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The role of the proteasome in mitochondrial protein quality control

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Abstract

The abundance of each cellular protein is dynamically adjusted to the prevailing metabolic and stress conditions by modulation of their synthesis and degradation rates. The proteasome represents the major machinery for the degradation of proteins in eukaryotic cells. How the ubiquitin-proteasome system (UPS) controls protein levels and removes superfluous and damaged proteins from the cytosol and the nucleus is well characterized. However, recent studies showed that the proteasome also plays a crucial role in mitochondrial protein quality control. This mitochondria-associated degradation (MAD) thereby acts on two layers: first, the proteasome removes mature, functionally compromised or mislocalized proteins from the mitochondrial surface; and second, the proteasome cleanses the mitochondrial import pore of import intermediates of nascent proteins that are stalled during translocation. In this review, we provide an overview about the components and their specific functions that facilitate proteasomal degradation of mitochondrial proteins in the yeast *Saccharomyces cerevisiae*. Thereby we explain how the proteasome, in conjunction with a set of intramitochondrial proteases, maintains mitochondrial protein homeostasis and dynamically adapts the levels of mitochondrial proteins to specific conditions.

KEYWORDS

mitochondria, mitochondria-associated degradation, proteasome, protein degradation, protein import, ubiquitin

Abbreviations: AAA, ATPase associated with various cellular activities; CAT, carboxy-terminal Alanine and Threonine tail; DUB, deubiquitinating enzymes; E1, ubiquitin-activating enzymes; E2, ubiquitin-conjugating enzyme; E3, ubiquitin ligase; ER, endoplasmic reticulum; ERAD, endoplasmic-reticulum associated degradation; GET, guided entry of tail-anchored proteins; IM, inner membrane; IMS, intermembrane space; MAD, mitochondria-associated degradation; MitCOM, high resolution complexome profiling of the mitochondrial proteome; mitoCPR, mitochondrial compromised protein import response; mitoNUC, nuclear-associated mitoprotein degradation; mitoRQC, mitochondria-associated ribosome-associated quality control pathway; mitoTAD, mitochondrial protein translocation-associated degradation; mPOS, mitochondrial precursor overaccumulation stress; MPP, matrix processing peptidase; MTS, mitochondrial targeting sequence or presequence; OM, outer membrane; PAM, presequence translocase-associated motor; ROS, reactive oxygen species; RQC, ribosome-associated quality control; TA, tail-anchored; TCA, tricarboxylate; TIM, translocase of the inner membrane; TOM, translocase of the outer membrane; Ub, ubiquitin; UBA, ubiquitin-associated; UBL, ubiquitin-like; UBX, ubiquitin regulatory X; UPS, ubiquitin-proteasome system.

1 | INTRODUCTION

Eukaryotic cells evolved from a merger of an archaea, which served as host cell, and an endosymbiotic bacterium. During the last 2 billion years of evolution, the bacterium developed from an independent organism into an intracellular organelle that is deeply integrated into and controlled by extramitochondrial structures, such as the nucleus, the cytosol, and other compartments.[1] The abundance of mitochondrial proteins is tightly regulated and dynamically adapted to the prevailing conditions.[2] The levels of enzymes of the citric acid cycle and the respiratory chain found at different growth conditions document this adaptation impressively (Figure 1). When yeast cells are grown on glucose, the expression of these components is repressed and ATP is produced by fermentation. Upon switch to non-fermentable carbon sources such as lactate, glycerol or ethanol, these enzymes are highly expressed and populate in high density in the matrix and inner membrane of mitochondria.

This metabolism-driven remodeling of the proteome is the result of changes in protein synthesis, but also the regulation of protein degradation plays an important role. In case of the respiratory system, this adaptation can be massive when cells are shifted from respiration to fermentation where many mitochondrial enzymes become dispensable or even detrimental. In this review we summarize the current knowledge of these processes and describe how the UPS controls mitochondrial proteins. Since most of what we know is deduced from studies carried out in the baker's yeast *S. cerevisiae*, we specifically focus on the situation in yeast.

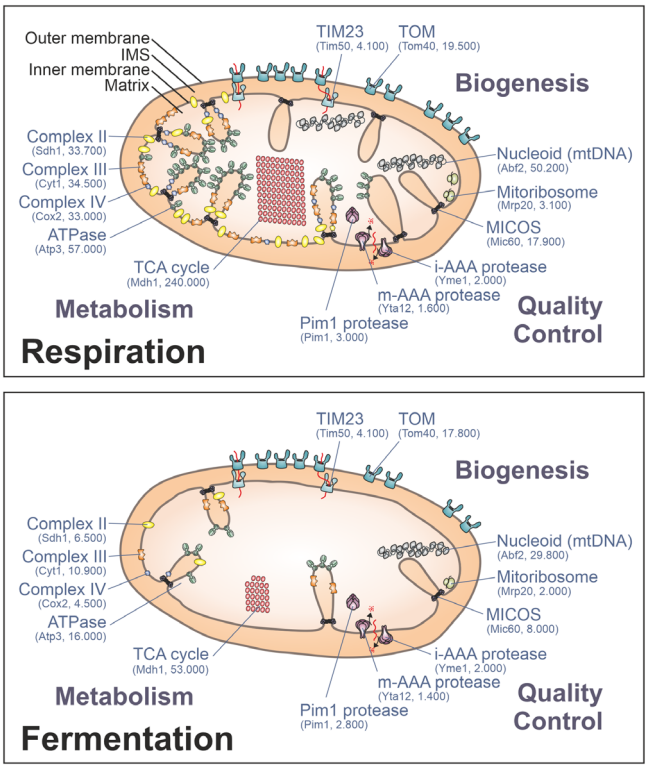

FIGURE 1 The protein composition of mitochondria depends on the metabolic conditions. Mitochondria consist of a large number of proteins which exhibit many different functions. The abundance of these proteins depends on the growth conditions. Yeast cells which grow by fermentation contain a lower mitochondrial mass than respiring cells. However, respiration specifically increases the levels of the enzymes of the respiratory chain and the tricarboxylate (TCA) cycle, whereas the levels of biogenesis and quality control factors are rather constant. The numbers depict proteins/cell based on quantitative mass spectrometry measurements[2] for individual proteins. For most proteins depicted, one symbol represents roughly 2,000 copies/cell.

