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Minireview

# Evolution of YidC/Oxa1/Alb3 insertases: three independent gene duplications followed by functional specialization in bacteria, mitochondria and chloroplasts

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## Abstract

Members of the YidC/Oxa1/Alb3 protein family facilitate the insertion, folding and assembly of proteins of the inner membranes of bacteria and mitochondria and the thylakoid membrane of plastids. All homologs share a conserved hydrophobic core region comprising five transmembrane domains. On the basis of phylogenetic analyses, six subgroups of the family can be distinguished which presumably arose from three independent gene duplications followed by functional specialization. During evolution of bacteria, mitochondria and chloroplasts, subgroup-specific regions were added to the core domain to facilitate the association with ribosomes or other components contributing to the substrate spectrum of YidC/Oxa1/Alb3 proteins.

**Keywords:** complex assembly; membrane biogenesis; protein evolution; protein folding; respiratory chain.

## Introduction

Over the past three decades, various chaperone systems were identified and characterized that control the folding of thousands of cellular proteins. Almost all known client proteins of the general chaperone systems are soluble proteins or domains of membrane proteins that are exposed to the aqueous surrounding of the membrane. On the contrary, almost nothing is known about the folding of membrane-embedded proteins. Either these proteins fold and assemble independently of accessory components, which appears unlikely, or these factors still need to be identified. Perhaps we know these components already for a long time but their primary activity might have obscured their function in protein folding. Indeed, an active role of the Sec translocon in protein folding in bacteria and the endoplasmic reticulum was recently proposed (Shimohata et al., 2007; Skach, 2009). In membranes of bacteria and organelles of bacterial origin, the function of the Sec translocon in insertion, folding and assembly is complemented by members of the YidC/Oxa1/Alb3 family of proteins. These ubiquitously distributed and multifarious membrane proteins are described in this review article.

## The YidC/Oxa1/Alb3 family: distribution and structure

Members of the YidC/Oxa1/Alb3 family are present in the inner membrane of eubacteria (YidC), the inner membrane of mitochondria (Cox18 and Oxa1) and thylakoid membranes of plastids (Alb3 and Alb4). They are involved in the biogenesis of electron transport complexes and the $F_oF_1$-ATPase, as well as of other membrane proteins (for review see Stuart, 2002; Kuhn et al., 2003; van der Laan et al., 2005; Yi and Dalbey, 2005; Kiefer and Kuhn, 2007; Bonnefoy et al., 2009). *Archaea* do not contain *bona fide* members of the family, neither does the membrane of the endoplasmic reticulum.

All members share a common core region of approximately 250–300 residues in length comprising five transmembrane domains (Figure 1, shown as red cylinders). This region exhibits the insertase activity of the proteins. In particular, the first and second of these transmembrane domains (i.e., transmembrane domains two and three of the *Escherichia coli* YidC) share several conserved residues that might contact substrate proteins; mutations in these positions cause loss-of-function phenotypes (Lemaire et al., 2004; Yuan et al., 2007; Yu et al., 2008). In contrast, the three C-terminal transmembrane domains are highly variable and can even be replaced by unrelated, hydrophobic stretches (Yuan et al., 2007).

The hydrophobic core domain can be functionally exchanged between different members of the YidC/Oxa1/Alb3

