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REVIEWS

Spotlight

ER Stress Priming of Mitochondrial Respiratory suPERKomplex Assembly

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Assembly factors are necessary for the formation of mitochondrial supercomplexes (SCs) and in making cellular respiration more efficient. In a recent study, Balsa *et al.* (*Mol. Cell*, 2019) report that nutrient-induced endoplasmic reticulum (ER) stress engages PERK–eIF2α-mediated transcription of the SCs assembly factor SCAF1, events that coordinate ER stress and SCs formation to improve bioenergetics.

Cells are exposed to continuous microenvironmental changes that activate different signaling pathways to maintain the intracellular homeostasis. Following stimuli such as nutrient deprivation, specific metabolic adaptations result from coordination of the cellular organelle responses, with the ultimate purpose of promoting cell survival whenever viability is not irreversibly compromised. Two key organelles involved in the cellular stress response are the ER and mitochondria. While the ER controls the folding, glycosylation, and release of proteins, the main role of mitochondria relies on energy production from respiration. Both organelles form an extended, physically and functionally interconnected network through dynamic contact sites known as mitochondrial-associated membranes (MAMs), which promote calcium transport, lipid trafficking, and exchange of metabolites [1]. Despite the growing number of studies on the subject, it is not clear how the ER–mitochondria 'crosstalk' coordinates respiration and bioenergetics, especially when mitochondrial and ER homeostasis are disrupted in pathological conditions that trigger the unfolded protein response (UPR).

In a recent study, Balsa *et al.* [2] shed light on the molecular events controlling mitochondrial respiratory capacity during nutrient stress. To this end, they capitalize on the reported ability of glucose-free, galactose-supplemented media to foster mitochondrial respiration in conditions of blunted glycolysis and forced mitochondrial ATP production [3]. The analysis of the respiratory efficiency in such conditions confirms an increase in complex I (CI)-driven respiration and respiratory SCs formation. This is concomitant with the presence of highly packed and numerous cristae in mitochondria from cells grown in galactose. In the search for pathways challenged by a glycolytic shut-off, a comprehensive metabolomic analysis revealed uridine diphosphate-*N*-acetylglucosamine (UDP-GlcNac) as the most downregulated hit, indicative of impaired glycosylation by the hexosamine pathway at the ER and, hence, indicative of ER stress.

Among the ER stress sensors analyzed in the search for specific targets, PERK emerged as the only candidate accounting for higher respiratory SCs assembly and capacity upon galactose challenge (Figure 1). Accordingly, *in vitro* and *in vivo* experiments identified Ser51 phosphorylation of the PERK target eIF2α as part of the active pathway involved in the respiratory engagement of mitochondria. Transcripts of assembly factor SCAF1 (COX7A2L), key in SCs formation involving mitochondrial complexes III and IV [4], were markedly upregulated upon galactose incubation and ER stress induction, requiring ATF4 acting downstream of eIF2α, as confirmed with genetic and pharmacological approaches. Notably, bioenergetics were similarly compromised in both ATF4- and SCAF1-deleted cells. However, their metabolic profiles did not fully match, suggesting a more complex ER–mitochondrial crosstalk in metabolic handling [5]. Thus, it is likely parallel pathways converge to upregulate SCAF1 or other, still unknown, assembly factors.

To explore whether cristae tightening was responsible for the increased SCs assembly [3,6,7], Balsa *et al.* turned to cellular models of OPA1 and MICOS genetic ablation, both master scaffolds of cristae junctions and inner membrane anchoring and, thus, crucial to build orthodox cristae [8]. The lack of either protein confirmed the disruption of SCs and cristae; however, their absence was not recovered by SCAF1 overexpression, indicating that increased SCs assembly itself was not sufficient to restore ultrastructure in this scenario. It is tempting to speculate that, conversely, reduced cristae width may recover compromised SCs assembly in the absence of SCAF1, as demonstrated by the ability of cristae tightening by OPA1 to blunt aberrant mitochondrial function driven by mutations in the complex IV assembly factor COX15 [9]. The possibility that OPA1 functions as an assembly factor *per se* is unlikely, since it does not co-migrate with SCs in native conditions [6]. Interestingly, ER stress and PERK–eIF2α foster mitochondrial elongation in a YME1L-dependent manner [10], which may engage OPA1 cleavage [11] in shaping mitochondrial ultrastructure upon galactose incubation [3], although no OPA1 processing has been observed with some ER stressors [10]. A missing piece to further complete the picture may be ATP synthase, regarded as a key candidate in

