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BBAMCR-17164; No. of pages: 8; 4C: 2, 3, 4, 6

Biochimica et Biophysica Acta xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamcr

Review

The membrane insertase YidC☆

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ARTICLE INFO

Article history:
Received 31 October 2013
Received in revised form 19 December 2013
Accepted 31 December 2013
Available online xxxx

Keywords:
Membrane insertase
Sec translocase
Topology
Membrane targeting
Mitochondrion
Thylakoid

ABSTRACT

The membrane insertases YidC–Oxa1–Alb3 provide a simple cellular system that catalyzes the transmembrane topology of newly synthesized membrane proteins. The insertases are composed of a single protein with 5 to 6 transmembrane (TM) helices that contact hydrophobic segments of the substrate proteins. Since YidC also cooperates with the Sec translocase it is widely involved in the assembly of many different membrane proteins including proteins that obtain complex membrane topologies. Homologues found in mitochondria (Oxa1) and thylakoids (Alb3) point to a common evolutionary origin and also demonstrate the general importance of this cellular process. This article is part of a Special Issue entitled: Protein Trafficking & Secretion.

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1. Introduction: The task of membrane insertion

Lipid membranes surround all living cells. Whereas Gram positive bacteria have a single cell membrane, Gram negative bacteria possess two, the inner and the outer membranes. Eukaryotic cells contain numerous membrane-surrounded organelles and therefore can harbor over 10 different membrane systems each specified by a unique set of membrane proteins. Animal cells have the endoplasmic reticulum (ER), the Golgi membrane, the plasma membrane, the lysosomal membrane, the peroxisomal membrane, the nuclear envelope, and the inner and outer mitochondrial membranes. Plant cells contain, in addition, the chloroplasts with their inner and outer membranes and the thylakoid membrane.

Besides lipids, membranes have numerous intrinsic proteins that play vital roles for the cell and make up approximately 30% the entire proteome in an organism [1]. They function in signaling, ion and sugar transport as well as in respiration and photosynthesis. To ensure the proper insertion of the proteins into the membrane, there are two main protein transport systems in bacteria, namely, the Sec translocase and the YidC insertase. These translocases promote the translocation of hydrophilic domains across the hydrophobic barrier of the membrane and allow the membrane protein's TM segments to insert into the lipid bilayer. They are found in all three domains of life.

This review will focus on the YidC insertases and their role in the insertion of proteins into the inner (cytoplasmic) membrane of bacteria. We will also examine the evolutionarily conserved pathways of YidC homologues in mitochondria and chloroplasts.

2. The membrane insertase YidC

The *Escherichia coli* YidC is a 61 kD protein of the inner (cytoplasmic) membrane and is composed of 6 transmembrane (TM) segments and a large periplasmic domain in between TM1 and TM2 [2]. It is a very abundant protein with roughly 2500 copies per cell [3] compared to 500 SecYEG proteins [4]. YidC functions as an insertase catalyzing the transmembrane insertion of newly synthesized membrane proteins without containing an energy resource domain such as an ATPase. Most likely, YidC uses hydrophobic force to promote membrane insertion just by binding nascent chains and facilitating their entrance into the lipid bilayer.

Structure function studies have shown that the 5 C-terminal TM segments are particularly important for its insertase function [5]. On the other hand, the large periplasmic protein domain does not seem to be involved in the insertase function since over 90% of this domain can be deleted without impacting membrane insertion. X-ray crystallographic analysis has revealed that the periplasmic domain has a super-β-sandwich fold [6,7]. One possible function of this domain is that it may be involved in the folding of the periplasmic regions of inserted substrates.

Abbreviations: ANS, anilino-1-naphthalenesulfonic acid; DM, decylmaltoside; Ea, activation energy; FRET, fluorescence energy transfer; GABA, gamma-aminobutyric acid; GES scale, Goldman–Engelman–Steitz scale; SRP, signal recognition particle; TIC, transporter across the chloroplast inner membrane; TM, transmembrane; TOC, transporter across the chloroplast outer membrane

☆ This article is part of a Special Issue entitled: Protein Trafficking & Secretion.

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0167-4889/$ – see front matter © 2014 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.bbamcr.2013.12.022

Please cite this article as: R.E. Dalbey, et al., The membrane insertase YidC, Biochim. Biophys. Acta (2014), http://dx.doi.org/10.1016/j.bbamcr.2013.12.022

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Based on alkaline phosphatase fusion analysis and hydrophobicity, the location of the TM segments of the *E. coli* YidC was predicted [2]. TM1 spans the membrane from residue 6 to 23 with the N-terminus facing the cytoplasm and is lipid embedded (Fig. 1). Proximal to TM2 is a surface exposed membrane-associated helix (residues 330 to 352), which is important for function [5]. TM2 spans the membrane from 354 to 370 and contains several crucial residues, that when mutated to serines, inactivate the protein [5]. TM3 is long, from 417 to 442 and predicted to be tilted. This region contains a number of helix breaking amino acid residues, including P419, G421, G422, P425, and P431 near the cytoplasmic side of the TM segment. Interestingly, TM3 contains a PXXG motif starting at P419 and ending at G422. Such motifs have previously been shown to increase the flexibility in channel proteins [8]. Two mutations, C423R and P431L, both localized in TM3 cause a cold-sensitive phenotype emphasizing the importance of this region for YidC activity [9]. TM4 is predicted to span the membrane from 463 to 481. TM5 and TM6 are predicted to span the membrane from 494 to 510 and from 512 to 529, respectively, with a short, flexible loop in between [10]. The cytoplasmic tail at the C-terminus of YidC is rather short and can also be deleted without any impact on YidC function [5]. In many YidC homologues this region is extended and interacts with the ribosomal exit channel [11].