2 | PROTEIN DEGRADATION BY MITOCHONDRIAL PROTEASES

Mitochondria contain several different proteases which cooperate in protein degradation. In structure and function, these enzymes are related to their bacterial ancestors. Previous excellent reviews described these proteases in depth[3]: The hexameric Pim1 protease, a homolog of the bacterial Lon protease, serves a major degradation machinery of the mitochondrial matrix. Its activity is complemented by two AAA (ATPase associated with various cellular activities)-type proteases that are embedded into the inner membrane, the m-AAA protease facing the matrix and the i-AAA protease facing the intermembrane space (IMS). In addition to these broad-range proteases, the stress-induced metalloprotease Oma1 and the rhomboid protease Pcp1 proteolyze a smaller, more defined set of substrates. These five intramitochondrial proteases overlap in activity to some degree. They play roles in the proteolytic maturation of newly synthesized proteins but predominantly serve as quality control factors which cleanse functionally compromised or superfluous proteins from mitochondria.

3 | THE PROTEASOME AS QUALITY CONTROL FACTOR FOR MATURE MITOCHONDRIAL PROTEINS

Protein degradation in the cytosol and nucleus is carried out by the UPS (for review see[4]). Proteins are marked for proteasomal degradation by the covalent attachment of ubiquitin (Ub) chains. Ubiquitin is a highly conserved protein of 76 residues that is covalently attached via its C-terminus to lysine residues of target proteins; the

ubiquitination reaction includes that of already protein-bound ubiquitin moieties thereby forming polyubiquitin chains. Ubiquitination is exhibited by a cascade of enzymes: ubiquitin-activating enzymes (E1, Uba1 in yeast) form a thioester with ubiquitin and transfer it via ubiquitin-conjugating enzymes (E2 enzymes) to the target protein employing ubiquitin ligases (E3 enzymes) as substrate-specifying factors. Deubiquitinating enzymes (DUBs) remove ubiquitin residues from proteins to save proteins from degradation.

3.1 | Protein degradation by the proteasome

The 26S proteasome is a 2.5 MDa complex that consists of a catalytically active 20S core complex and 19S regulatory subunits. The 20S particle consists of four stacked rings including three catalytically active protease subunits with caspase-like, trypsin-like as well as chymotrypsin-like activity that are oriented towards the lumen of the complex. Substrate insertion is facilitated by the 19S particle which recognizes substrates by affinity to their ubiquitin chains, and which removes ubiquitin by inbuilt DUBs. Its hexameric ATP-hydrolyzing AAA complex, formed by Rpt1-6, pushes substrates into the catalytic core of the proteasome where they are shredded into small peptides.

Cdc48 (p97 or VCP in mammals) is an essential and highly conserved cytosolic AAA ATPase that promotes protein unfolding and often assists proteasomal degradation. Its function is important for the degradation of subunits of multimeric complexes, membrane-embedded proteins or polypeptides that are entangled into aggregates.[5] Cdc48 often employs substrate-specifying cofactors or adaptors which are characterized by the presence of conserved UBX (ubiquitin regulatory X) as well as ubiquitin-binding domains.[6] Distinct populations of Cdc48/p97 complexes exist in cells, each specialized by specific adaptors to mediate unfolding of selective sets of substrates.

The function of Cdc48 is particularly well understood in the context of endoplasmic reticulum-associated degradation (ERAD). Several ER membrane proteins, including Doa10, Ubx2, and Hrd1, serve as Cdc48-binding adaptors to support its ATP-driven extraction of proteins from the ER membrane.[7]

The UPS also plays a crucial role for the surveillance of mitochondrial proteins. The proteasome is not found within mitochondria, but it has access to outer membrane or IMS proteins which expose domains to the cytosol and controls mitochondrial precursor proteins after their synthesis on cytosolic ribosomes. Both protein quality control processes are part of the so-called MAD in analogy to ERAD. Table 1 provides an overview about the components involved in MAD.

3.2 | Degradation of mitochondrial outer membrane proteins

The mitochondrial outer membrane protein Fzo1 was the first mitochondrial component discovered to be regulated by the UPS.[8,9] Fzo1 is a GTPase of the dynamin family which exposes extended coiled coil-forming domains into the cytosol that mediate outer membrane fusion in a process that conceptually resembles the SNARE-mediated fusion of other cellular membranes.[10] Ubiquitination of Fzo1 is mediated by the ubiquitin ligases Mdm30 and Mfb1 and is critical to maintain the competence of Fzo1 to trans-dimerize and thereby to promote mitochondrial fusion.[9,11] Ubiquitination by Mdm30 and Mfb1 and deubiquitination by the DUBs Ubp2 and Ubp12 orchestrate a complex ubiquitin-dependent remodeling of Fzo1 that is energized by the hexameric AAA protein Cdc48 (Figure 2a, left-hand side) but independent of proteasomal degradation.[12] In this case, ubiquitination might be used to allow the ATP-dependent Cdc48-driven unwinding of trans-dimerized Fzo1.