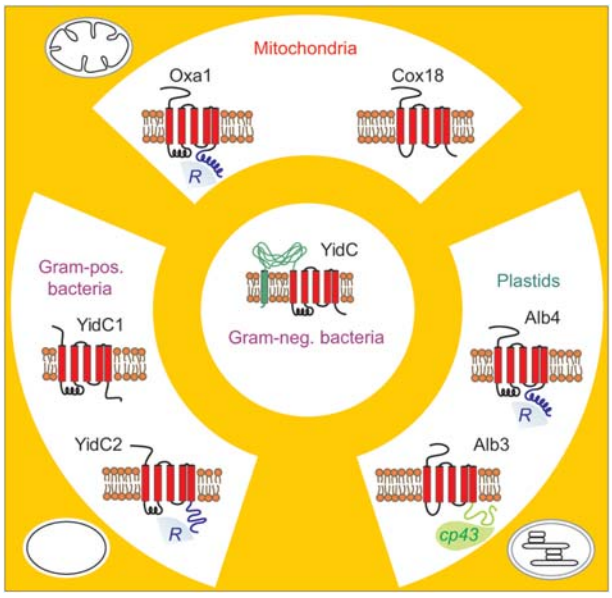


**Figure 1** Functional specialization of its members shaped the YidC/Oxa1/Alb3 family.
Gram-negative bacteria contain only one paralog (YidC) shown in the center. This is characterized by a cleft-forming periplasmic domain (shown in green). Gram-positive bacteria, mitochondria and plastids contain two different paralogs each which are functionally and structurally distinct. These paralogs acquired additional features, for example, to bind to ribosomes (*R*) or the cpSRP43 protein (*cp43*). All proteins presumably developed from a common ancestor which in some aspects might be similar to the YidC proteins found in Gram-negative bacteria. This is supported by the observation that the *E. coli* YidC and other members can be functionally exchanged, whereas many of the more specialized members shown in the periphery cannot complement each other.

family (Jiang et al., 2002; Funes et al., 2004a, 2009; Preuss et al., 2005; van Bloois et al., 2007; Dong et al., 2008). This core domain is flanked by subtype-specific regions: YidC proteins of Gram-negative bacteria comprise an additional N-terminal transmembrane segment that is separated from the hydrophobic core domain by a large periplasmic domain of unknown function (Figure 1, central panel). The crystal structure of this periplasmic region was recently solved showing a cleft-forming structure similar to sugar-binding domains of galactose mutarotases (Oliver and Paetzel, 2008; Ravaud et al., 2008). This periplasmic domain is absent in YidC proteins of Gram-positive bacteria and in eukaryotic homologs and might represent a rather recent acquisition of certain eubacteria. Representatives of mitochondria, plastids and Gram-positive bacteria often show hydrophilic extensions that mediate the interaction with ribosomes or other components (see below and Figure 1, peripheral panels).

## Molecular function of YidC/Oxa1/Alb3 proteins

What is the molecular function of members of the YidC/Oxa1/Alb3 family? Despite 15 years of vivid research, the mechanistic details by which these proteins facilitate the biogenesis of membrane proteins are still not entirely clear. The founding member of this family, Oxa1, was initially identified as a factor required for Oxidase assembly because Oxa1-deficient yeast mutants lack cytochrome *c* oxidase in their mitochondria (Bauer et al., 1994; Bonnefoy et al., 1994). Further analysis then revealed that Oxa1 plays an important role in a very early, co-translational reaction and strongly promotes the translocation of the N-terminus of subunit 2 of cytochrome *c* oxidase (Cox2) across the inner membrane (He and Fox, 1997; Hell et al., 1997). The role of Oxa1 in mitochondria is presumably similar to that of YidC in bacteria because expression of Oxa1 in bacteria complements YidC-deficient strains (van Bloois et al., 2005). Similar to Oxa1, YidC carries out an early step in the biogenesis of subunit 2 of cytochrome oxidase which in bacteria is called CyoA (Figure 2A) (van der Laan et al., 2003). The role of YidC as an insertase that promotes the integration of its substrates into lipid bilayers was clearly demonstrated by reconstitution experiments (Serek et al., 2004; van der Laan et al., 2004). In this process, the nature of the substrates strongly influences the efficiency by which YidC stimulates membrane insertion: YidC clearly increased the insertion rate of proteins that expose small, mainly negatively charged tails or loops to the *trans* side of the membrane, whereas large, complex protein segments are not translocated by YidC and depend

