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Review

Assembly of β-barrel proteins in the mitochondrial outer membrane

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ABSTRACT

Mitochondria evolved through endosymbiosis of a Gram-negative progenitor with a host cell to generate eukaryotes. Therefore, the outer membrane of mitochondria and Gram-negative bacteria contain pore proteins with β-barrel topology. After synthesis in the cytosol, β-barrel precursor proteins are first transported into the mitochondrial intermembrane space. Folding and membrane integration of β-barrel proteins depend on the mitochondrial sorting and assembly machinery (SAM) located in the outer membrane, which is related to the β-barrel assembly machinery (BAM) in bacteria. The SAM complex recognizes β-barrel proteins by a β-signal in the C-terminal β-strand that is required to initiate β-barrel protein insertion into the outer membrane. In addition, the SAM complex is crucial to form membrane contacts with the inner mitochondrial membrane by interacting with the mitochondrial contact site and cristae organizing system (MICOS) and shares a subunit with the endoplasmic reticulum–mitochondria encounter structure (ERMES) that links the outer mitochondrial membrane to the endoplasmic reticulum (ER).

1. Introduction

Biological membranes are mainly composed of lipids and proteins, which separate different subcompartments of the cell. Hydrophilic molecules are transported across membranes by integral proteins forming transporters or channels. These proteins can be composed of α-helical transmembrane segments, or in case of the outer membrane of Gram-negative bacteria, β-barrel structures [1]. β-Barrel membrane proteins are circular enclosed β-sheets with hydrophobic residues facing to the lipid face on the outside and hydrophilic residues facing the interior of the pore. In addition to metabolite and protein transport, β-barrel proteins also function in regulatory and signaling processes [2,3].

These unique β-barrel transmembrane proteins of Gram-negative bacteria were inherited during the evolution of eukaryotes when ancestors of Gram-negative bacteria were engulfed by the host cell to form mitochondria and plastids [4,5]. Due to their origin, mitochondria contain an inner and an outer membrane. The hydrophilic subcompartments are called intermembrane space and mitochondrial matrix as the equivalent to the bacterial periplasm and cytosol, respectively. Mitochondria are crucial for the oxidative energy metabolism of eukaryotic cells. Under aerobic conditions, mitochondria produce over 90% of adenosine triphosphate (ATP) in eukaryotes to support the cellular metabolism. The respiratory chain complexes of the inner membrane catalyze these reactions. The inner membrane has a larger surface area compared to the outer membrane by formation of membrane invaginations with variable morphology termed cristae [6].

The endosymbiosis also included a major genomic rearrangement where the majority of genes were lost from the genome of the endosymbiont [4,5]. Most of the roughly 1000 mitochondrial proteins in eukaryotes are encoded on nuclear DNA [7–9]. This required the development of a powerful protein import system, which not only recognizes the mitochondrial precursor proteins synthesized in the cytosol, but also ensures an efficient transport to the four mitochondrial subcompartments [10–15]. Many genes, which were transferred from the endosymbiont's genome to the nucleus, acquired an extension on the 5′ end encoding for a mitochondrial targeting signal. Only roughly one percent of the mitochondrial proteins remained encoded on the mitochondrial genome. These mitochondrial-encoded proteins are translated in the matrix and most of them are subsequently exported into the inner mitochondrial membrane with the help of the export and oxidase assembly machinery (OXA) of the inner membrane (Fig. 1) [16]. Since yeast is the best studied model organism for mitochondrial protein import, the nomenclature in this review follows the names of the *Saccharomyces* genome database (www.yeastgenome.org).

Abbreviations: BAM, bacterial beta-barrel assembly machinery; C-terminus, carboxy-terminus; ER, endoplasmic reticulum; ERMES, endoplasmic reticulum–mitochondria encounter structure; MICOS, mitochondrial contact site and cristae organizing system; MIM, mitochondrial import complex; N-terminus, amino-terminus; SAM, sorting and assembly machinery; TIM, translocase of the inner membrane; TOM, translocase of the outer membrane

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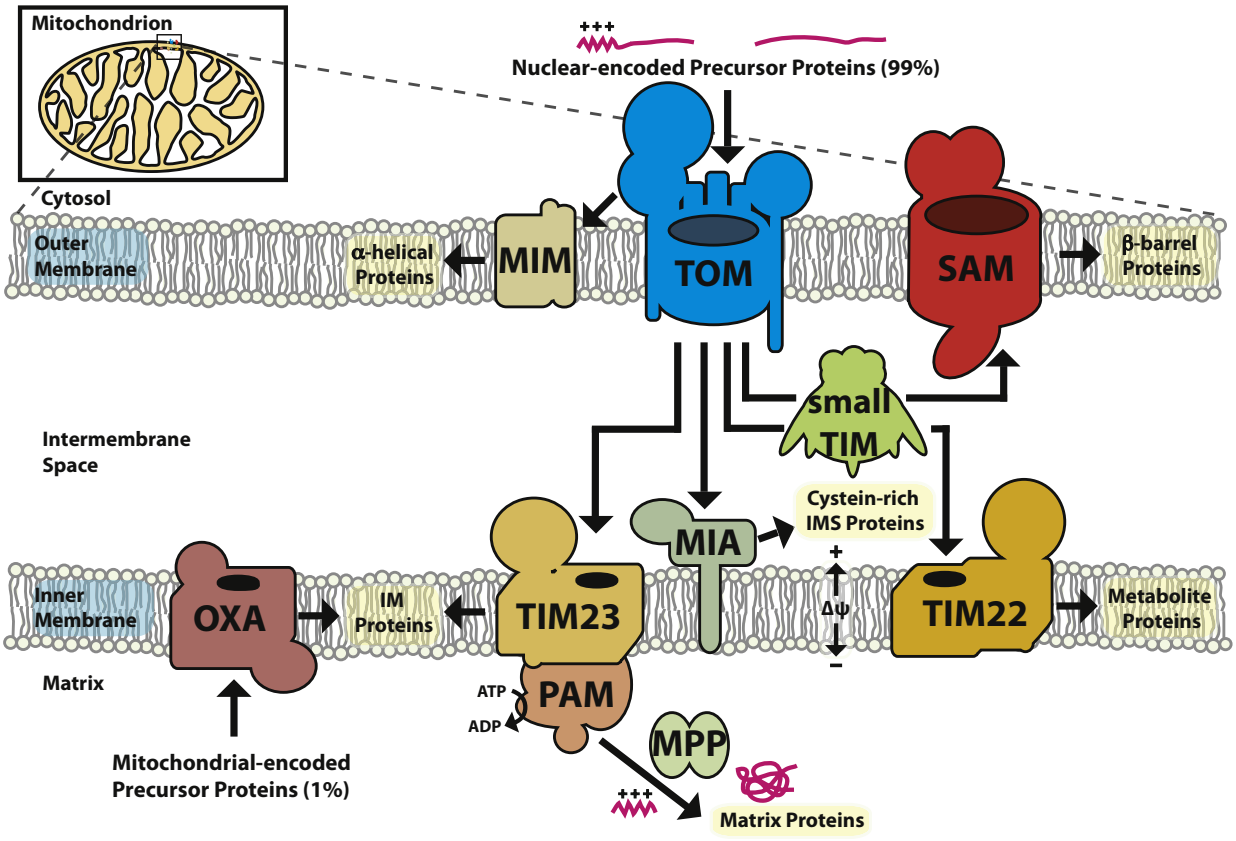

Fig. 1. Mitochondrial protein import pathways. The vast majority of mitochondrial proteins are encoded on nuclear DNA, synthesized in the cytosol und subsequently imported by the translocase of the outer membrane (TOM). At the TOM complex, import pathways diverge depending on the destination of the protein. α-Helical proteins of the outer membrane can be assembled by the mitochondrial import machinery (MIM), while β-barrel proteins are imported into the intermembrane space (IMS) and escorted by small TIM chaperones to the sorting and assembly machinery (SAM). The SAM machinery inserts and assembles the β-barrel proteins into the outer membrane. Metabolite carrier proteins are guided by small TIM chaperones to the carrier translocase of the inner membrane (TIM22) for membrane potential (Δψ)-dependent membrane insertion. Cysteine-rich intermembrane space proteins are imported and assembled by the mitochondrial intermembrane space machinery (MIA). Mitochondrial matrix proteins are translocated by the Δψ-dependent presequence translocase of the inner membrane (TIM23) and the ATP-driven presequence translocase-associated motor (PAM). After reaching the matrix, the presequences of these proteins are cleaved off by the mitochondrial processing peptidase (MPP). TIM23 also imports proteins of the inner membrane (IM) while the biogenesis of mitochondrial-encoded inner membrane proteins depends on the export and oxidase assembly machinery (OXA) of the inner membrane.