However, Mdm30-mediated ubiquitination of Fzo1 can also drive its proteasomal degradation. In old cells and cells of disturbed lipid composition, Fzo1 is ubiquitinated by the ubiquitin ligases Mdm30 and Rsp5.[13,14] Only in the absence of both of these E3 proteins, Fzo1 remains fully stable indicating that they cooperate in Fzo1 ubiquitination. Again, the two functionally distinct DUBs Ubp2 and Ubp12 control and finetune the reaction.[15] Ubiquitinated Fzo1 is bound by Doa1, a Cdc48 adaptor that promotes Cdc48-driven unfolding and membrane extraction of Fzo1.[16] Degradation of Fzo1 leads to mitochondrial fragmentation. Other outer membrane proteins, such as Tom70, Msp1, and Mdm34 are turned over in a comparable way, however, ubiquitination of these proteins might be predominantly mediated by Rsp5 and independent of Mdm30.[16]

3.3 | Degradation of mitochondrial IMS and inner membrane proteins

The role of the proteasome in the surveillance of the mitochondrial proteome might not be restricted to outer membrane proteins. Apart from that, proteins of the IMS, in some cases even inner membrane proteins, can be controlled by the UPS. This requires their retrotranslocation across the outer membrane which is mediated by the

TABLE 1 Components involved in mitochondria-associated degradation (MAD).

Function	Name	Comments
E3 ubiquitin ligase	Rsp5	Ubiquitinates proteins in the cytosol
E3 ubiquitin ligase	Mdm30	OM-bound SKP-cullin-1-F-box ligase
E3 ubiquitin ligase	Mbp1	OM-bound SKP-cullin-1-F-box ligase
Deubiquitinating enzyme (DUB)	Ubp2	Cytosolic ubiquitin protease that counteracts Rsp5
Deubiquitinating enzyme (DUB)	Ubp12	Cytosolic ubiquitin protease
mitoCPR, mitochondrial compromised protein import response		
Transcription factor	Pdr3	Transcription factor of pleiotropic drug resistance
Msp1 recruitment	Cis1	Recruits Msp1 to Tom70.
AAA ATPase	Msp1 (ATAD1 in humans)	Outer membrane-bound extractor
mitoTAD, mitochondrial protein translocation-associated degradation		
Cdc48 recruitment	Ubx2	Outer membrane and ER protein
AAA ATPase	Cdc48 (p97/VCP in humans)	Extractor, unfoldase
Cdc48 cofactor	Ufd1	
Cdc48 cofactor	Npl4	
Pth2-Dsk2 pathway		
E3 ubiquitin ligase	Rsp5	Ubiquitinates proteins in the cytosol
Deubiquitinating enzyme (DUB)	Ubp16	Cytosolic ubiquitin protease that counteracts Rsp5
Peptidy-tRNA-hydrolase	Pth2	
Ubiquitin-binding protein	Dsk2 (Ubiquilin in humans)	Promotes proteasomal degradation
mitoRQC		
Cdc48 recruitment	Vms1	Peptidyl hydrolase which also binds Cdc48-Npl4
Mitoprotein-induced stress response		
Transcription factor	Rpn4	Major regulator of proteasome expression
Transcription factor	Hsf1	Major regulator of heat shock response

protein-conducting channel of the translocase of the outer membrane (TOM) complex (Figure 2b). For example, reduction of the disulfide bonds of IMS proteins induces their retrotranslocation, at least *in vitro*.[17,18] These proteins are initially imported by the mitochondrial disulfide relay[19] which employs the oxidoreductase Mia40 as crucial component to mediate substrate oxidation in the IMS. How substrates are retrotranslocated and whether this requires ubiquitination and Cdc48-driven extraction is not known.

Even some inner membrane proteins might be controlled by the proteasome: Nde1, the enzyme that feeds electrons from NADH into the respiratory chain in yeast, is linked to the inner membrane by an N-terminal membrane anchor. In cells of compromised mitochondrial activity, Nde1 exposes its C-terminus to the mitochondrial surface, presumably owing to its incomplete import reaction.[20] The proteasome, in conjunction with Doa1 and Cdc48, forms a cytosolic fragment of Nde1 which is highly toxic, so that cells with compromised mitochondria are purged from yeast populations. Nde1 is related to the mammalian apoptosis inducing factor, which likewise serves as quality control factor that can induce cell death in compromised cells.[21]

4 | THE PROTEASOME AS QUALITY CONTROL FACTOR OF MITOCHONDRIAL BIOGENESIS

4.1 | Biogenesis of mitochondrial proteins

Mitochondrial biogenesis strongly relies on the expression of nuclear encoded proteins. In yeast, only 8 of the 900–1,000, in humans only 13 of the about 1,500 mitochondrial proteins are encoded on the mitochondrial genome.[2,22] All other proteins are synthesized on cytosolic ribosomes and imported into mitochondria (Figure 3a). Most mitochondrial proteins are imported

