The conserved role of YidC in membrane protein biogenesis

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Abstract

YidC insertase plays a pivotal role in the membrane integration, folding and assembly of several proteins including energy-transducing respiratory complexes, both autonomously and in concert with the SecYEG channel in bacteria. The YidC family of proteins are widely conserved in all domains of life with new members recently identified in the eukaryotic ER membrane. Bacterial and organellar members share the conserved 5 TM core which forms a unique hydrophilic cavity in the inner leaflet of the bilayer accessible from the cytoplasm and the lipid phase. In this chapter, we discuss the YidC family of proteins focusing on its mechanism of substrate insertion independently and in association with the Sec translocon.

Introduction

Membrane proteins constitute about 30% of the cellular proteome (1) and perform critical functions like signal transduction, molecular transport and cell adhesion. The molecular machineries that catalyse their targeting, insertion and assembly in the different cellular and subcellular membranes are remarkably conserved. Sec translocon is responsible for moving the majority of the proteins across/into the bacterial, archaeal, thylakoidal and ER membranes in an unfolded state (2). In bacteria, it is proposed to form a holo-complex composed of the heterotrimeric protein channel SecYEG, and the accessory elements SecDFYajC, SecA ATPase and YidC (3).

As part of the holo-complex, YidC operates in various capacities ranging from assisting in the membrane insertion process and the lateral clearance of the substrate TM segments from the channel to serving as a foldase for Sec-dependent proteins (4). In addition to this, YidC facilitates the membrane insertion of small membrane protein substrates independently (5). While larger proteins are typically targeted by the SRP-FtsY partnership to the Sec holotranslocon, smaller substrates that cannot engage SRP are post-translationally delivered to YidC (6). However, certain YidC-only substrates like MscL (7) and the tail-anchored proteins TssL (8), DjlC and Flk (9) employ SRP for targeting.

YidC/Alb3/Oxa1 family proteins are highly conserved insertases that operate in the bacterial, thylakoidal and mitochondrial inner membrane respectively (10). Structurally, they are helical bundles formed by 5 core TM segments (Fig 1). YidC is required for the insertion and assembly of several respiratory and energy-transducing proteins (11) like the subunits of the $F1F_O$ATPase (12), Cytochrome *o* Oxidase (13) and NADH dehydrogenase (14). In Gram-negative bacteria, YidC has an additional N-terminal TM segment that acts as a membrane anchor followed by a large beta-sandwich fold within the first periplasmic domain (15). Although these regions are largely non-essential for function (16), they have contact sites to SecY (17) and SecDF (18), suggesting a kinetic role in the protein insertion and substrate folding process. Most Gram-positive bacteria possess two paralogs: YidC1 and YidC2. While

YidC1 is constitutively expressed, YidC2 gene expression is controlled by a MifM sensor protein in *B. subtilis* (19). Though the paralogs are functionally exchangeable, YidC1 is specifically required for the sporulation process (20).

In archaea, DUF106 protein has a three-TM core with a low structural homology to the bacterial YidC, but its protein insertion function remains to be tested (21). Eukaryotes contain multiple YidC paralogs and some of them can replace *E. coli* YidC at least partially, indicating shared functionality in the cell (22-24). In plants, the paralogs Alb3 and Alb4 exist in the thylakoid membrane of chloroplasts (25, 26). The primary substrates of Alb3 are a subset of the light-harvesting chlorophyll binding protein subunits (27), whereas Alb4 is involved in the biogenesis of chloroplast $F1F_O$ATPase assembly (28). A prominent feature of Alb3 is the presence of a long cytoplasmic C-terminal domain which acts as an anchor for SRP43 (29). Both post-translational and co-translational targeting occurs and Alb3 is known to interact with the chloroplast SecYE translocon like its bacterial counterparts (30). Oxa1 and Oxa2 paralogs are found in the mitochondrial inner membrane of eukaryotic cells (31, 32). Sec is absent in this membrane, so Oxa1 is believed to facilitate the insertion of all mitochondrial DNA encoded membrane proteins independently (33). Oxa1 has a C-terminal extension which is the ribosome-docking site for translating substrates that are co-translationally inserted (34). Oxa2 performs similar insertion function for certain respiratory proteins post-translationally (35).