2. Protein import into mitochondria: the translocase of the outer membrane

The vast majority of mitochondrial proteins are synthesized on cytosolic ribosomes. Subsequently, the targeting signals of the mitochondrial precursor proteins are recognized by import receptors and the preproteins are imported from the cytosol into one of the four different mitochondrial subcompartments (Fig. 1). The majority of the mitochondrial precursor proteins contain N-terminal targeting signals called presequences which are cleaved off after import into the organelle [17]. In contrast, the other precursor proteins harbor internal targeting signals within the mature protein sequence. The first barrier the precursor proteins encounter is the mitochondrial outer membrane. A dedicated import machinery called the translocase of the outer mitochondrial membrane (TOM) acts as a general import pore for most mitochondrial precursor proteins (Fig. 1) [18]. TOM consists of the membrane-integral receptor subunits Tom20, Tom22, Tom70 and the β-barrel protein Tom40, which forms the protein translocation channel embedded in the outer membrane (Fig. 2) [19–23]. In addition, three small Tom proteins with a molecular weight of 5, 6, and 7 kDa, respectively, are required for the dynamics and stability of the TOM complex [24–27]. The receptor proteins Tom20 and Tom70 are only loosely associated, while Tom22 is the central organizer for the assembly of the mature TOM complex [28]. The TOM complex contains two to three stain-filled pits as observed by negative stain electron microscopy likely representing multiple protein translocation pores [29,30].

The N-terminal mitochondrial presequences are usually positively charged but vary in length and sequence. Mitochondrial presequences form amphipathic α-helices and the hydrophobic side of the helix is recognized by the presequence-binding groove of Tom20 [31]. The presequences are transferred to the import channel Tom40 with the help of Tom22 and Tom5 [24,28,32]. Subsequently, the precursor protein is imported in a linear unfolded conformation led by the N-terminus. Mitochondrial precursor proteins with internal targeting signal are guided by the cytosolic Hsp70–Hsp90 chaperone system to the import receptor Tom70 [33–35]. The Tom70-bound precursor proteins are subsequently transferred to the Tom40 import channel to traverse the outer membrane in a loop conformation [36]. Protein import into mitochondria is regulated by phosphorylation of precursor proteins and TOM subunits by cytosolic kinases [37–41].

3. Sorting of precursor proteins into the mitochondrial subcompartments

α-Helical outer membrane protein precursors form specific cytosolic intermediates with chaperones and some of them are recruited to the outer membrane by TOM receptors [42–48]. The assembly of various α-helical outer membrane proteins depends on the mitochondrial import complex (MIM) which consists of the two single spanning outer membrane proteins Mim1 and Mim2 [46,47,49–53]. Most α-helical outer membrane proteins seem to be inserted from the cytosolic face of the outer membrane. Mistargeted proteins of the ER and

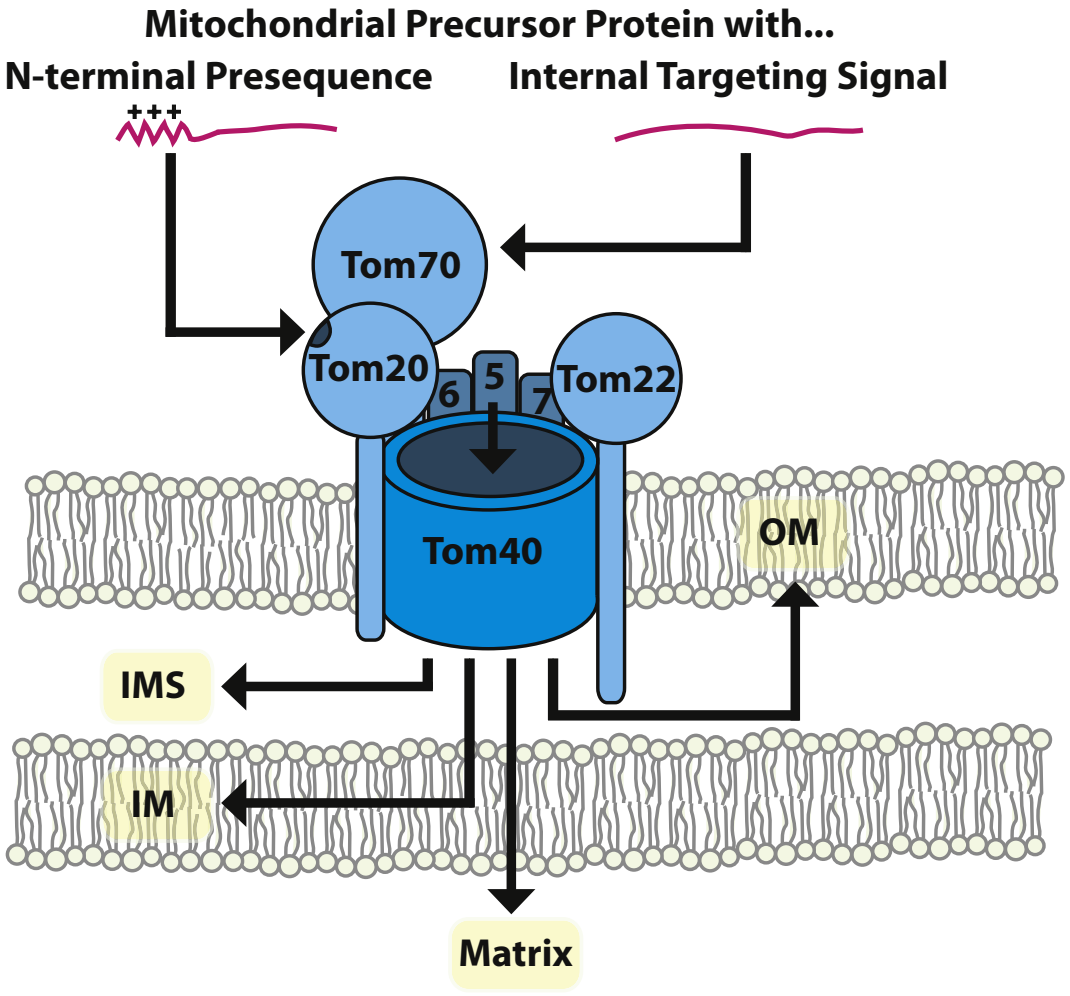

Fig. 2. The translocase of the outer mitochondrial membrane (TOM). The TOM complex consists of the receptor proteins Tom20, Tom22, and Tom70, the protein conducting channel Tom40 and the small proteins Tom5, Tom6, and Tom7, which regulate the assembly and stability of the translocase. Mitochondrial precursor proteins reaching the TOM complex carry either an N-terminal presequence or internal targeting signals. Tom20 carries a binding grove for N-terminal presequences and Tom70 is the first recognition site of precursors with internal mitochondrial targeting signals. After translocation through the Tom40 channel, diverse protein translocation machineries further sort the precursor proteins to the mitochondrial subcompartments. OM, outer membrane; IMS, intermembrane space; IM, inner membrane.

peroxisomes with a C-terminal α-helical transmembrane segment are subsequently degraded by the outer membrane AAA-ATPase Msp1 to maintain the organelle-specific outer membrane protein composition [54,55].