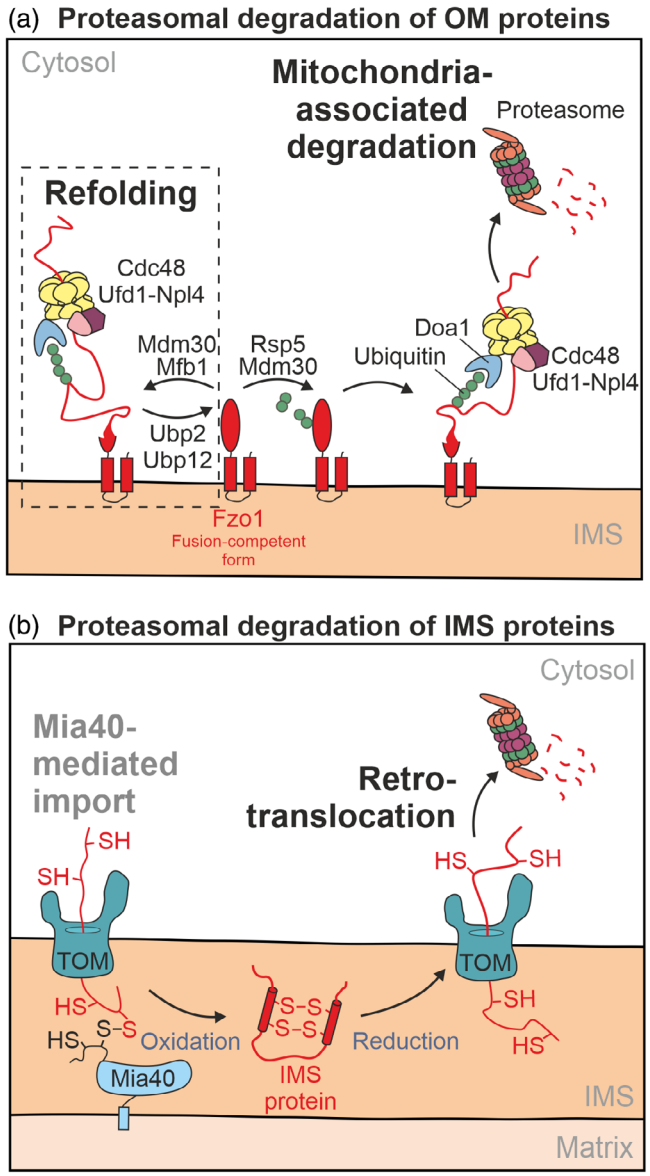

FIGURE 2 Mitochondria-associated degradation (MAD) facilitates the proteasomal degradation of mitochondrial proteins. (a) Ubiquitination of Fzo1 is crucial for maintaining the protein in its functional, fusion-competent state. The ubiquitin ligases Mdm30 and Mfb1 ubiquitinate Fzo1 to allow its Cdc48-mediated refolding (left-hand side). However, ubiquitination (by Mdm30 and Rps5) can also prime Fzo1 for proteasomal degradation (right-hand side). In this case, Doa1 serves as adaptor that bridges the ubiquitin chain attached to Fzo1 to the Cdc48-Ufd1-Npl4 complex for active unfolding and extraction from the mitochondrial outer membrane. (b) Many proteins of the IMS are imported by the oxidoreductase Mia40 which forms a transient mixed disulfide with incoming polypeptides and catalyzes their oxidation. Misfolded or partially reduced Mia40 substrates can be released to the cytosol through the TOM pore for proteasomal degradation in a process called retrotranslocation.

post-translationally, but a co-translational import mode was observed for a small number of proteins, most of which were hydrophobic inner membrane proteins.[23]

About 60% of all mitochondrial proteins are targeted to the matrix by use of an N-terminal mitochondrial targeting sequence (MTS or presequence). In the cytosol, these precursors are stabilized by chaperones of the Hsp70, Hsp40, and Hsp90 families and ushered to the mitochondrial surface receptors Tom20 and Tom70.[24,25] Proteins on the surface of the ER can facilitate the intracellular targeting to mitochondria along the ER-SURF pathway (Figure 3a).[26]

The TOM complex serves as the main entry gate into mitochondria which directs precursors through its pore-forming subunit Tom40 across the outer membrane.[27] In a subsequent step, the translocase of the inner mitochondrial membrane (TIM23) complex and the matrix-localized import motor (or PAM complex) facilitate precursor translocation into the matrix in a reaction driven by the inner membrane potential and ATP hydrolysis. In the matrix, the matrix processing peptidase (MPP) clips off the presequence and initiates folding of the matured proteins by the mitochondrial chaperone network. Proteins which lack presequences embark on a multitude of alternative intramitochondrial transport routes to their specific destination (See[28] for details).

4.2 | Proteasomal degradation of non-imported precursors from the cytosol

Import of precursors into mitochondria competes with their cytosolic degradation. Proteasomal removal of non-imported precursor proteins is crucial for cellular protein homeostasis (proteostasis). It is not known whether and how precursors are specifically recognized in the yeast cytosol and subjected to degradation. However, in mammalian cells, ubiquilins serve as such triage factors for specific precursors[29] and the homolog of ubiquilin, Dsk2, might also control precursor stability in yeast[30] (see below). The observation that the modification of precursor proteins by the ubiquitin-like adaptor SUMO contributes to the stability and import efficiency of individual precursor proteins suggests that a so far uncharacterized regulatory network controls the spatial and temporal degradation of precursors in the cytosol of yeast.[31]

Already under physiological non-stressed conditions, the UPS removes fractions of mitochondrial proteins from the cytosol and thereby regulates mitochondrial biogenesis (Figure 3b).[17] When mitochondrial import is impaired, nascent precursors are diverted to proteasomal degradation to prevent their accumulation in the cytosol.[32] Under these conditions the capacity of the entire UPS can be significantly increased.[33,34] Interestingly, the stability of precursors in the cytosol differs considerably, indicating that specific signals regulate individual