Until recently the presence of YidC homologs in the ER was unknown (36). Anghel *et al* (37) employed phylogenic homology studies and identified three Oxa1-like highly conserved proteins: TMCO1, EMC3 and Get1 which are all involved in the ER membrane protein translocation process in eukaryotes. The study found that Get1 was evolutionarily related to the DUF106 group of proteins, which consisted of EMC3 and the archaeal DUF106 protein. Get1 is a part of the tail-anchored protein insertion complex and substrates of this pathway have a C-terminally located TM segment that is post-translationally targeted to the ER membrane (38). The ER Membrane Complex 3 (EMC3) promotes the co-translational membrane insertion of multi-pass ER proteins with charged TM segments (39, 40). TMCO1 is predicted to insert newly synthesized ER membrane proteins co-translationally, but it also engages with the Sec translocon like YidC (37).

YidC-only Pathway

YidC's function was first annotated in 2000 (5); it was shown to be essential in *E.coli* and required for the insertion of phage proteins Pf3 coat and M13 Procoat which were previously thought to insert by an unassisted mechanism. The minimal functional unit is monomeric (41) even though YidC can dimerize under certain conditions (42). It was shown using reconstituted proteoliposomes that YidC is sufficient for the membrane integration of Pf3 (43). In addition to this, YidC is responsible for the membrane insertion of subunit c of ATP synthase (12), the mechanosensitive channel protein MscL (7) and the C-terminal tail-anchored proteins TssL (44), DjlC and Flk (9). A common feature of the YidC-only pathway substrates is that they contain short translocated regions followed by one or two TM segments (45).

Crystal structures of YidC from Gram-positive (46) and Gram-negative bacteria (47) uncovered important mechanistic details about its function. The conserved 5 TM core of YidC forms a unique hydrophilic cavity in the inner leaflet facing the cytoplasm but is closed from the periplasmic side. The groove contains a conserved positive charge which was shown to be critical for function in gram-positive bacteria but not in the gram-negative homolog (48). Kumazaki *et al* showed that MifM substrate could be crosslinked to the groove (46). Hence it is proposed that the positive charge interacts electrostatically with the charges on the substrate hydrophilic regions to recruit it into the groove and reduce its membrane-crossing distance (Fig 2). Consistent with this, negative charges on the substrate N-tail or TM segment have been proposed to act as YidC-only pathway determinants (49, 50). The proton motive force (PMF) is implied to play a role in releasing the hydrophilic domain from the groove but it is unclear whether this occurs and, if so, how it occurs. Further reduction in membrane crossing distance for the substrate was suggested by MD simulation studies (51) which found thinning of the membrane region around YidC.

The major substrate contact sites of YidC are the hydrophobic residues found in TM3 and TM5 that were shown by crosslinking studies to bind the substrate TM segment of Pf3 coat (52) and MscL (53). This suggests that YidC facilitates substrate insertion through hydrophobic interactions via a greasy-sliding mechanism (Fig 2). In line with this, Cryo-EM studies showed that the TM segment of the F0c substrate is in proximity to the greasy slide (54). Substrate insertion kinetics was studied in real-time using time resolved single-molecule FRET analysis (55) which showed that the entire process of substrate contact, insertion and separation from YidC occurred within 20 ms and Pf3 inserted into reconstituted YidC proteoliposomes at the rate of 500 molecules per second.

Another feature of YidC is the cytosolic loops C1, C2 and the C-terminal tail region, of which the latter two constitute the protein docking sites for receiving its translating substrates. C1 loop forms a helical hairpin that is essential for function (48) and is believed to be highly dynamic based on their relative positions in the crystal structures. Crosslinking studies performed by Koch’s group show that the C1 loop interacts with SRP and FtsY, highlighting its role in recruiting substrates (17). Similarly, Driessen et al found that the C2 loop and C-terminal region of YidC provide stable docking sites for ribosome nascent chain complexes (56). These studies define the role played by the different regions of YidC leading to a better understanding of the mechanism of its insertion function.

YidC-Sec Pathway

Substrate specificity studies indicate that YidC has limited potential to function independently and the translocation of energetically unfavourable regions of substrates require both YidC and Sec (57). Several essential inner membrane proteins like ATP synthase subunit a, b (6, 58) and subunit II of Cytochrome b0 oxidase (13, 59), TatC (60, 61) and anaerobic respiratory protein NuoK (50) are inserted by the combined efforts of YidC and Sec. This phenomenon may also occur in higher eukaryotes in the ER and thylakoidal membrane where YidC and Sec homologs are known to interact. The bacterial holo-translocon (HTL), made up of SecYEG, SecDFYajC and YidC, is proposed to be an efficient insertion machine for the membrane protein substrates of the YidC-Sec pathway (62).