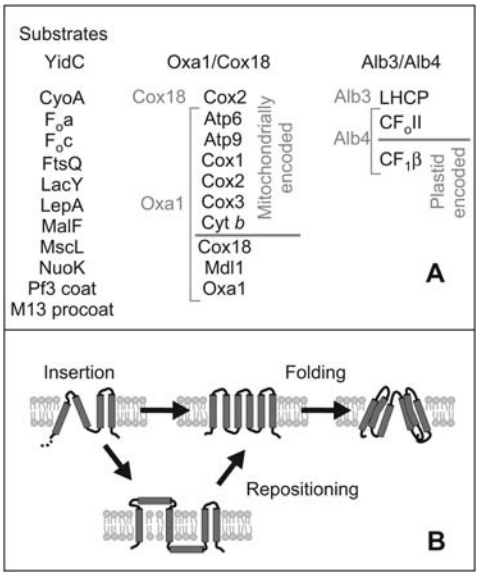


**Figure 2** Molecular function of YidC/Oxa1/Alb3 proteins.
(A) Known examples for proteins that employ YidC, Oxa1/Cox18, Alb3/Alb4 for their insertion or folding. In particular in bacteria, the number of substrates is presumably strongly underestimated. Two recent studies suggest that YidC plays, directly or indirectly, a crucial role for many inner membrane proteins (Price et al., 2010) and presumably also for certain secreted proteins (Jong et al., 2010). (B) The biogenesis of membrane proteins requires their insertion into the lipid bilayer of the membrane and their folding. In some cases, the repositioning of transmembrane segments is required. All three reactions are presumably facilitated by members of the YidC/Oxa1/Alb3 family, but the underlying molecular mechanisms are still unresolved.

on the Sec translocon (Samuelson et al., 2000; Froderberg et al., 2003; Price and Driessen, 2010). Hence, YidC is not a general translocase like the Sec translocon but rather functions as an enzyme that increases the efficiency by which proteins are inserted; thereby, it might be restricted to substrates that have the ability to also spontaneously insert into lipid bilayers, although with rates that might not be physiologically relevant.

In addition to its role in protein insertion, members of the YidC/Oxa1/Alb3 family contribute to the folding and assembly of membrane proteins (Figure 2B; Nagamori et al., 2004; Wagner et al., 2008). It was proposed that they function as membrane-embedded chaperones which interact with folding intermediates (Dalbey and Kuhn, 2004). Indeed, they were found to bind and stabilize relatively long-lived assembly intermediates of the $F_o$ part of the ATPase in bacteria, mitochondria and plastids (Figure 2A; Jia et al., 2007; Stiburek et al., 2007; Kol et al., 2008; Benz et al., 2009; Saller et al., 2009). Whether Oxa1 prevents unwanted interactions of these intermediates or plays a more active role in the folding or remodeling of ATPase subunits is not known. This chaperone-like function is not restricted to complexes of the electron transfer chain: although the bacterial lactose permease (LacY) is initially inserted into the inner membrane in a YidC-independent manner, YidC interacts with LacY and promotes the folding into its native, functional structure (Figure 2A; Nagamori et al., 2004). Mechanistically, this folding activity is presumably similar to the function of insertase. In both processes, transmembrane domains of substrate proteins need to be moved back and forth through membranes. Moreover, for some model proteins it was shown that correct folding requires the topological repositioning for which individual transmembrane domains have to be inverted (Figure 2B; Kauko et al., 2010). Whether these reactions occur spontaneously or whether they need to be assisted by specific factors is unknown, but YidC would certainly be a candidate that might catalyze such a reaction.

## Phylogeny of the family

The combination of a sequence-conserved core domain with subtype-specific flanking regions makes the YidC/Oxa1/Alb3 protein family an interesting example to study the evolution of membrane proteins (Yen et al., 2001; Funes et al., 2009; Zhang et al., 2009). A phylogenetic tree of the family is shown in Figure 3. This tree shows six subbranches: YidC/YidC1 and YidC2 in bacteria, Oxa1 and Cox18/Oxa2 in mitochondria, and Alb3 and Alb4 in plastids. These subbranches presumably represent monophyletic subgroups of common ancestry, although it has to be noted that this analysis was made on the basis of a rather small number of sequences with some homologs showing only a relative low degree of conservation.