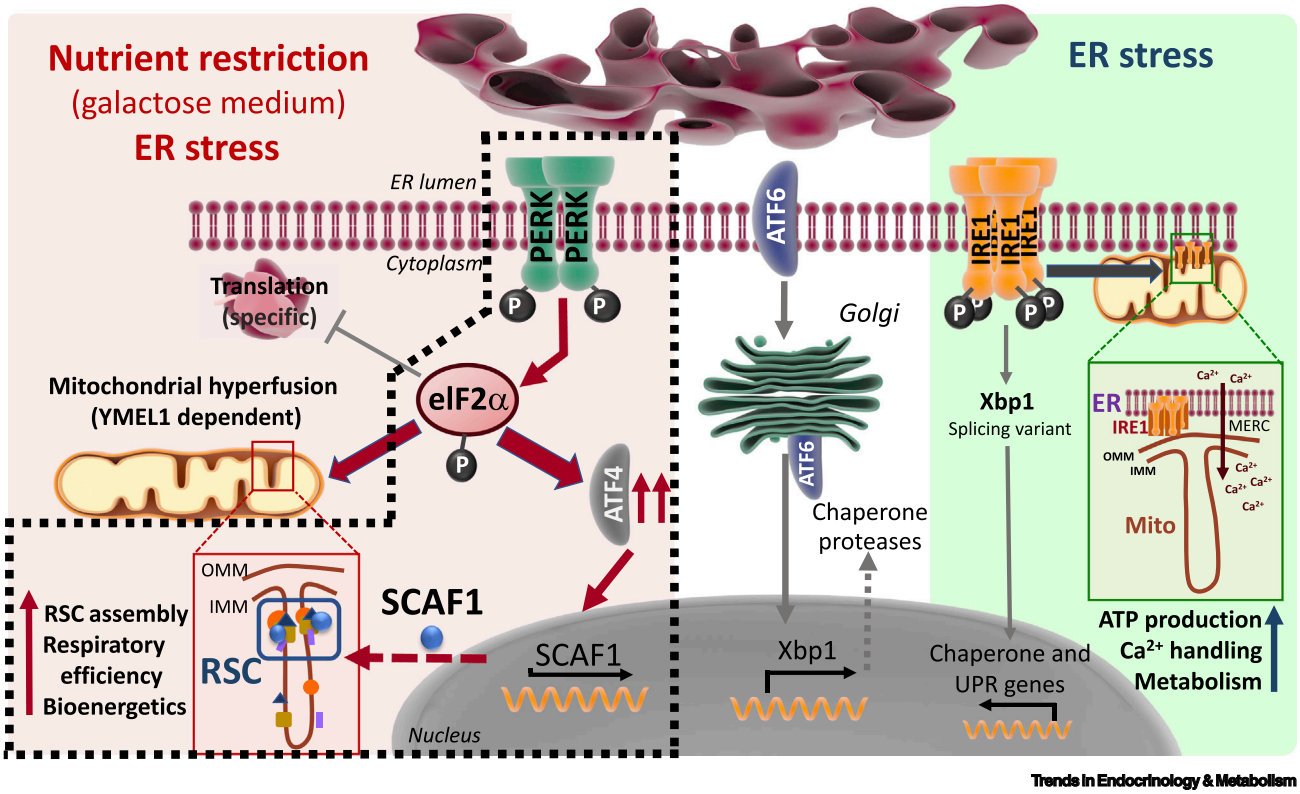

Figure 1. Endoplasmic Reticulum (ER) Stress Sensors and Activated Response Pathways.

During glucose deprivation, PERK, IRE1, and ATF6 are activated. Consequently, PERK and IRE1 homo-oligomerize and autophosphorylate, while ATF6 translocates to the Golgi apparatus, where it is processed to induce the transcription of chaperones and other unfolded protein response (UPR) genes. Similarly, IRE1 induces the expression of a Xbp1 splicing variant to transcribe UPR-related genes, whereas IRE1 serves to modulate mitochondrial–ER contacts (mitochondrial-associated membranes; MAMs) for Ca^{2+} transfer to mitochondria and metabolic activation. A parallel pathway induces eIF2α phosphorylation to act as a key regulator of different adaptive events: translation inhibition, YME1L-mediated mitochondrial hyperfusion, and ATF4-mediated gene expression. The latter, as recently demonstrated by Balsa *et al.* [2], drives the transcription of the respiratory chain supercomplexes assembly factor SCAF1 (dashed box). The upregulation of SCAF1, only if accompanied by the tightening of the cristae, promotes respiratory supercomplexes (RSCs) assembly, higher respiratory capacity, and improved bioenergetics. Abbreviations: IMM, inner mitochondrial membrane; OMM, outer mitochondrial membrane.