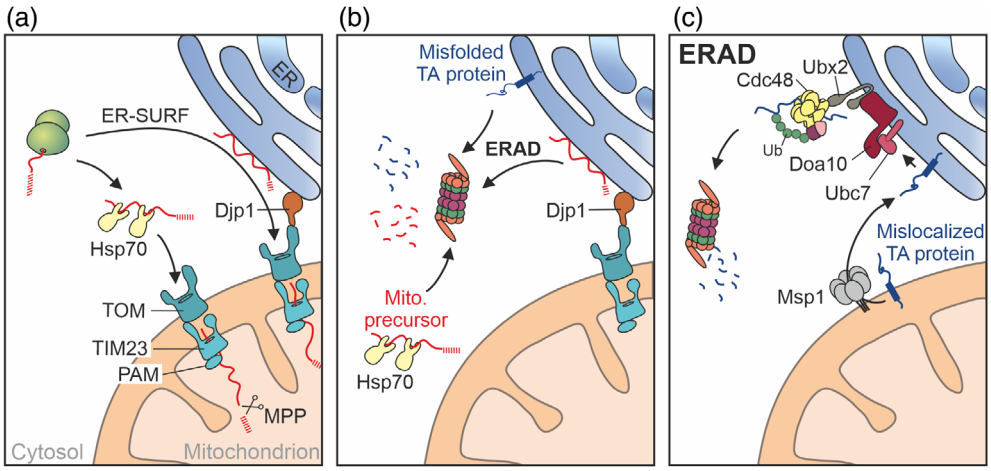

FIGURE 3 Protein quality control of non-imported or mislocalized mitochondrial precursors. (a) Most mitochondrial proteins are imported into mitochondria in a post-translational reaction. Cytosolic chaperones such as Hsp70 as well as factors on the ER surface facilitate the targeting to the mitochondrial outer membrane. N-terminal presequences (also MTS) direct precursors through the TOM and TIM23 translocases in the outer and inner mitochondrial membrane. The import motor (PAM) drives protein translocation by ATP hydrolysis. In the matrix, the matrix processing peptidase (MPP) removes the MTS by proteolytic processing from the mature proteins. (b) Degradation of cytosolic and mislocalized precursors is mediated by the UPS. ER-associated mitochondrial proteins are cleared off by the ERAD system. (c) Tail-anchored proteins that are mistargeted to the mitochondrial outer membrane are extracted by Msp1, a hexameric AAA protein in the outer membrane. These proteins can then insert into the ER membrane to be targeted to the proteasome in a Doa10- and Cdc48-dependent manner.

turnover rates. Proteasomal degradation of precursors can also occur on the surface of the ER or in the nucleus.[26,35] Binding of precursors to the ER surface (Figure 3b) might reduce their toxicity and promote their proteasomal degradation.[26,36–38] For proteasome-dependent degradation of precursors in the nucleus, even a specific term (nuclear-associated mitoprotein degradation, mitoNUC) was coined. Disturbance of the nuclear UPS system leads to the accumulation of mislocalized precursors in intra-nuclear inclusions, thereby reducing the toxicity of the non-imported precursors.[35,39]

4.3 | Proteasomal degradation of mislocalized proteins from the outer membrane

Tail-anchored (TA) proteins contain a single transmembrane domain at their C-terminus that anchors the proteins into the membrane of the ER, mitochondria or peroxisomes, respectively. Characteristics such as hydrophobicity and charge of the transmembrane domain and the short stretch downstream of it determine the specific targeting localization of TA proteins.[40] In vivo, TA proteins bind to membranes of the ER, of mitochondria and of peroxisomes, albeit with strong individual preferences.[41] Accordingly, when TA insertion into the ER is compromised, for example in mutants of the guided entry of tail-anchored protein (GET) pathway, ER-destined TA proteins are mislocalized to the outer membrane of mitochondria.[42,43] The AAA ATPase Msp1 (ATAD1 in mammals) recognizes these mislocalized proteins and facilitates their extraction (Figure 3c). Msp1, resembles in structure an outer membrane-bound, Cdc48-like extraction machine.[44] In contrast to Cdc48, Msp1 does not require cofactors to extricate TA proteins from lipid bilayers. After Msp1-mediated extraction, TA proteins are released into the cytosol and transferred to the ER surface for correct localization or for degradation by the ERAD machinery (Figure 3c).[38] The specific fate of the TA proteins on the ER surface depends on their individual interaction with components of the GET pathway (promoting insertion) and of the ERAD machinery (promoting degradation). Degradation of ER-bound TA proteins relies on the E3 protein Doa10 (MARCH6 in mammals) and the E2 proteins Ubc6 and Ubc7 which ubiquitinate these proteins on the ER surface.[45] Cdc48, together with its cofactors Npl4 and Ufd1, subsequently extracts the ubiquitinated TA proteins from the ER membrane promoting their proteasomal degradation.[38]

4.4 | Proteasomal degradation of stalled import intermediates

The TOM complex represents the main entry gate for precursor proteins into mitochondria. Therefore, clogging of the TOM complex by stalled translocation intermediates