SecYEG forms a channel through which substrate polar domains are exported across the membrane whereas the TM segments exit the channel with the help of YidC via a lateral gate formed by TM 2b and TM7 of SecY (63, 64) (Fig 3). Consistent with this, lateral gate of SecY can be photo-crosslinked to YidC (65). It is predicted that the greasy slide of YidC might contact the SecY lateral gate and move the substrate TM segment via hydrophobic interactions from within the channel and into the lipid bilayer. Recent insight into how this partnership works has revealed that the first TM of *E.coli* YidC contacts SecY and SecG (17). It is proposed that this TM may enter the channel and draw the TM segments out through the lateral gate, but this remains to be tested. The study also reported C1 loop as a contact site for SecY.

In addition to this, YidC is also known to act as a folding and packaging site for Sec-dependent proteins (66). Nagamori *et al* (67) found that LacY protein required YidC to achieve its functional folded form using monoclonal antibodies recognizing specific conformational domains. Strikingly, the translocation of the six periplasmic domains of LacY required only SecYEG while the folding of the protein was dependent on YidC (68). YidC's role in folding LacY was further explored by Serduik *et al* by using single molecule force spectroscopy (69). A mechanical pulling force was applied on a single LacY molecule to unfold it and extract it from a membrane using the stylus of a cantilever. This protein was then slowly allowed to refold into another membrane in the presence of YidC. The study showed that only in the presence of YidC, LacY could fold back to its stable form in the membrane.

The accessory elements SecDFYajC is believed to promote YidC's interaction with the Sec channel (70). SecDF was shown to contact the periplasmic domain of *E. coli* YidC using affinity pull-down experiments (18). This interaction may indicate the shared functional role of SecDF and periplasmic domain of YidC in the substrate folding process. The crystal structure of SecDF and electrophysiological experiments revealed a proton-transport mechanism which could provide the energetic driving force for pulling the substrate out of the Sec channel during translocation and prevent its back-sliding (71). Substrates of this pathway are targeted to the holotranslocon by SRP and its membrane-associated receptor FtsY for co-translational insertion (6).

Conclusion

YidC family of proteins catalyse the unfavourable movement of polar domains of membrane proteins across the hydrophobic lipid bilayer and function as a chaperone for a subset of proteins to ensure that their functional conformation is reached as well. The complex interplay between the various components of the insertion pathway have been explored in recent research. Though the crystal structure of YidC advanced our understanding of how these insertases function, the exact mechanism by which the substrate moves through YidC or the YidC/Sec Holocomplex during the membrane insertion process needs to be elucidated. It is anticipated that the mechanistic details unravelled in *E. coli* could be applied to similar pathways operating in higher organisms due to the conserved nature of the proteins involved.

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Figure 1. YidC family of proteins. Top panel: Structural homology in the YidC/Alb3/Oxa1 family shown by highlighting the conserved TMs in Green (TM1), Red (TM2), Cyan (TM3), Purple (TM4) and Yellow (TM5) respectively. YidC structure is adapted from the crystal structure solved in *Bacillus halodurans* (PDB: 3WO7); Alb3 and Oxa1 structures are 3D computational models made using SWISS-MODEL workspace as described in (72). Bottom panel: Newly identified members of Oxa1 superfamily highlighting the conserved three TM segments in Green (TM1), Red (TM2) and Yellow (TM3) respectively. Archaeal DUF106 structure is adapted from the crystal structure solved in *Methanocaldococcus jannaschii* (PDB: 5C8J); Yeast Get1, Human TMCO1 and Human EMC3 structures are evolutionary covariance-based 3D models adapted from (36, 37). The cytoplasmic regions of these models were modified as described in (36).

Figure 2. Model of YidC-mediated membrane insertion of Pf3 coat protein. This figure is adapted from a review by Kiefer *et al* (73) (A) Binding of Pf3 coat protein to YidC. (B) Pf3 TM segment interacts with the cytoplasmic part of the greasy slide and the N-terminal tail of Pf3 (blue) enters the hydrophilic cavity of YidC possessing the conserved Arg residue (red). (C) Pf3 coat TM segment inserts across the YidC “greasy slide” formed by TM3 and TM5 (purple) and release of the N-tail into the periplasmic space. (D) Release of Pf3 into the bilayer.