On the intermembrane space side of the TOM channel, the precursor proteins are sorted to different translocation machineries facilitating their intra-mitochondrial sorting and assembly into one of the four different mitochondrial subcompartments (Fig. 1 and 2). Remarkably, the most abundant α-helical outer membrane protein OM45 is first imported with the help of the TOM complex and seems to insert from the intermembrane space side into the outer membrane [56,57]. Mitochondrial precursor proteins with an N-terminal presequence are transferred to the presequence translocase of the inner mitochondrial membrane (TIM23 complex). The core of the TIM23 translocase consists of Tim23, Tim17 and Tim50. Tim23 and Tim17 contain four transmembrane segments which are involved in the formation of the translocation channel [58,59]. The other core subunit Tim50 harbors a transmembrane segment and an intermembrane space domain implicated to function as lid of the channel and as a receptor domain for presequence proteins [60–65]. Initiation of translocation by the TIM23 complex requires the mitochondrial membrane potential which promotes transport of positively charged presequences across the inner membrane [66,67]. On the matrix side, precursor proteins are handed over to the presequence translocase associated import motor (PAM). The core of PAM is the mitochondrial Hsp70 chaperone (mtHsp70/Ssc1) which is responsible for the ATP-dependent transport of the mature part of the precursor proteins into the mitochondrial matrix [68]. The activity of mtHsp70 during preprotein transport is controlled by co-chaperones like the nucleotide exchange factor Mge1 and the J-proteins Pam16–Pam18 (Tim16–Tim14) [69–73]. Presequences are cleaved off by the mitochondrial processing peptidase (MPP) which is localized in the mitochondrial matrix [74–79]. In case cleavage by MPP generates an N-terminus with a destabilizing amino acid, the precursor is further processed by Icp55 or Oct1 to generate an N-terminus exposing a stabilizing amino acid [80,81]. Hydrophobic transmembrane segments within precursor proteins act as stop-transfer signals to enable lateral insertion of the α-helical membrane anchor which can be independent of the import motor PAM [82,83]. This inner membrane sorting depends on the Mgr2–Tim21 adapter of the TIM23 complex which couples the translocase to the respiratory chain supercomplex consisting of complexes III and IV [84–86]. The change between lateral inner membrane sorting and matrix import requires dynamic rearrangements of the TIM23 complex [87–89]. In humans, several subunit- and isoform-specific TIM23 translocases exist and Tim21 promotes the assembly of presequence-containing subunits into respiratory chain intermediates [90,91]. The inner membrane protease IMP cleaves off targeting signals or transmembrane segments to release some intermembrane space proteins [92–97].

However, most intermembrane space proteins are small and are directly imported from the cytosol with internal targeting signals [98,99]. In the intermembrane space, they are trapped by cofactor insertion or by oxidation [100]. Oxidative folding is mediated by the mitochondrial intermembrane space assembly machinery (MIA) consisting of the oxidoreductase Mia40 and the sulfhydryl oxidase Erv1 [101–107]. Electrons, liberated by disulfide formation by Mia40, can be transferred via Erv1 and cytochrome *c* to the respiratory chain [108–111]. Mia40 has chaperone-like properties to catalyze disulfide bond formation and folding of substrates [112,113]. Most MIA substrates contain characteristic cysteine motifs (CX_3C or CX_9C) which are required to generate intramolecular disulfide bonds between two adjacent α-helices [114,115]. In case of the small Tim proteins, the oxidized monomers can assemble into hexameric chaperone complexes in the intermembrane space [116,117]. In addition, MIA can also oxidize inner membrane proteins or presequence proteins in transit to the mitochondrial matrix and inner membrane [118–120].

Hydrophobic metabolite carrier proteins of the inner membrane are guided through the intermembrane space with the help of the small TIM chaperone complexes and are transferred to the carrier translocase of the inner membrane (TIM22 complex). The carrier translocase consists of the channel forming subunit Tim22, the putative receptor subunit Tim54 which is associated with a specific small Tim complex, and a module consisting of Tim18 and Sdh3 [121–127]. The mitochondrial membrane potential is required to insert polytopic carrier proteins into the inner membrane [128].

4. Export of β-barrel proteins into the outer mitochondrial membrane

4.1. The sorting and assembly machinery of the outer membrane

The mitochondrial outer membrane in fungus and animal kingdoms exclusively contains β-barrel proteins. Examples are the abundant outer membrane protein porin (VDAC, voltage-dependent anion channel), required for metabolite transport, and Tom40, the protein conducting channel of the TOM complex. Similar to other mitochondrial precursors, β-barrel proteins are first recognized by TOM receptors [42,43,129–131] before they are imported across the outer membrane with the help of the TOM complex [132]. Subsequently, β-barrel precursors are exported with the help of the sorting and assembly machinery of the outer membrane (SAM/TOB) required for β-barrel protein membrane insertion into the outer membrane [132–136]. Close to the C-terminal end, mitochondrial β-barrel proteins harbor a β-signal with the sequence motif PoXGXXHyXHy (Po, polar; G, glycine; Hy, large hydrophobic) which is required for β-barrel precursor recognition by the SAM complex [137,138]. SAM consists of three core subunits named Sam50 (Tob55, Omp85), Sam37 (Mas37, Tom37), and Sam35 (Tob38, Tom38) in a 1:1:1 stoichiometry as well as the auxiliary subunit Mdm10 (*mitochondrial distribution and morphology* protein) (Fig. 3) [132,133,139–145]. Sam50 forms a β-barrel membrane protein composed of 16 β-strands and exposes an N-terminal polypeptide transport-associated domain (POTRA) into the intermembrane space [145–147]. Sam37 and Sam35 associate with Sam50 on the cytosolic face of the outer membrane and are homologs to the mammalian proteins metaxin 1 and metaxin 2 [139,142,148–153]. The β-signal receptor Sam35 and the channel forming Sam50 are essential for β-barrel biogenesis [133,137,140–144,153–155]. The POTRA domain of Sam50 was implicated as receptor for β-barrel precursors, however, the deletion of the full-length POTRA domain does not interfere with SAM precursor protein interaction [137,156]. The POTRA domains form two anti-parallel α-helices overlaid with a three-stranded mixed β-sheet which can bind β-strands by β-augmentation [157–160]. In the absence of the POTRA domain, the release of β-barrel precursors from the SAM complex is affected [161]. Sam37 is required for SAM complex stability. In addition, a role of Sam37 for the release of β-barrel proteins was proposed [154].

The assembly of the β-barrel protein Tom40 is a complicated process [129,131]. After the import through the TOM complex, the Tom40 precursor is transferred to the SAM_{core} complex consisting of Sam50, Sam37 and Sam35 (Fig. 3) [132,133,141,162]. At the SAM complex, the β-barrel protein Tom40 already associates with α-helical small Tom proteins and subsequently an assembly intermediate containing Tom40 and small Tom proteins is released [163]. The direct interaction between SAM and small Tom proteins could be the reason that Tom5 and Tom6 can act as multicopy suppressors of the SAM37 deletion strain [163,164]. The efficient transfer of the α-helical receptor Tom22 to the Tom40-small Tom intermediate is dependent on the SAM_{holo} complex containing Mdm10, a porin-related β-barrel membrane protein itself (Fig. 3) [165,166]. An alternative model suggests that Mdm10 regulates the displacement of the Tom40 precursor from the SAM complex, to