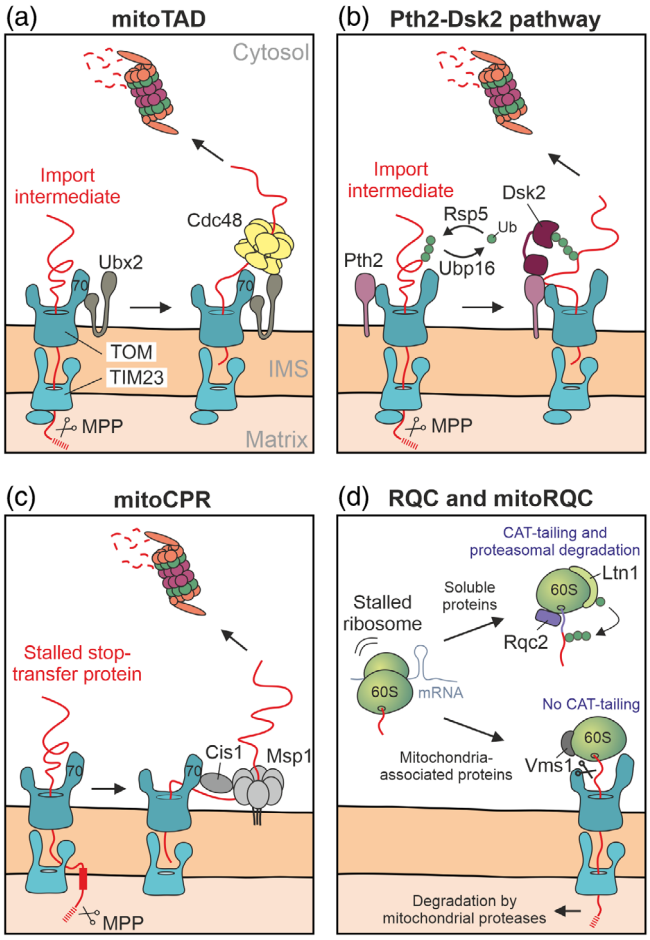

FIGURE 4 Surveillance of the mitochondrial import channel by protein quality control factors. (a) Ubx2 together with the cytosolic extractor protein Cdc48 continuously monitors and extracts stalled import intermediates from the TOM complex. This pathway is referred to as mitoTAD. (b) Pth2 and Dsk2 constitute a second system for the removal of stalled import intermediates from the mitochondrial entry gate. Rsp5 ubiquitinates arrested precursors and Pth2-bound Dsk2 facilitates the transfer to the proteasome. (c) Under mitochondrial import stress conditions, synthesis of the connector protein Cis1 is induced, which recruits Msp1 to Tom70 of the TOM complex. Msp1 extracts precursor proteins such as stalled inner membrane proteins and facilitates their degradation by the proteasome. (d) During mitoRQC, non-productive translation intermediates, which end up on the mitochondrial import machinery, are removed by Vms1 which prevents Ltn1-mediated CAT tailing of the RQC system.

severely affects the functionality and viability of cells.[34,46] Recently, three distinct mechanisms were described for the removal of stalled intermediates from the TOM pore (Figure 4).

To avoid clogging of the import pore by extraction of stalled precursors, the TOM complex is continuously monitored by the mitochondrial protein translocation-associated degradation (mitoTAD) pathway.[47] Ubx2 serves as central factor of this monitoring process (Figure 4a). Ubx2 is a membrane protein that is present in the ER and the mitochondrial membrane, where it promotes protein degradation by ERAD and MAD, respectively. It recruits the extractor protein Cdc48 together with its cofactors Npl4 and Ufd1 to cleanse proteins from the surface of the ER (Figure 3c)[7] as well as from the TOM complex (Figure 4a). Ubx2 recruitment to mitochondria occurs by its direct binding to the outer membrane receptor Tom70.

Pth2 and Dsk2 are core factors in an alternative, mitoTAD-independent mechanism for the degradation of stalled import intermediates (Figure 4b). They were recently identified in a high-resolution complexome profiling study which analyzed protein associations in the mitochondrial proteome (MitCOM) as interactors of the TOM complex.[30] Pth2 is a peptidyl-tRNA hydrolase of the outer membrane that also serves as binding partner for the cytosolic ubiquilin homolog Dsk2. Ubiquilins contain ubiquitin-associated (UBA) and ubiquitin-like (UBL) domains. Dsk1, together with Pth2, binds polyubiquitinated proteins at the TOM complex and ushers them to the proteasome for degradation.[48,49] Ubiquitination of stalled import intermediates is catalyzed by the E3 protein Rsp5 and is responsible for the removal of proteins from the TOM complex via the Pth2-Dsk2 pathway. Other ubiquitin ligases, such as Mdm30 and Mfb1, that ubiquitinate resident outer membrane proteins (Figure 2a), or Doa10 and Hrd1, that ubiquitinate ER proteins (Figure 3c), seem dispensable for the ubiquitination of precursors at the TOM complex. The deubiquitinating enzyme Ubp16 counteracts Rsp5-mediated ubiquitin attachment on the mitochondrial surface.[30,50] Just like Ubx2, also Dsk2 plays an active role in ERAD.

Whereas Ubx2 and Pth2/Dsk2 are permanently associated with the TOM complex, factors of the mitochondrial compromised protein import response (mitoCPR) system are only recruited upon mitochondrial protein import stress[46] (Figure 4c). Adverse conditions, such as reduction of the membrane potential ($\Delta\Psi$) or overexpression of stop-transfer proteins which clog the import machinery, initiate mitoCPR by induction of the stress-responsive protein Cis1. Cis1 recruits the extractor protein Msp1 to the mitochondrial outer membrane and connects it to Tom70 and the TOM complex. Msp1 serves then as ATP-driven extractor for the stalled import intermediates and passes them on to the proteasome for degradation.[51] It is not known whether ubiquitination and components of the mitoTAD pathway support Msp1-mediated protein degradation on the mitochondrial outer membrane, however, this might be expected.

Clogging of the TOM complex can also be caused by ribosome stalling during translation. Series of rare

codons, secondary structures of the mRNA or poly(A) sequences are just some of the reasons why translation can stall. Nascent polypeptides that stalled on free cytosolic ribosomes are cleared by the proteasome in a process called ribosome-associated quality control (RQC). After dissociation of the ribosome and ubiquitination of the stalled nascent polypeptide by the E3 protein Ltn1 (Listerin in mammals), Cdc48 facilitates proteasomal clearance of the polypeptide (Figure 4d).[52,53] In case all lysine residues of the nascent polypeptide are hidden by the stalled ribosome, further amino acids (alanine and threonine residues) are added to its C-terminal end (Carboxy-terminal Alanine and Threonine [CAT] tailing).[54] As soon as lysine residues become accessible, the polypeptide is ubiquitinated and degraded. But even without ubiquitination, CAT tails serve as degrons to promote the proteasomal removal of non-productive nascent polypeptides from ribosomes.[55] If synthesis of mitochondrial precursors stalls, the ribosome-nascent polypeptide complex tightly docks onto the mitochondrial import machinery (Figure 4d). In this case, mitochondrial RQC (mitoRQC) removes the nascent polypeptides to disengage the TOM pore and thus to restore the mitochondrial import capacity. Since under these conditions, nascent polypeptides continuously pass from the ribosomal exit tunnel into the TOM channel, lysine residues and therefore the whole CAT-tailed polypeptide are protected from the cytosolic UPS. As imported CAT-tailed polypeptides can form toxic aggregates in the mitochondrial matrix,[56] cells established a mechanism to prevent CAT-tail formation of stalled mitochondria-associated polypeptides. The Cdc48-binding protein Vms1 (for VCP/Cdc48-associated mitochondrial stress-responsive) is a peptidyl-tRNA hydrolase that associates with stalled ribosomes on the mitochondrial surface.[56,57] Binding of Vms1 prevents the addition of CAT-tails to nascent polypeptides (Figure 4d). Thus, Vms1 competes with the CAT-tailing machinery and limits the release of aggregation-prone CAT-tailed polypeptides into mitochondria. Imported aberrant polypeptides are cleared by the intramitochondrial proteases such as Pim1 (Figure 1). Pth2 presumably supports Vms1 in the removal of stalled ribosomes on the mitochondrial surface, but the specific substrate spectra of these two mitochondria-associated peptidyl-tRNA hydrolases is not entirely clear.