The cladogram suggests that the different subgroups developed by three independent gene duplications that occurred in Gram-positive bacteria, mitochondria or chloroplasts (Figure 3). Specialization then shaped the different subgroups and allowed them to acquire specific flanking regions, functional properties and substrate specificity (Figure 1). Hence, the YidC/Oxa1/Alb3 family is an excellent example of gene duplication as a mechanism by which evolution works. The six different subgroups will be introduced in the following section.

## Bacteria: YidC, YidC1 and YidC2

Gram-negative bacteria such as *E. coli* contain only one single member of the YidC/Oxa1/Alb3 protein family. YidC was first identified as an essential protein insertion machinery which cooperates with the Sec translocon for the integration of proteins into the *E. coli* inner membrane (Saaf et al., 1998; Samuelson et al., 2000; Scotti et al., 2000). It can mediate the insertion of some membrane proteins independently of factors of the Sec translocon or the signal recognition particle, but still in a co-translational process (van der Laan et al., 2004). In this reaction, YidC might physically bind the ribosome, despite the absence of a C-terminal ribosome binding tail on YidC (de Gier and Luirink, 2003; Kohler et al., 2009).

The insertion of more complex proteins or those with larger periplasmic domains, however, requires the cooperation of YidC with the Sec translocon. Initial studies suggested a physical association of YidC with the Sec translocase but the nature and dynamics of this association are still not well understood (Scotti et al., 2000; Beck et al., 2001; Nouwen and Driessen, 2002). Possibly, the large periplasmic loop that is characteristic for YidC proteins of Gram-negative bacteria mediates the interaction with components of the Sec translocon (Xie et al., 2006).

The genomes of most Gram-positive bacteria encode two YidC proteins (Yen et al., 2001; Funes et al., 2009). Two YidC homologs were first identified in *Bacillus subtilis*. Both proteins appear to overlap in their activity because only simultaneous deletion of both leads to a lethal phenotype (Murakami et al., 2002; Tjalsma et al., 2003; Saller et al., 2009). One of these homologs, SpoIIIJ, was found to be essential for sporulation. The other YidC homolog, YgjG, is upregulated when the rate of membrane insertion declines; this is facilitated by an elegant regulatory mechanism: directly upstream of the gene for YgjG is a small reading frame which expresses the SpoIIIJ substrate YqzJ (MifM). If YqzJ is efficiently synthesized and inserted into the membrane, an mRNA hairpin is formed hiding the Shine-Dalgarno sequence of the gene for YgjG thereby preventing expression of this second YidC homolog. But when SpoIIIJ is absent or limiting for protein insertion, the C-terminal region of YqzJ acts as a translational arrest domain that stalls the translating ribosome and disrupts the hairpin. Hence, under conditions at which the levels of SpoIIIJ are not sufficient to promote protein insertion, the second YidC homolog, YqjG, is synthesized (Chiba et al., 2009).

Studies on the cariogenic oral pathogen *Streptococcus mutans* indicate a distinct, although overlapping function of the two YidC paralogs in Gram-positive bacteria (Hasona et