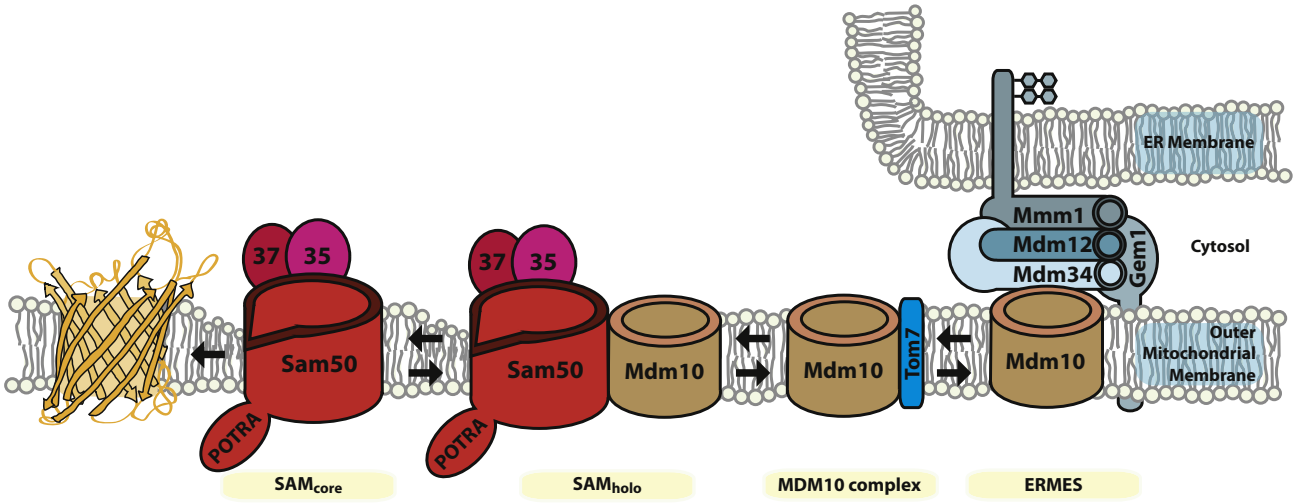

Fig. 3. The sorting and assembly machinery (SAM) of the outer membrane and the endoplasmic reticulum–mitochondria encounter structure (ERMES) are linked by Mdm10. The SAM complex is essential for the biogenesis of mitochondrial outer membrane β-barrel proteins and several subcomplexes. The SAM_{core} complex consists of the β-barrel protein Sam50, the receptor subunits Sam35 and Sam37. Upon binding of the β-barrel membrane protein Mdm10 the SAM_{holo} complex is formed. The dissociation of Mdm10 from the SAM_{holo} complex is regulated by binding to Tom7, a small subunit of the TOM complex. In addition, Mdm10 is required for ERMES complex formation. The ERMES complex tethers the endoplasmic reticulum (ER) membrane to the outer mitochondrial membrane. Further ERMES subunits are Mmm1, embedded in the ER membrane, as well as Mdm12, Mdm34 and Gem1.

enhance the efficiency of TOM complex assembly [167]. Due to the SAM-mediated transfer of small Tom proteins and the central organizer Tom22, the Tom40 channels assemble into the mature TOM complex consisting of membrane integral α-helical and β-barrel proteins [168–170]. Therefore it can be speculated that the SAM complex acquired an auxiliary function in the assembly of α-helical outer membrane proteins due to its role in the biogenesis of the β-barrel protein Tom40.

The significance of Mdm10 for TOM assembly is evident in *mdm10* deletion mutants in which the assembly of Tom40 is reduced while concomitantly the assembly of porin is enhanced [165]. However, Mdm10 is not only a subunit of the SAM_{holo} complex but also forms a complex with the bona fide TOM complex subunit Tom7 [171,172] (Fig. 3). In *tom7* deletion mutants, most of the SAM_{core} complexes are associated with Mdm10 to form SAM_{holo} complexes. In consequence, the assembly of Tom40 is enhanced due to the presence of more SAM_{holo} complexes and the assembly of porin is likely reduced due to a lack of sufficient SAM_{core} complexes [170–173]. Thus, Tom7 determines the activity of the SAM complex by regulation of the association of Mdm10 with SAM.

4.2. The ER-mitochondria encounter structure

In addition to the SAM complex and the complex with Tom7, Mdm10 is also a subunit of the endoplasmic reticulum–mitochondria encounter structure (ERMES) which tethers mitochondria to the ER [174]. ERMES consists of the mitochondrial outer membrane proteins Mdm10 and Gem1(Miro), Mdm12, Mdm34(Mmm2) and the ER membrane-integral subunit Mmm1 [175–178]. ERMES is crucial for mitophagy and also spatially and functionally linked to ER-associated mitochondrial division [179,180]. The *maintenance of mitochondrial morphology* protein Mmm1 consists of a glycosylated N-terminus facing the ER-lumen followed by a single-spanning transmembrane domain and a cytosolic SMP (synaptotagmin-like, mitochondrial and lipid-binding protein) domain [176,177,181,182]. Mdm12 and Mdm34 also contain a SMP domain and both proteins are required to form the tethering complex between mitochondria and the ER [183,184]. SMP domains belong to the proposed TULIP (tubular lipid-binding) domain superfamily, which form tubular cavities for substrate binding [182]. So far, there are different views on the role of ERMES to facilitate lipid transfer between the ER membrane and the mitochondrial outer membrane [176,185–187]. The most predominant lipid defect of ERMES mutants is a reduction of the membrane lipid cardiolipin which is synthesized inside of the mitochondrion in the inner membrane [176,187,188]. In addition, ERMES subunits are required for the maintenance of mitochondrial morphology, mitochondrial genome maintenance and assembly of outer membrane proteins. In particular, the assembly of β-barrel outer membrane proteins is affected in Mmm1, Mdm10, Mdm12 and Mdm34 mutants [173,189,190]. The growth defect of the SAM37 deletion strain is rescued by overexpression of Mdm10 and the ERMES subunits Mmm1 and Mdm12 [189]. In addition, the SAM complex associates with Mdm10 to mediate the assembly of the TOM complex. Thus, Mdm10 functionally links the protein biogenesis machinery SAM to the ER-mitochondria tethering complex ERMES. Interestingly, the overexpression of the Mdm10 complementing outer membrane protein Mcp1 rescues the morphology defect in the MDM10 deletion strain but does not rescue the β-barrel protein assembly defect of Tom40 [191]. This observation highlights the role of Mdm10 in mitochondrial protein biogenesis.

4.3. The mitochondrial contact site and cristae organizing system

The mitochondrial outer membrane does not only form membrane contact sites to the ER but also to the inner mitochondrial membrane. The inner membrane of mitochondria closely aligned to the outer membrane is called boundary membrane. In addition, the inner membrane forms large invaginations called cristae, which are linked to the inner boundary membrane by tubular membrane structures called crista junctions. The mitochondrial contact site and cristae organizing system (MICOS) is required for the maintenance of the typical mitochondrial ultrastructure and facilitates both, the formation of membrane contact sites and crista junctions (Fig. 4) [192–196]. MICOS is conserved among eukaryotes and composed of six major subunits named Mic60 (Mitofilin/Fcj1/Aim28), Mic27 (Aim37/Mcs27), Mic26 (Mos2/Mio27/Mcs29), Mic19 (Aim13/Mcs19), Mic12 (Aim5/Mcs12), and Mic10 (Mos1/Mio10/Mcs10) [197–203]. All MICOS subunits, except for Mic19, are integral membrane proteins and expose soluble domains into the intermembrane space. In the absence of the core subunits Mic10 and Mic60, the crista membranes detach from the inner boundary membrane and accumulate as internal membrane stacks in the mitochondrial matrix as observed by electron microscopy [199–201, 204–206]. Sam50 was identified as a specific MICOS interaction partner [198,199,207,208] and C-terminal truncations of Mic60 or deletion of the POTRA domain of Sam50 specifically abolishes the interaction between SAM and MICOS [209–211]. Deletion of MIC60 inhibits the assembly of the β-barrel protein Tom40 and knockdown of SAM_{core} subunits also affects the biogenesis of respiratory chain complexes [208,209]. Thus, SAM and MICOS are crucial for the formation of membrane contact sites between the inner and the outer membrane.