5 | STRESS RESPONSES LAUNCHED BY IMBALANCED PROTEOSTASIS

Aberrant accumulation of precursors in the cytosol induces proteotoxic stress that compromises cell viability. Cells developed a highly concerted and multifaceted response network to counteract accumulation of mitochondrial precursor proteins. Different cellular response pathways were described independently in the past, which are all part of one interrelated response network, the mitoprotein-induced stress response.[58] The mitochondrial unfolded protein response (UPRmt) and the mitochondrial precursor overaccumulation stress (mPOS) response reduce protein synthesis in the cytosol, particularly that of mitochondrial precursor proteins.[59,60] Many proteins of the respiratory chain are under control of the HAP complex, a transcription factor that binds to CCAAT motives in promoters reduced expression. The accumulation of precursor proteins in the cytosol prevents the expression of these genes, suggesting a specific repression of HAP activity.[34] Additionally, accumulated precursors induce the heat shock response, thereby increasing the levels of many chaperones and the proteolytic capacity of the UPS; this cellular response to mitochondrial dysfunction was also called the unfolded protein response activated by mistargeting of proteins (UPRam).[33,34,46] The heat shock transcription factor Hsf1 plays a central role in this context: it is not only activated upon heat stress, but also during the shift from fermentation to respiration and upon mitochondrial import impairment, thus at conditions at which mitochondrial precursors accumulate in the cytosol.[34,61,62] Such precursor proteins can sequester cytosolic chaperones which leads to the release and activation of Hsf1. This triggers a multi-level cascade of gene inductions, including expression of the transcription factor Rpn4 that, in turn, induces proteasomal genes to increase UPS capacity. Taken together, these pathways reduce the burden of the cellular proteostasis by increasing the number of chaperones, by increasing proteasomal activity, and by clearing stalled import intermediates from the import pore.

6 | THE PROTEASOME SUPPORTS METABOLIC ADAPTATION OF MITOCHONDRIAL FUNCTIONS

The abundance of many proteins strongly depends on the prevailing metabolic condition (Figure 1). For example, changes from fermentation to respiration (also called diauxic shift) and vice versa are associated with a complex remodeling of the proteome which is the consequence of altered protein synthesis and protein degradation. The glucose-induced degradation deficient (GID) pathway is a regulatory program that is activated once cells switch from respiration to fermentation, thus from glucose synthesis to glucose degradation (Figure 5a). The GID complex serves as an E3 protein with the inbuilt ubiquitin

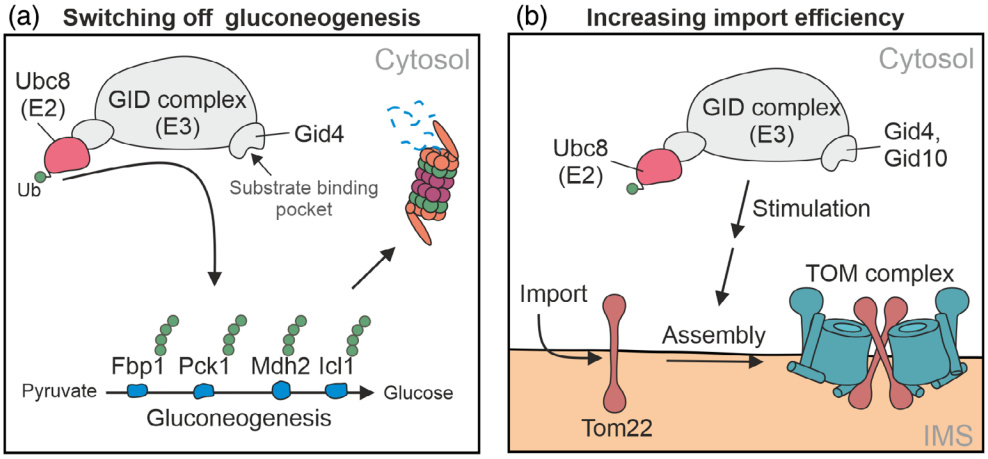

FIGURE 5 The GID complex remodels the cytosolic and mitochondrial proteome during metabolic adaptations. (a) Addition of glucose to respiring cells induces the expression of Gid4, which serves as substrate-specifying factor of the GID complex, a multisubunit ubiquitin ligase of the cytosol. The GID complex uses its inbuilt E2 protein Ubc8 for ubiquitination and degradation of several gluconeogenic enzymes, in particular of Fbp1, Pck1, Mdh2 and Icl1. (b) Ubc8 and the GID complex are also critical for the assembly of the receptor Tom22 into a fully functional TOM complex. In this case, the substrate-specifying factors Gid4 and Gid10 are important but their specific target is still unknown. However, the activation of the GID complex upon metabolic adaptations apparently increases the import capacity of mitochondria, presumably to prevent the cytosolic accumulation of non-imported precursor proteins.

