty acids by β-oxidation, and also activate mitochondrial retrograde signaling to enhance the capacity of the glyoxylate cycle. Mitochondrial retrograde signaling is also activated by reduced levels of cytosolic ATP, to upregulate the capacity of the TCA cycle.

Figure 4. Mitochondrial unfolded protein response in C. elegans. Insufficiency of folding or degradation capacity in the mitochondria
activates the mitochondrial unfolded protein response to enhance the capacity of the organelle.

(3,653 words, excluding references)
Figure 1. H. Yoshida

- Organelle
- Demand for organelle function
- Augmentation of organelle function
- Signal transduction
- Sensor
- Nucleus
- Transcription factor
- Enhancer
- Target genes
- Proteins involved in organelle function
- Organelle autoregulation
Figure 2. H. Yoshida

ER chaperones - unfolded proteins - degradation - Golgi apparatus

ERAD - unfolded proteins

PERK - ATF4

ATF6

IRE1 - pXB1(S)

ERAD - pXB1(U)

XBP1 pre-mRNA - XBP1 mature mRNA

cytoplasmic splicing

target genes - AARE - unfolded proteins

ER chaperones - ERSE

ERAD - unfolded proteins

ERAD - BiP, GRP94, calreticulin, PDI, P5, XBP1

proteins related to translation, antioxidative enzymes, CHOP, apoptosis

nucleus

ER - ribosome - translational attenuation

translation attenuation
Figure 3. H. Yoshida
Figure 4. H. Yoshida

mitochondria

folded proteins \[\rightarrow\] unfolded proteins \[\rightarrow\] CLPP-1

mitochondrial chaperones (HSP-6, HSP-60)

mitochondrial chaperones (HSP-6, HSP-60)

UBL-5

CLPP-1

SPG-7

degraded

peptides

DVE-1

UBL-5

Nucleus

target genes

?