4.4. The relation of SAM to the bacterial β-barrel assembly machinery BAM

Bacterial β-barrel membrane proteins are synthesized in the cytosol. They are secreted by the SEC translocase across the inner membrane into the bacterial periplasm and subsequently inserted with the help of the bacterial β-barrel machinery (BAM) into the Gram-negative outer membrane [212–216]. Even though eukaryotic β-barrel proteins could in principle be directly inserted from the cytosol into the mitochondrial outer membrane, they are first imported into the mitochondrial intermembrane space [42,43,129,131]. Thus, both mitochondrial and bacterial β-barrel precursor proteins are inserted from the intermembrane space/periplasmic side into the respective outer membranes (Fig. 5). The reason for this similarity in membrane insertion is the evolutionary relation of the SAM and BAM complexes. The two core subunits Sam50 and BamA (Omp85, YaeT) are homologs and therefore the topological constraints for β-barrel membrane protein insertion were evolutionarily retained [133,140,141,217–221]. During the evolution of mitochondria from the Gram-negative ancestor, the genes encoding β-barrel proteins were transferred to the host cell nucleus. A prerequisite for the successful relocation of β-barrel protein encoding genes was the import into the intermembrane space to allow the topological conserved membrane integration from the periplasmic/intermembrane space side mediated by the BAM/SAM complex. Even though both machineries are evolutionary conserved and still fulfill the same function, all the other BAM and SAM subunits have no apparent homology or conservation. The BAM complex consists of BamA and a number of other outer membrane lipoproteins named BamB to BamF mainly located in the periplasm [222–225]. During evolution from BamA to Sam50, only one POTRA domain was retained in Sam50 and the bacterial auxiliary Bam subunits were replaced through the mitochondrial specific subunits Sam35 and Sam37 exposed to the cytosol of eukaryotes (Fig. 5) [137,146,158,226]. Since the bacterial BAM complex can assemble mitochondrial β-barrel proteins and the mitochondrial SAM complex can assemble bacterial β-barrel proteins, the two machineries are also functionally conserved [227–234]. In addition, some bacteria also contain the translocation and assembly module (TAM) dedicated for the biogenesis of specific autotransporter β-barrel membrane proteins for passenger domain secretion [235]. The TAM core protein TamA also belongs to the Omp85 protein family, like Sam50 and BamA. Other β-helical proteins are directly secreted by a further bacterial Omp85 homolog called FhaC [157,236].

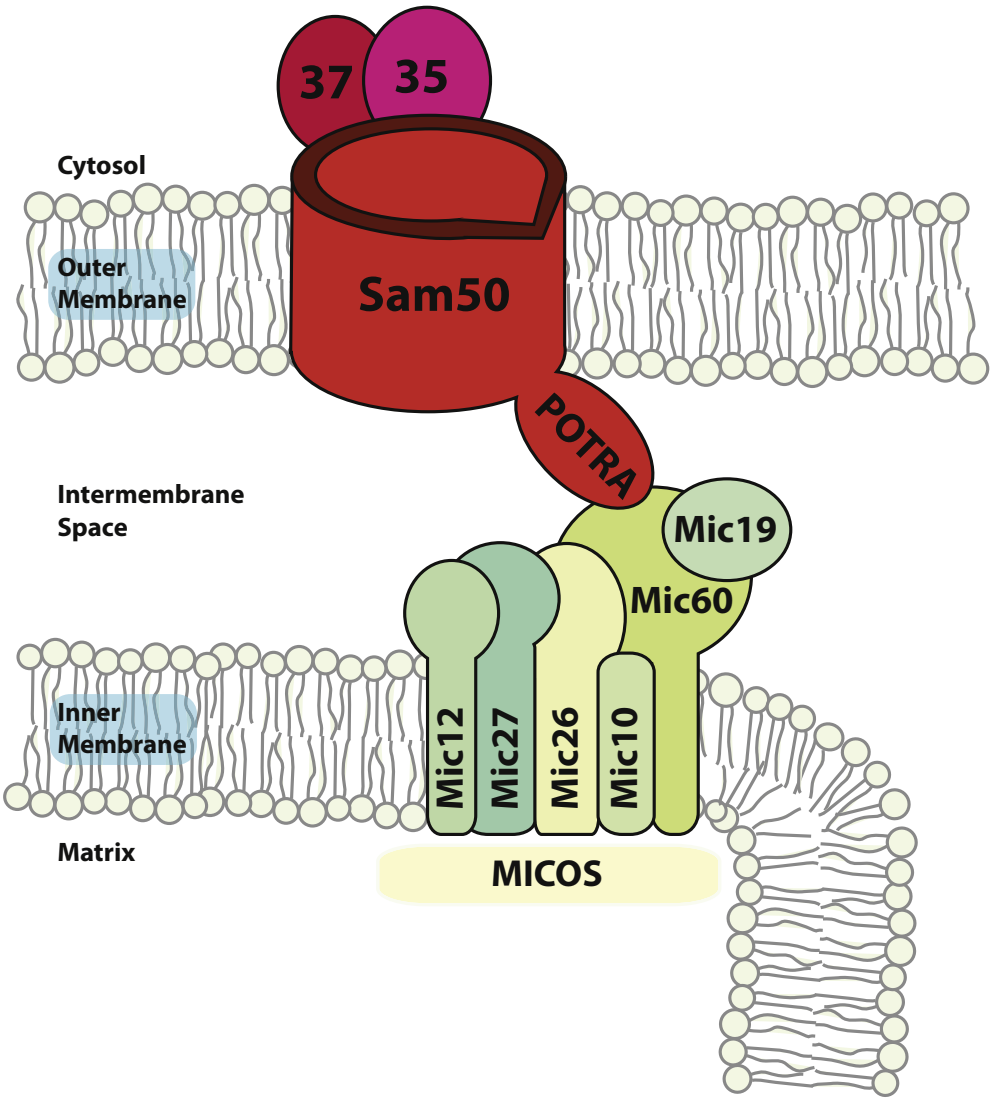

Fig. 4. Direct link between the sorting and assembly machinery SAM and the mitochondrial contact site and cristae organizing system MICOS. The SAM complex directly associates with the MICOS complex via the polypeptide transport-associated (POTRA) domain of Sam50 and the C-terminus of Mic60, a subunit of MICOS. The MICOS complex is located at the inner mitochondrial membrane and is made up of five integral subunits (Mic60, Mic27, Mic26, Mic12, Mic10), and one peripheral subunit (Mic19). The MICOS complex is required for the maintenance of the mitochondrial inner membrane architecture.

Both mitochondrial and bacterial β-barrel precursor proteins require distinct intermembrane space and periplasmic chaperones for their transfer to the SAM and BAM complexes, respectively. The mitochondrial intermembrane space contains small Tim chaperones. Both, the Tim9–Tim10 and the homologous Tim8–Tim13 complexes, are required for the transfer of β-barrel proteins to the SAM complex [237–241]. The small Tim proteins assemble into circular hexameric structures with tentacle-like extensions forming a large cavity [116,117]. In the bacterial periplasm, Skp and SurA are regarded as chaperones required for β-barrel protein biogenesis [242–244]. Both are not homologous to the mitochondrial small Tim chaperones in the intermembrane space. Nevertheless, Skp shows structural similarities to small Tims and SurA has similar substrate specificity like the Tim chaperones [116,245–247]. It is likely that these intermembrane space/periplasmic chaperones can bind the substrate domains in an unfolded molten globule-like state similar to Skp [248]. This could help prevent unproductive β-strand associations within the precursor to increase the efficiency of β-barrel membrane protein insertion. The importance of the intermembrane space/periplasmic chaperone system is underlined by the fact that efficient β-barrel membrane protein reconstitution was shown to depend on the presence of specific chaperones [249,250].

4.5. The mechanism of β-barrel membrane protein insertion

Even though the subunits of the SAM and the BAM complex are characterized, the precise mechanism of β-barrel formation and membrane insertion in vivo remains obscure. Both, Sam50 and BamA are in vivo essential for insertion of β-barrel proteins into their target membranes. Structural studies on BamA and TamA provided novel insights into the possible mechanism of β-barrel membrane protein maturation [251–254]. Here we discuss three different models for Sam50/BamA-mediated β-barrel membrane insertion. Possible mechanisms include the folding of the β-barrel outside of the Sam50/BamA channel (model 1), lateral release of β-strands over the lowest point of the β-barrel rim of Sam50/BamA (model 2), and lateral opening of Sam50/BamA barrel for direct membrane integration of substrate protein β-strands (model 3) [133,134,141,215,251–256]. Model 1 is attractive, because the formation of the nascent barrel outside of the Sam50/BamA cavity would be at its final destination in the outer membrane (Fig. 6, left). However, it is not clear how a cavity could be formed within the lipid bilayer of the outer membrane to allow the translocation of hydrophilic loops of β-hairpins through the outer membrane. Model 2, the lateral release over the lowest point of the β-barrel rim,