To determine structural features of the YidC protein, a low resolution structure of *E. coli* YidC has been obtained by analyzing 2D crystals with cryo-electron microscopy [12]. Two different dimer formations were found in the crystal and were assigned to anti-parallel orientations. The proposed substrate pore resided in a horseshoe-like structure consistent with a model where the substrate enters and leaves YidC laterally. YidC–ribosome complexes have also been investigated by cryo-electron microscopy [13]. Nascent chain complexes with SecM-stalled $F_{O}c$ protein revealed a YidC-moiety located at the ribosome exit channel. This structure in decylmaltoside (DM) had a resolution of 14.4 Å. The electron density was modeled with a dimeric YidC but the contribution of the bound detergent was not considered. A higher resolution model of a YidC–ribosome complex at 8.6 Å was recently obtained with a C-terminally extended YidC interacting with the ribosomal protein L29 [14] (Fig. 2). At this resolution it is clear that YidC was bound to the ribosome as a monomer and the electron density showed individual transmembrane domains. This structure allowed to orient the C-terminal domain of YidC with respect to the ribosomal protein L29. In this latter study, a YidC nascent chain complex with MscL was obtained by arresting MscL with a TnaC sequence added after TM2 of MscL.

In addition to the cryo-electron microscopy studies, the oligomeric state of YidC has been investigated with fluorescence cross correlation spectroscopy (FCCS) with two differently labeled YidC proteins [15]. These structural studies showed monomers of YidC bound to ribosome–nascent–chain (RNC) complexes. Only when RNC was limiting some YidC oligomers were observed. In contrast, earlier studies by Boy and Koch [16] had shown by Blue-Native PAGE that YidC is exclusively dimeric and dissociates in the presence of SDS to monomers. Therefore, it appears, that YidC can oligomerize but the minimal functional unit is a monomeric YidC.

3. Gene organization of YidC

In *E. coli*, YidC is located at 83.69 min on the chromosome. A promoter region is present within the upstream gene *yidD* and a terminator stem loop is positioned 22 bp after the stop codon of the YidC gene, suggesting a monocistronic transcription of the YidC gene [17]. However, YidC might also be part of a 5-gene operon encoding proteins involved in protein synthesis and membrane biogenesis [18]. The gene order is: *rpmH*, *rnpA*, *yidD*, YidC, and *trmE*. Briefly, *rpmH* codes for the ribosomal protein L34 a protein that is in proximity to the L23 protein located at the docking site where SRP and trigger factor bind the nascent chain at the ribosome exit region. *rmpA* encodes the protein component of the RNase P. RNase P not only processes precursors of tRNA molecules but also cleaves the 4.5S RNA of SRP. In this operon, *trmE* encodes an enzyme involved in tRNA modification and which is involved in glutamate-dependent acid resistance. Interestingly, overexpression of the GadX and GadY transactivators involved in glutamate-dependent acid resistance alleviates the growth defect of YidC depletion, suggesting that one consequence of YidC depletion is an increased acidity in the cytoplasm [19]. The GadX/GadY transactivators may help alleviate this acidity increase by regulating the amounts of glutamate

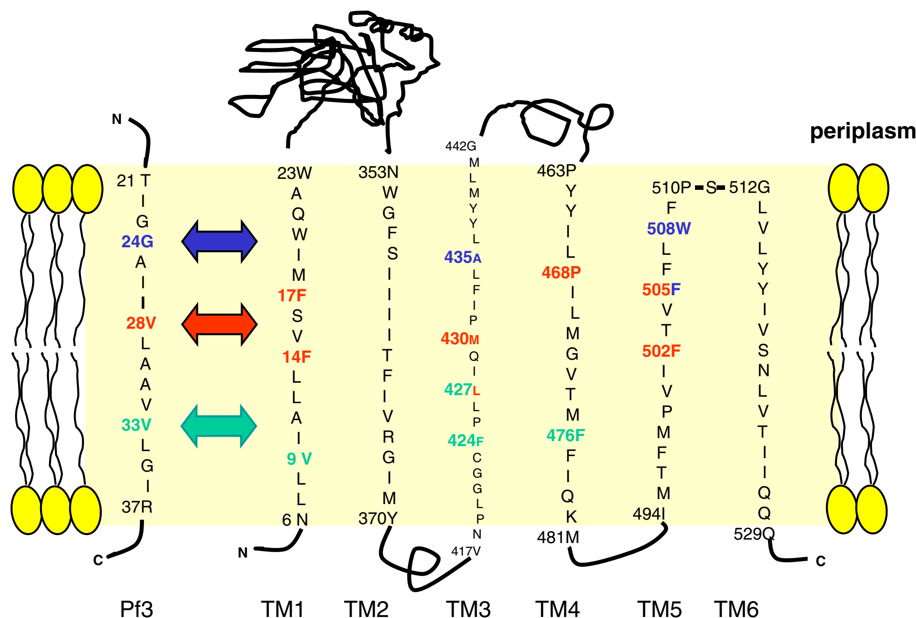

Fig. 1. Topology and contact sites of membrane insertase YidC and its substrate Pf3 coat protein. The sequence of the transmembrane (TM) segments of the Pf3 coat protein and the 6 TMs of YidC are shown, highlighting the observed disulfide cross-links (residues involved are marked by the corresponding color) between the two proteins [51]. A single cysteine was placed into the Pf3 coat protein at positions 24 (periplasmic leaflet, blue), 28 (membrane center, red) or 33 (cytoplasmic leaflet, green) and expressed for 30 s in the presence of YidC that had a single cysteine at one of the amino acid residues in the TM segments. The cross-links were identified after immunoprecipitation and PAGE.

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