Figure 3. Model of YidC-Sec insertion pathway. (A) SRP-bound substrate is co-translationally targeted to the Sec holotranslocon (SecDFYajC not represented) via the membrane-associated SRP-receptor FtsY. (B) Substrate amino-terminal TM segment exit the SecYEG channel through a lateral gate with the assistance of YidC andthe second TM

segment initiates translocation. (C)The model substrate shown here, F_Oa, is inserted into the bilayer.

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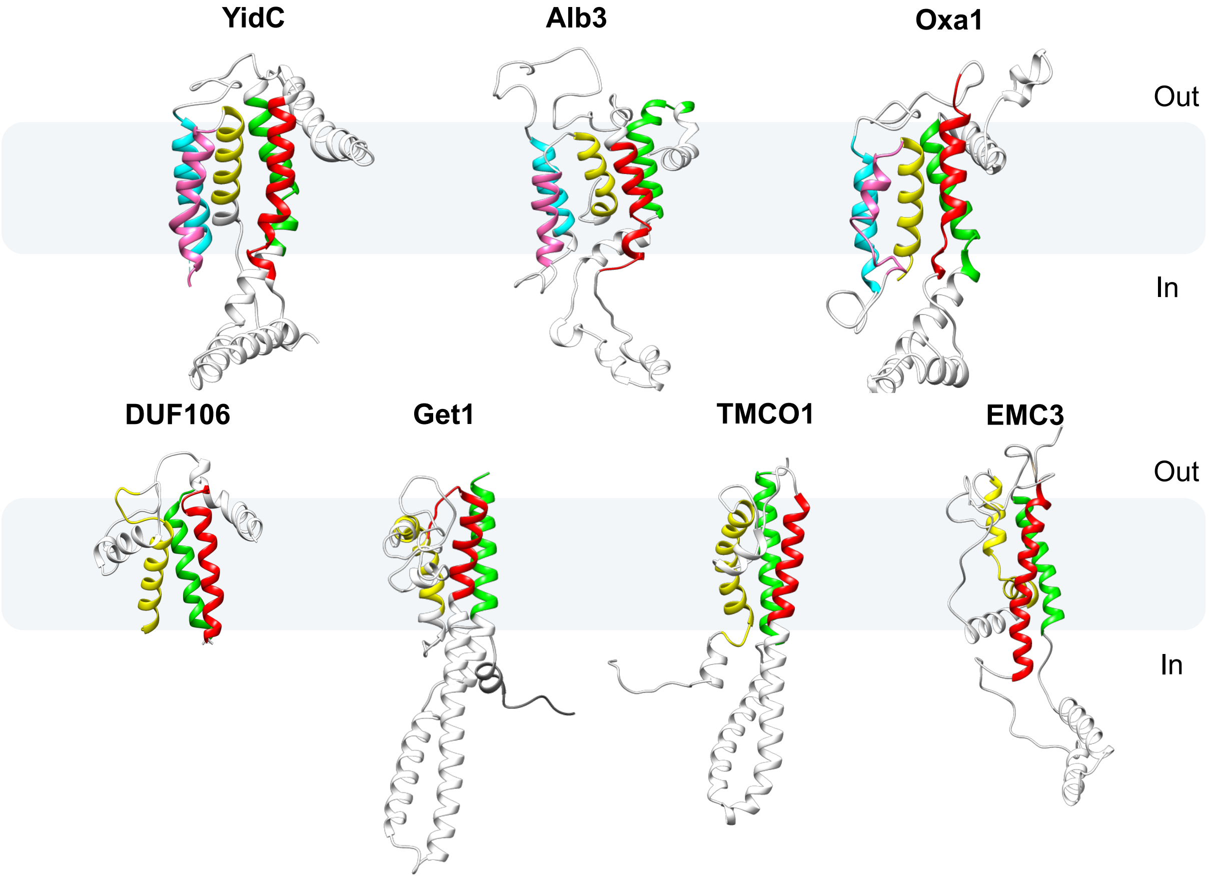
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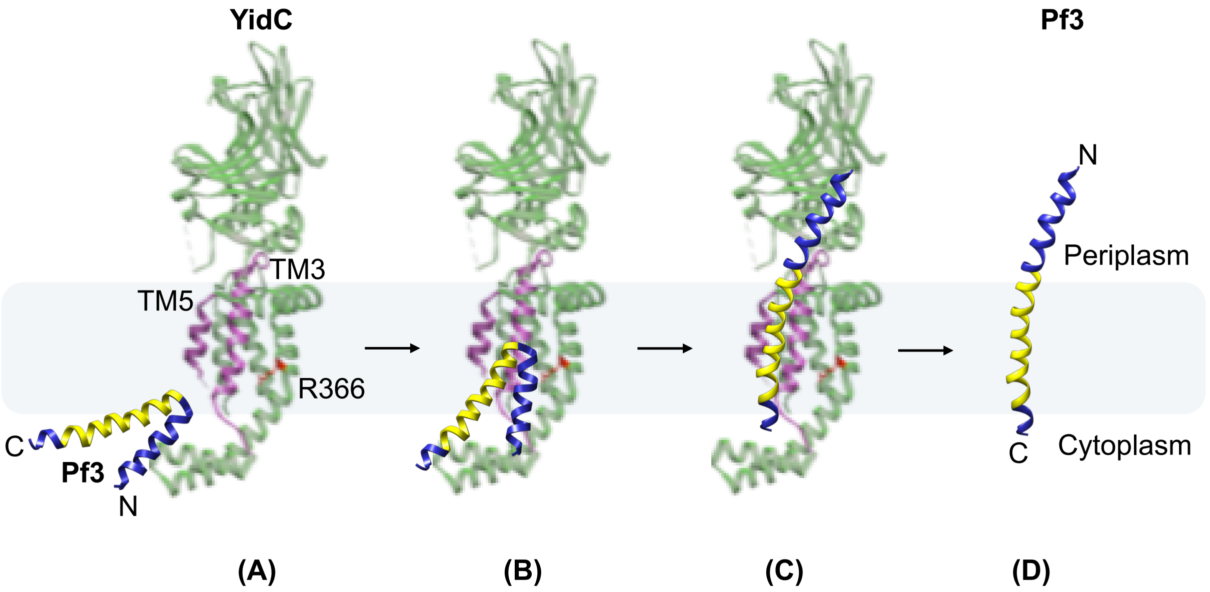
YidC
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C
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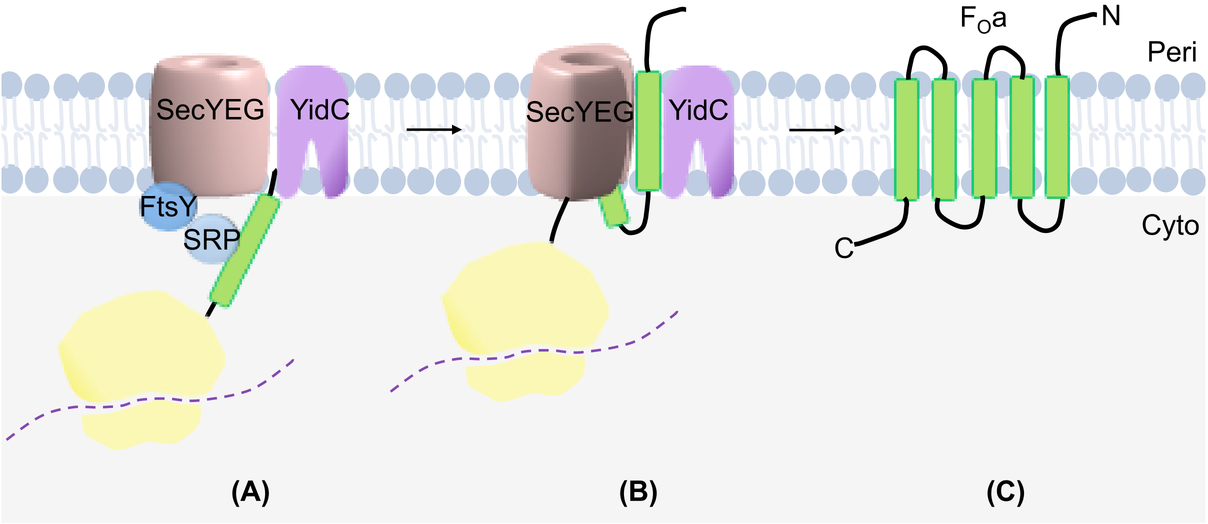
(B)
(C)
(D)


SecYEG
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(A)
(B)
(C)