recapitulating the ultrastructural and bioenergetic features observed under the galactose medium [3]. ATPase dimerization, critical in bending the inner membrane and holding cristae tips [12], is induced by growth in galactose medium, sensed by OPA1 [7] and its solute carrier interactor SLC25A [3]. As a result, ATPase dimers and ultrastructure remodeling may coordinate an intrinsic mitochondrial response with that derived from ER stress and nuclear transcription of SCAF1 in the assembly of more efficient SCs. Another question is whether, and how, other unknown assembly factors may take over SCAF1 function when this is absent or dysfunctional, as physiologically apparent in the widespread C57BL/6J mouse strain [4].

PERK activation recovers bioenergetics and cell growth in human cellular models of mitochondriopathies caused by marginal CI activity (ND1 or ND6 missense mutations) or assembly (ACAD9), but not when CI (ND4 and ND6 nonmissense mutations) or other electron transport chain complexes [Rieske knockout (KO), COX10 KO, or MELAS] are absent [2]. Therefore, at the very least, a residual abundance of complexes appears to be required for reassembly into SCs and the restoration of mitochondrial function.

While extending the ability of cristae remodeling to counteract deficient SCs assembly [9], the parallel nutrient and ER stress shows as a novel form of ER–mitochondrial regulation. Importantly, these findings provide an exciting rationale for tuning bioenergetics through modulation of ER stress in the fostering of SCs assembly under altered

bioenergetic and metabolism, which occurs in mitochondriopathies, cancer, or other metabolic diseases, such as type 2 diabetes mellitus, obesity, or nonalcoholic fatty liver disease.

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Spotlight

Lots of Movement in Gut and Parkinson's Research

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A new mouse model of Parkinson's disease (PD) demonstrates α-synuclein pathology spreading from the gut to the brain via the vagus nerve (Kim *et al.*, *Neuron*, 2019). The pathology is associated with motor and non-motor behavioral deficits in wild-type mice. These findings support the idea that the gut could be a starting point for PD.

An important feature of PD is the progressive accumulation of intraneuronal inclusions, termed Lewy pathology, which are partly composed of misfolded α-synuclein fibrils. The notion that Lewy pathology is first initiated in peripheral tissues outside the brain, for example in the enteric nervous system, and then progressively spreads to different interconnected brain areas was proposed by Braak and collaborators about 15 years ago. Based on the analysis of post-mortem tissue from PD patients, they suggested that Lewy pathology is present in the enteric nerves and the olfactory bulb, several years before the appearance of motor symptoms [1]. They also proposed that the anatomical distribution of α-synuclein pathology can be categorized into defined disease stages that correlate with the progression of symptoms. Thus, autonomic (e.g., constipation) and olfactory disturbances are frequently apparent in the prodromal phase (in the absence of classical motor deficits), and these disturbances are associated with Lewy pathology in the dorsal motor nucleus of the vagus and the olfactory bulb, respectively. It is suggested that, once the pathology reaches the midbrain, it is coupled with degeneration of dopaminergic neurons in the substantia nigra, resulting in the characteristic motor symptoms. In the latter stages of the disease, emotional and cognitive disturbances develop, concomitant with Lewy pathology reaching the cerebral cortex [1]. Around a decade ago, following the observation of Lewy pathology inside fetal neurons transplanted into PD patient brains, it was suggested that the progression of Lewy pathology in accordance with Braak's model is due to α-synuclein fibrils transferring between neurons, even between interconnected brain regions, seeding further aggregation of soluble α-synuclein [2].

Even though Braak's work transformed PD research, the ideas that the disease can start in the periphery and that misfolded α-synuclein acts in a prion-like fashion to cause pathology propagation are still widely debated. The absence of tools that allow the imaging of Lewy pathology longitudinally in living people is a limitation, necessitating the development of animal models to test these ideas *in vivo*. Previous studies inoculating recombinant preformed fibrils of α-synuclein into the gut have demonstrated propagation of α-synuclein pathology to the brain in rodents [3,4]. However, these initial models failed to display further spreading of pathology in the brain,