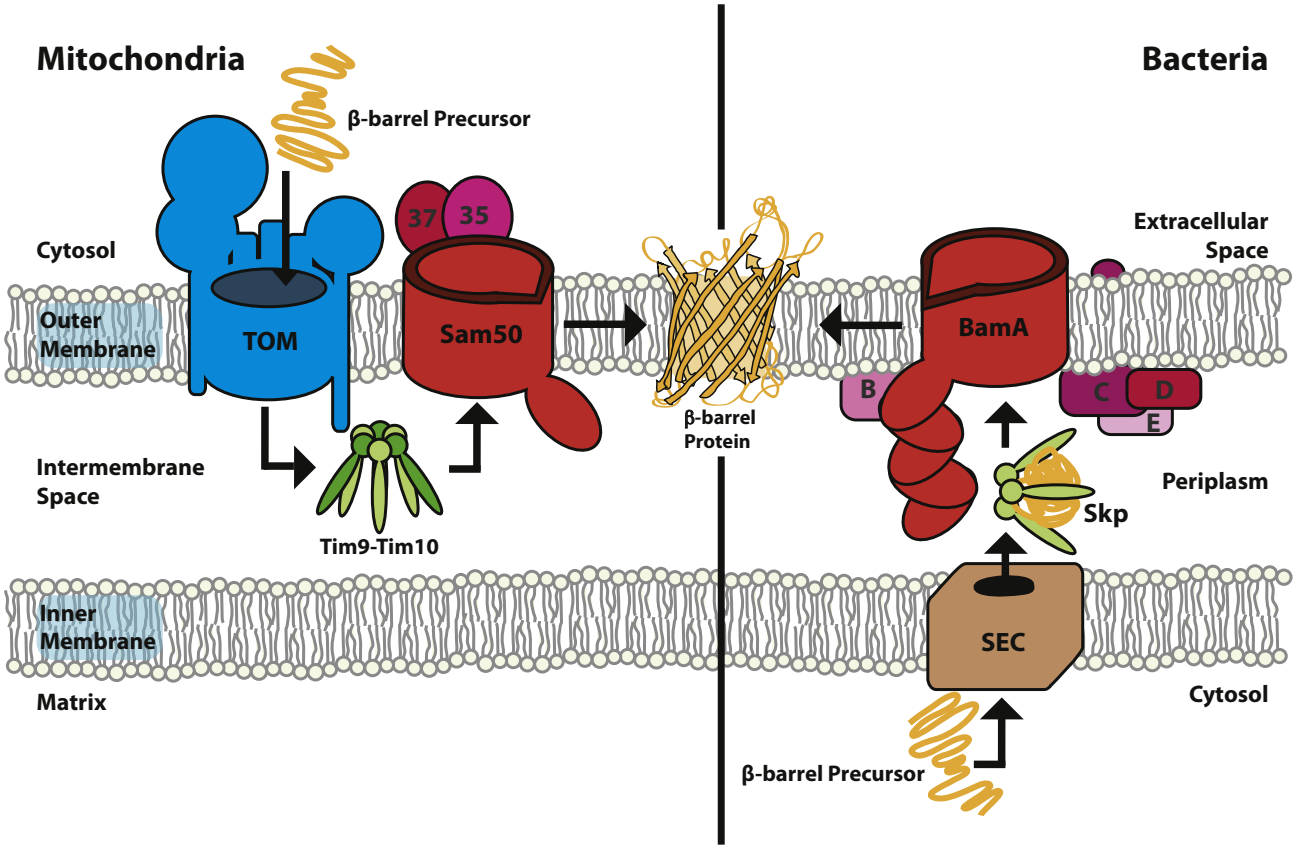

Fig. 5. Conservation between the mitochondrial sorting and assembly machinery SAM and the bacterial β-barrel assembly machinery BAM. In mitochondria, β-barrel precursor proteins are synthesized in the cytosol. The precursors are translocated through the translocase of the outer membrane (TOM) into the intermembrane space where small Tim complexes chaperone the hydrophobic proteins. Lastly, the SAM complex inserts and assembles β-barrel precursor proteins into the outer mitochondrial membrane. In bacteria, β-barrel precursor proteins are translocated from the cytosol via the SEC translocon into the periplasm. In the periplasm, Skp or SurA acts as chaperones to prevent aggregation of incoming precursors in the same manner as the small Tim complexes in mitochondria. The core subunits Sam50 of the SAM complex and BamA of the BAM complex are homologous and required for β-barrel protein membrane integration.

is the proposed mechanism for the biogenesis of lipopolysaccharides on the outer leaflet of the outer bacterial membrane [257–259] (Fig. 6, middle). Yet, the insertion of β-hairpins into both leaflets of the outer membrane would be more challenging. Model 3 was proposed in similarity to the biogenesis of α-helical membrane proteins in which the β-barrel would be released laterally into the membrane (Fig. 6, right). The lateral release in a simple form would require the breakage of the hydrogen bonds between the first and the last β-strand of Sam50/BamA. Folding of the nascent β-barrel inside of the Sam50/BamA barrel seems to be problematic not only for barrels of similar or larger sizes compared to Sam50/BamA, but also for the subsequent lateral membrane insertion. A lateral release of β-strands from the Sam50/BamA

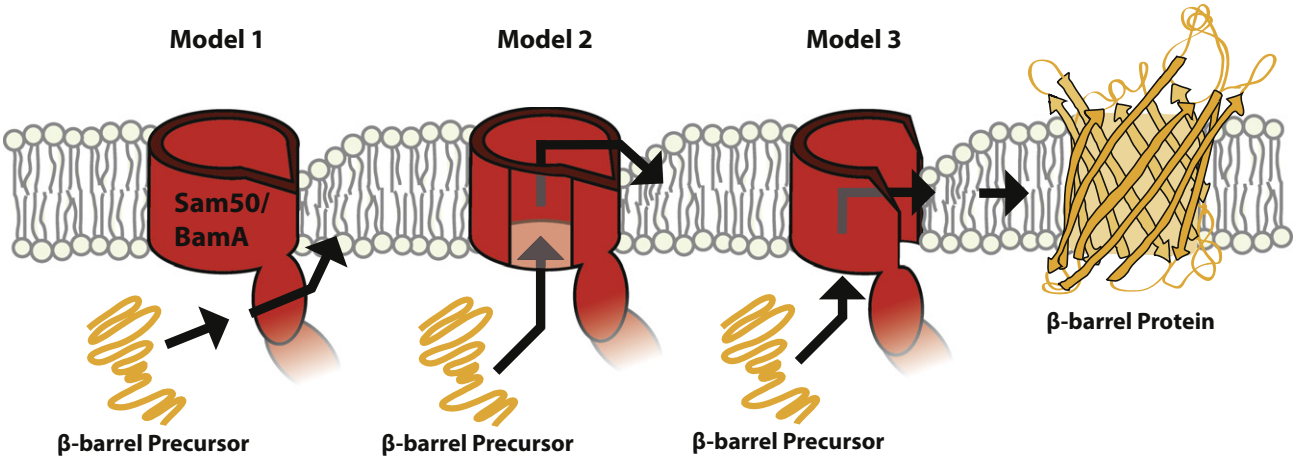

Fig. 6. Models for SAM/BAM-dependent biogenesis of β-barrel proteins. Various models for β-barrel membrane insertion are conceivable. The β-barrel precursor protein is folded outside of the Sam50/BamA pore and concurrently inserted into the outer membrane (model 1). The precursor is transported through the Sam50/BamA channel and consecutive β-hairpins are inserted by lifting the protein over the lowest rim of the Sam50 channel (model 2). After transport of the precursor into the Sam50 channel, the individual β-strands or the mature β-barrel get laterally released by opening the β-barrel of Sam50/BamA between the first and the last β-strand (model 3).