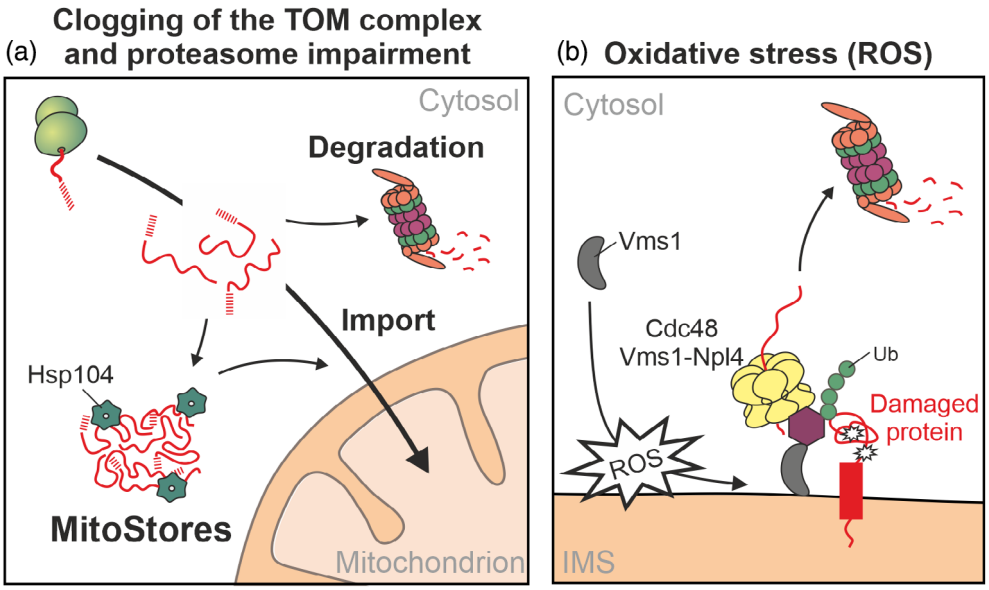

FIGURE 6 The UPS is a crucial element in stress reactions on the mitochondrial surface. (a) If the synthesis of mitochondrial precursors exceeds the capacity of the mitochondrial import machinery, precursor proteins are degraded by the proteasome or stored in a specific type of stress granule, called MitoStores. The chaperone Hsp104 plays a critical role in sequestration of precursors in MitoStores. (b) Oxidative stress and increased levels of reactive oxygen species (ROS) leads to the recruitment of Vms1 to the mitochondrial surface which induces the ubiquitination of damaged proteins, priming them for proteasomal degradation.

conjugase Ubc8. It binds its substrates via the substrate-binding subunits Gid4 and Gid10 and was initially discovered as crucial element for the ubiquitination and proteasomal removal of the gluconeogenic enzymes Fbp1, Pck1, Mdh2, and Icl1.[63,64] Glucose-induced shutdown (catabolic degradation) of gluconeogenic enzymes prevents excessive energy consumption by futile cycles.[65] In addition to their role in the degradation of gluconeogenic enzymes, Ubc8 and the GID complex are important for efficient protein import into mitochondria[66] (Figure 5b). Loss of Ubc8 or the substrate binding proteins of the GID complex (Gid4 and Gid10, respectively) results in decreased protein levels of a crucial TOM subunit, Tom22, and in incomplete assembly of the TOM

complex. Consequently, deletion of Ubc8 causes a wide-ranging depletion of mitochondrial proteins, revealing a role of the UPS in the promotion of mitochondrial biogenesis. To date, the specific target of ubiquitination in this process is not known.

7 | CONCLUSION

The UPS is the primary quality control authority of eukaryotic cells. It removes problematic proteins not only from the cytosol and the nucleus but also from the surface, and in certain cases even the interior of cellular organelles, such as the ER (ERAD) and mitochondria (MAD). The process of ERAD is well studied and its substrates, factors and mechanisms are relatively well characterized. In contrast, the process of MAD is still largely a *terra incognita* that needs to be explored. Neither ERAD nor MAD are essential for yeast cells and deletion mutants are largely unaffected as long as they are not challenged by stress conditions. This is because there are several layers of redundancies, for example different ubiquitin ligases that cooperate in ubiquitination. Moreover, if MAD fails to degrade proteins on the mitochondrial surface, aberrant proteins can be extracted by Msp1 and degraded in the cytosol or by ERAD. Finally, instead of degrading problematic proteins, cells have the capacity to sequester them in different types of stress granules such as Q bodies or JUNQs. Recently, a dedicated granule for the storage of mitochondrial precursor proteins was described.[67,68] These MitoStores can transiently buffer toxic effects of cytosolic precursor proteins and are controlled by small heat shock proteins such as Hsp42 (Figure 6a). Protein release from MitoStores is mediated by the disaggregase AAA chaperone Hsp104 which also controls other types of stress granules.[69]

How the different facets of quality control mechanisms on the mitochondrial surface are coordinated and balanced is largely unknown. However, adverse conditions, such as those arising upon oxidative stress can recruit specific factors to the mitochondrial surface to increase the proteolytic degradation of compromised proteins.[70] The protein Vms1 is recruited to the mitochondrial surface under these conditions. As described above, Vms1 is a mitoRQC factor but apparently its function is not restricted to the rescue of stalled ribosomes. Independently of mitoRQC, Vms1 can recruit Cdc48 to mitochondria to induce protein extraction and proteolysis (Figure 6b). Very similarly, Vms1 also associates with the ER surface to work in ERAD.[71]

Apparently, several complementary quality control systems ensure the proteolytic removal of problematic proteins. Some of these processes are permanent and constitutively monitor mitochondrial proteostasis. Others are only brought into action upon specific conditions, such as when precursors stall in the translocation machinery or when changes in the metabolic conditions necessitate proteome remodeling. It will be interesting to characterize this complex interplay in the future and to unravel how the different quality control systems orchestrate the function of the proteasome, and potentially also that of intramitochondrial proteases, in the context of surveillance of mitochondrial proteins.

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