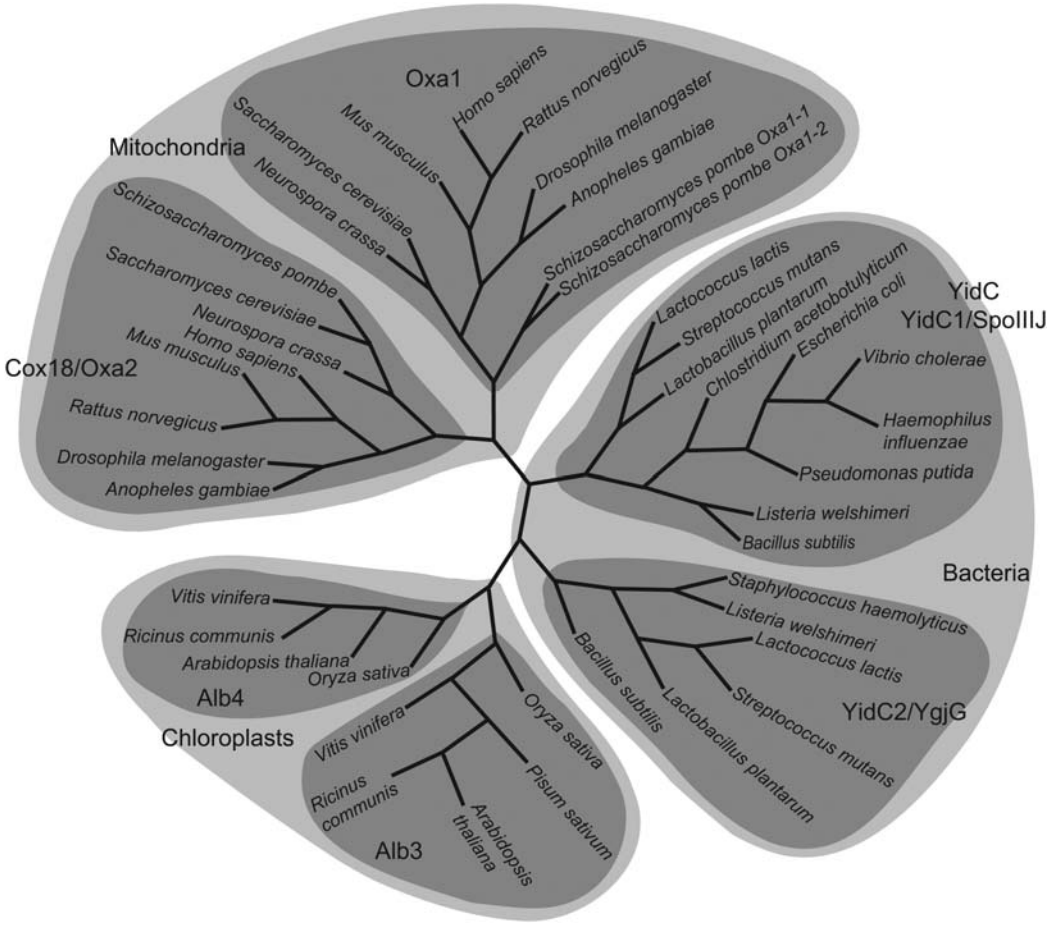


**Figure 3** Phylogeny of the YidC/Oxa1/Alb3 family of proteins.
Unrooted distance tree. Calculation and accession numbers of proteins are basically as published previously (Funes et al., 2009). Additional sequences were used for refinement of Alb3 and Alb4 subgroups. Their accession numbers are XP_002531362 (*R.c.* Alb3), XP_002284077 (*V.v.* Alb3), XP_002515035 (*R.c.* Alb4) and XP_002282031 (*V.v.* Alb4).

al., 2005; Funes et al., 2009). YidC2 (YgjG) contains a C-terminal ribosome-binding domain similar to that of Oxa1. YidC1 (SpoIIIJ) lacks this domain and structurally resembles YidC (Dong et al., 2008). Interestingly, deletion of the signal recognition particle (SRP) is tolerated in *S. mutans* although it is lethal in *E. coli*; however, its simultaneous deletion with YidC2 is lethal suggesting that YidC2 supports a co-translational insertion pathway in Gram-positive bacteria that does not rely on the signal recognition particle. Thus, a gene duplication of YidC proteins in Gram-positive bacteria obviously allowed the dedication of one paralog for a co-translational protein insertion route (Funes et al., 2009).

## Mitochondria: Oxa1 and Cox18

Mitochondria of animals, fungi and plants consistently contain homologs of both Oxa1 and Cox18 (Funes et al., 2004b). Both proteins, however, are absent in some respiration-deficient organisms such as *Encephalitozoon cuniculi* in which mitochondria were degenerated to mitosomes (Tsaousis et al., 2008).