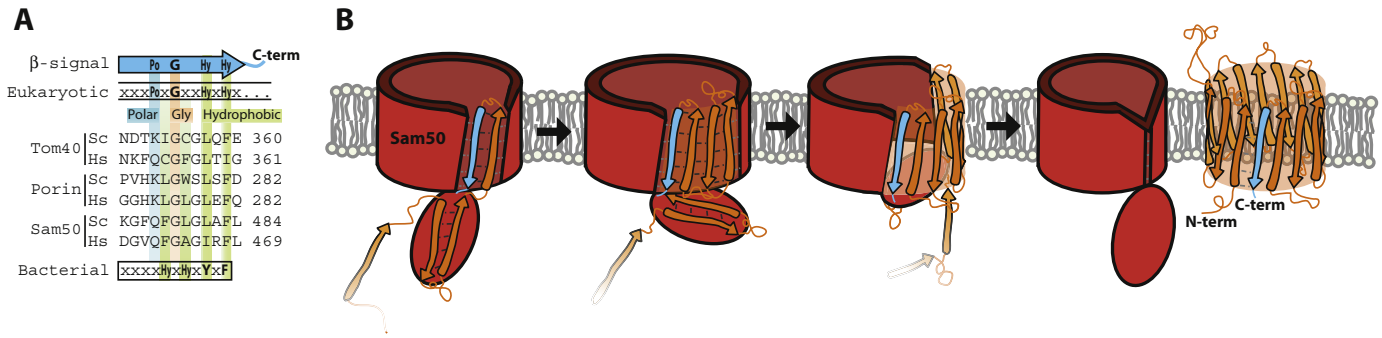

Fig. 7. The β-signal in the C-terminal β-strand is crucial for β-barrel membrane protein assembly. (A) Alignment of the predicted, most C-terminal β-strand of the β-barrel proteins Tom40, porin and Sam50 of *Saccharomyces cerevisiae* (Sc) and *Homo sapiens* (Hs) containing a conserved β-signal. (B) Model of β-barrel protein biogenesis involves the β-signal-dependent formation of a substrate β-hairpin between the first and the last β-strand of Sam50. The polypeptide transport-associated (POTRA) domain enhances β-hairpin formation of consecutive β-strands via β-strand augmentation for subsequent insertion cycles into the endogenous barrel of Sam50. After all substrate β-strands are inserted, the nascent β-barrel protein is laterally released into the outer membrane and Sam50 resumes its original β-barrel confirmation. N-term, amino-terminus; C-term, carboxy-terminus.

pore would be a feasible mechanism as long as the hydrogen bonds are reversibly reformed by substrate interactions to the SAM/BAM complex. It is difficult to distinguish between the consecutive lateral release of individual β-strands or β-hairpins and the integration of the nascent β-barrel into the mature barrel of Sam50/BamA followed by partitioning into two individual barrels. The assembly of all β-strands of the substrate into the Sam50/BamA barrel would require a substrate specific protein sorting to achieve the assembly of a single bacterial β-barrel consisting of multiple oligomeric subunits. In contrast, consecutive lateral release of β-hairpins would allow the membrane integration of all β-barrel substrate proteins in an equal manner. The changes in SAM/BAM channel activity upon stimulation with the β-signal were one of the first evidences for a dynamic rearrangement of the Sam50/BamA barrels [137,260]. Further experimental evidence for the possibility of a lateral release comes from the structures of BamA and its homolog TamA [252–254]. The contact between β-strand 1 and β-strand 16 in BamA and TamA is especially weakened and therefore creates a potential lateral gate for substrate β-strand access to the lipid bilayer [251].

To understand the mechanism of β-barrel membrane protein folding in mitochondria and bacteria, the topology of the β-barrel proteins should be taken into account. In bacteria, β-barrel membrane proteins harbor an even number of transmembrane β-strands with both termini facing the periplasm [1]. In mitochondria, β-barrel membrane proteins can contain either an even or an odd number of β-strands. The Omp85 protein Sam50 is predicted to contain 16 β-strands and adopts a topology with its N-terminal POTRA domain and the C-terminus facing the intermembrane space similar to bacterial family members [217,235,261,262]. In contrast, the mitochondrial β-barrel proteins porin and Tom40 contain 19 transmembrane β-strands [147,263–268]. A detailed topology study of Tom40 confirmed the predicted intermembrane space orientation of the C-terminus and the cytosolic exposure of the

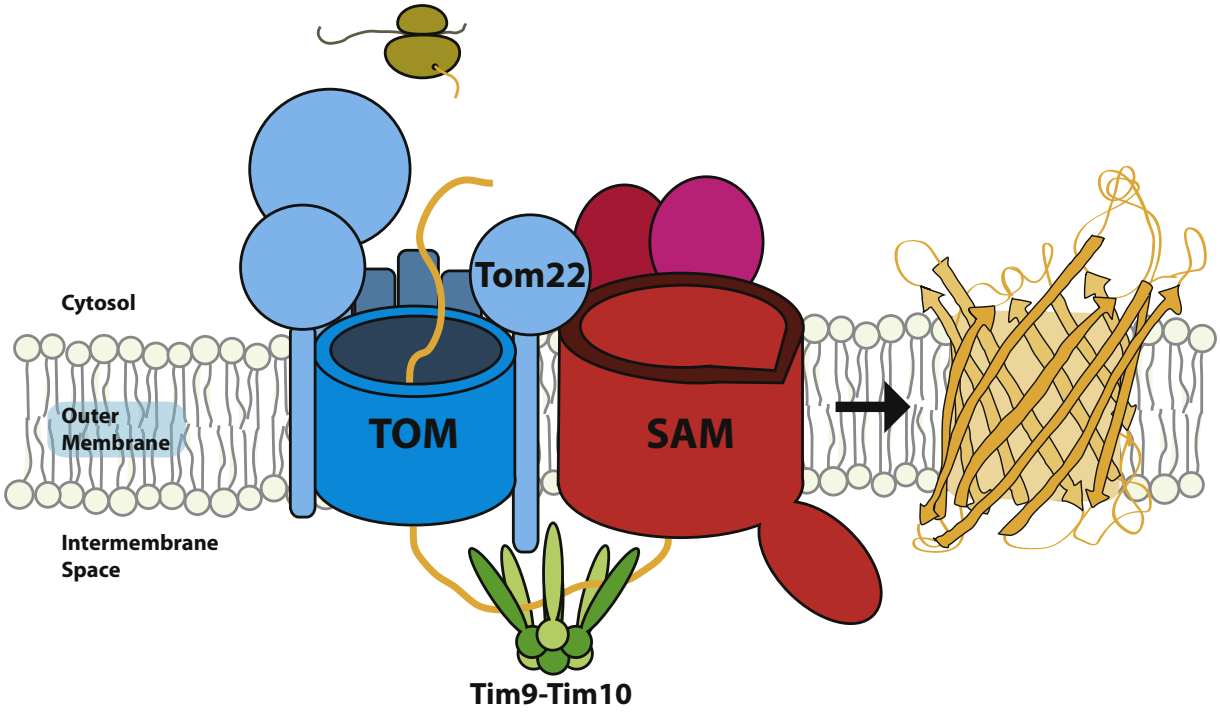

Fig. 8. The translocase of the outer membrane (TOM) and the sorting and assembly machinery (SAM) form a supercomplex. The central receptor subunit Tom22 of the translocase of the outer mitochondrial membrane interacts with the sorting and assembly machinery. The TOM–SAM supercomplex couples β-barrel protein import to β-barrel protein export into the outer membrane to promote the biogenesis of β-barrel membrane proteins. The intermembrane space exposed segments of the β-barrel precursors interact with chaperones like the Tim9–Tim10 complex.