Oxa1 has a rather broad substrate spectrum: on the one hand, it interacts with newly imported nuclear-encoded proteins and facilitates their membrane insertion (Herrmann et al., 1997; Hell et al., 1998). On the other hand, it binds to mitochondrial translation products and mediates their insertion in a co-translational process (Hell et al., 1997, 1998). This co-translational activity is supported by a C-terminal α-helical region of Oxa1 which binds to the large subunit of the mitochondrial ribosome in proximity to its polypeptide exit tunnel (Jia et al., 2003, 2009; Szyrach et al., 2003; Kohler et al., 2009; Gruschke et al., 2010). Owing to its importance for the biogenesis of mitochondrial translation products, mutants lacking Oxa1 show severely reduced levels of respiratory chain complexes I, III and IV and of the $F_oF_1$-ATPase (Bonnefoy et al., 1994; Hell et al., 2001). This co-translational insertion of nascent chains by Oxa1 is further supported by Mba1 which functions as a ribosome receptor of the inner membrane (Preuss et al., 2001; Ott et al., 2006).

Cox18 lacks such a ribosome-binding domain and presumably functions exclusively in a post-translational manner. The only known substrate of Cox18 is subunit 2 of cytochrome *c* oxidase (Figure 2A). This mitochondrially encoded

protein exposes both termini to the intermembrane space. The N-terminal region is exported in a co-translational, Oxa1-dependent reaction. Only after insertion of the first transmembrane domain, the long, highly negatively charged C-terminal region is translocated across the inner membrane in a step that requires Cox18 (Saracco and Fox, 2002). Cox18 cooperates with additional factors such as Mss2 and Pnt1 which might explain why it cannot be replaced by Oxa1 (Fiumera et al., 2007, 2009).

## Plastids: Alb3 and Alb4

Plastids of *Arabidopsis thaliana* and other plants contain two paralogs, Alb3 and Alb4, which differ in their function (Sundberg et al., 1997; Gerdes et al., 2006). Alb3 is specialized on the insertion of light harvesting complex proteins (LHCPs) (Figure 2A; Bellafiore et al., 2002). LHCPs contain three transmembrane domains and are the most abundant membrane proteins on earth. They are encoded in the nucleus, synthesized in the cytosol and translocated into the stroma where they bind to the plastid SRP. The plant SRP contains a special subunit, cpSRP43, instead of the 4.5S RNA moiety found in canonical SRPs. The C-terminus of Alb3 represents a cpSRP43-binding region and is crucial for the targeting of LHCPs to the thylakoid membrane (Moore et al., 2003; Falk et al., 2010). Alb4 lacks this domain and cannot compensate for the loss of Alb3. Upon expression in mitochondria, Alb4 can functionally replace Oxa1 (Funes et al., 2004a). In plastids, Alb4 interacts with plastid-encoded ($CF_1\beta$) and nuclear-encoded ($CF_oII$) subunits of the $F_oF_1$-ATPase (Figure 2A; Benz et al., 2009). Thus, Alb4, similar to YidC and Oxa1, plays a role in the assembly of the ATPase, whereas Alb3 represents a plant-specific factor for the biogenesis of LHCPs.

## Conclusion

Although the molecular function of members of the YidC/Oxa1/Alb3 family is still not entirely clear, it is evident that all homologs are involved in the insertion, folding and assembly of membrane proteins. In these processes, they transiently interact with their substrates and can stabilize assembly intermediates. Subclass-specific regions of YidC/Oxa1/Alb3 proteins mediate interactions with ribosomes, the SRP system or periplasmic components and play crucial roles in substrate recognition. Phylogenetic analysis of the family was very helpful to sort the various homologs into the six different subclasses and thus did not only reveal interesting insights into the evolution of the YidC/Oxa1/Alb3 family but also into the specific molecular function of different paralogs.

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