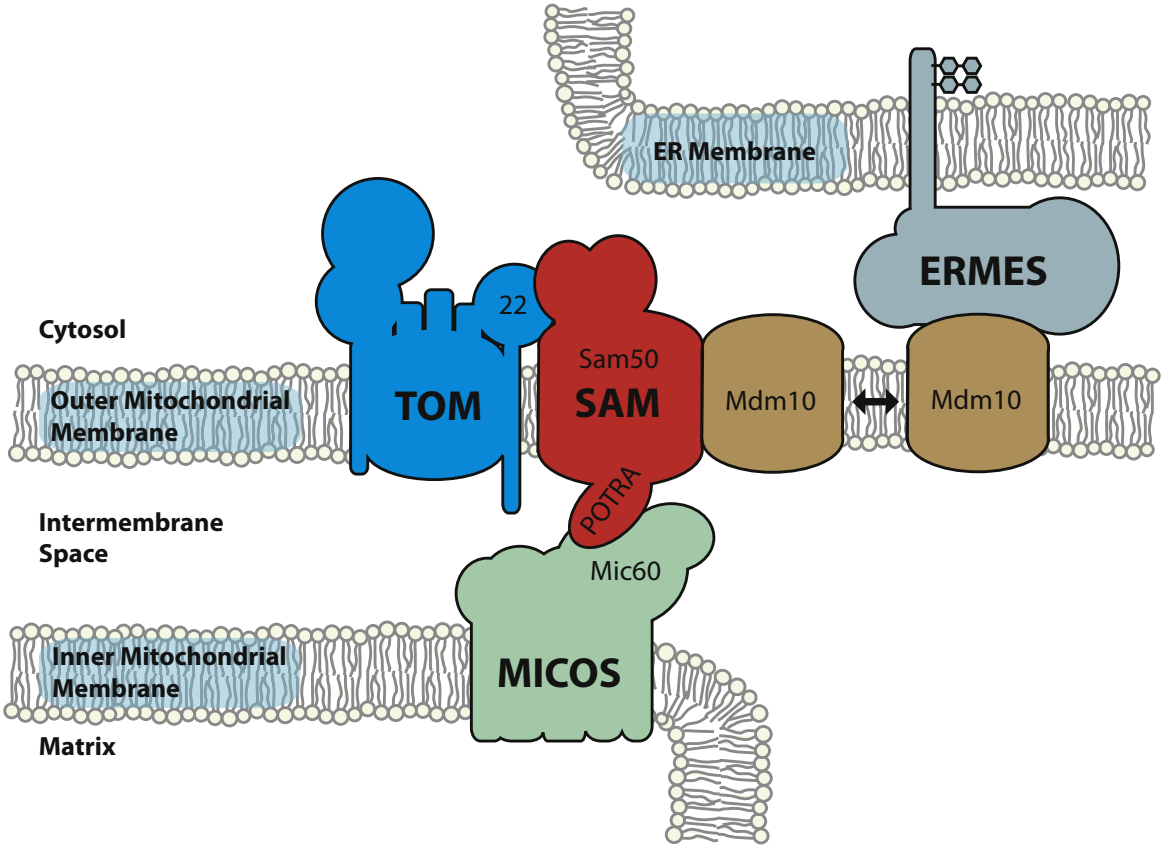

Fig. 9. The sorting and assembly machinery (SAM) is crucial for mitochondrial and endoplasmic reticulum (ER) membrane contact sites. SAM interacts with the translocase of the outer membrane (TOM) to form the TOM–SAM supercomplex and, via the polypeptide transport-associated (POTRA) domain, with the MICOS complex of the inner membrane. The SAM complex also shares the β-barrel protein Mdm10 with the ER-mitochondria encounter structure (ERMES). MICOS, mitochondrial contact site and cristae organizing system.

N-terminal loop of the first β-strand [269]. The mitochondrial β-signal in the C-terminal β-strand of the β-barrel precursor proteins descends from the simpler bacterial motif harboring a conserved tyrosine and phenylalanine (YxF) as C-terminal amino acids on the last β-strand (Fig. 7A) [137,270,271]. These β-signals are crucial for interactions with the SAM and BAM complexes and, consequently, crucial for β-barrel protein assembly [137,260,271]. Therefore, we speculate that β-barrel membrane protein folding is initiated by the formation of the C-terminal β-hairpin which contains the β-signal. The hairpin loop would be subsequently exported to the eukaryotic cytosol or the extracellular space of bacteria to form two initial transmembrane β-strands. In that way, the C-terminus remains in the intermembrane space or periplasm. Successive rounds of β-hairpin formation from the C- to the N-terminus would allow the formation of the mature β-barrel (Fig. 7B). In mitochondria, the formation and release of the β-barrel are enhanced by the POTRA domain which could help to preform substrate β-hairpins by β-augmentation for coordinated membrane integration [161]. So far, no specific step in β-barrel protein assembly was identified which relies on external energy as, for example, analyzed by the reconstitution of the bacterial β-barrel assembly pathway [249,250]. Therefore, β-barrel membrane protein integration and assembly are considered to be driven by the formation of the hydrogen bonds of the circular enclosed β-sheet and the interaction of the membrane lipids with predominately hydrophobic residues facing the outside of the barrel [1,213,272]. This is underlined by the fact that the efficiency of the SAM/BAM independent reconstitution in vitro depends on the lipid composition of the liposomes [273,274]. For bacteria, the involvement of periplasmic lipids and lipopolysaccharides in β-barrel protein biogenesis is discussed, and, in mitochondria, β-barrel protein assembly is disturbed when the phospholipid metabolism of cardiolipin or phosphatidylethanolamine is affected [216,275–277]. We propose that the formation of hydrogen bonds between the first and the last β-strand during barrel formation might provide the energy to break the interaction of the β-signal with the SAM/BAM complex to allow the lateral dissociation of the mature barrel into the outer membrane.

4.6. Coupling of TOM dependent import and SAM dependent export

In eukaryotes, the β-barrel precursor proteins are synthesized in the cytosol and subsequently transported across the outer membrane with the help of the TOM complex. Mutation of the central import receptor Tom22 does not only inhibit β-barrel transport to mitochondria but also affects the folding efficiency of β-barrel proteins at the SAM complex. This observation can be explained by the formation of the TOM–SAM supercomplex (Fig. 8) that couples the import of β-barrel precursors into the intermembrane space to the export into the outer membrane [278]. TOM–SAM supercomplex formation strictly depends on the cytosolic receptor domain of Tom22. This coupling mechanism prevents the accumulation of hydrophobic β-barrel precursors in the intermembrane space and, therefore, the formation of unproductive β-sheets. Since transport to the intermembrane space and β-barrel formation are coupled in eukaryotes, we speculate that in bacteria the inner membrane translocation of β-barrel precursors by the SEC complex is coupled to the β-barrel assembly through the BAM complex. However, the coupling of TOM and SAM creates a new conceptual problem for the biogenesis of mitochondrial β-barrel precursors. The TOM complex is required for the import of all nuclear-encoded mitochondrial proteins and it is therefore more abundant compared to the SAM complex. Consequently, only a subset of TOM complexes can be associated with SAM complexes to mediate efficient β-barrel biogenesis. We proposed that the cytosolic domains of the SAM proteins are involved in targeting of β-barrel precursors to TOM–SAM supercomplexes in

order to avoid β-barrel precursor targeting to TOM complexes without SAM [279]. In addition, mRNA encoding β-barrel proteins were found to be targeted to mitochondria [280]. Therefore, it is feasible that β-barrel proteins are imported by employing a mechanism similar to co-translational protein translocation. Thus, hydrophobic β-barrel precursors might be only partially exposed to the hydrophilic cytosol and intermembrane space compartments to directly assemble into the outer membrane with the help of the SAM complex.

The β-barrel membrane protein assembly machineries in mitochondria and bacteria were discovered in 2003 [132,133,140–144,165,217,223]. It is reasonable to assume that many of the major proteins involved in β-barrel biogenesis were identified up to date. In contrast, the mechanistic insight of Sam50/BamA mediating β-barrel membrane protein folding remains enigmatic. Dedicated mechanistic studies will help to distinguish between the different models of β-barrel protein assembly within the channel, within the first and the last β-strand of Sam50/BamA or outside of the channel and additionally define the precise role of the POTRA domain(s) (Figs. 6 and 7). Similar to the discovery of SAM and BAM, it is likely that research on mitochondrial and bacterial β-barrel membrane protein biogenesis will also benefit in the future from each other, to reveal the mechanistic insights of β-barrel membrane protein folding. In summary, the mitochondrial sorting and assembly machinery mediates β-barrel protein formation in the outer membrane. The assembly of β-barrel proteins is essential for viability of eukaryotic cells, because more than 90% of the mitochondrial proteins are imported across the outer mitochondrial membrane through the protein conducting β-barrel channel Tom40 [281]. In addition, the SAM complex also plays a critical role in the formation of the mitochondrial membrane contact sites to the inner membrane and the ER membrane (Fig. 9). First, SAM interacts with MICOS located in the inner membrane. Second, the auxiliary SAM complex subunit Mdm10, which is shared with ERMES, is required for the tethering of the outer membrane to the ER membrane. Therefore, the SAM complex represents an important hub mediating connections between the inner mitochondrial membrane and the ER membrane (ERMIONE) [193].

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