

Publication

Functional asymmetry within the Sec61p translocon

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The Sec61 translocon forms a pore to translocate polypeptide sequences across the membrane and offers a lateral gate for membrane integration of hydrophobic (H) segments. A central constriction of six apolar residues has been shown to form a seal, but also to determine the hydrophobicity threshold for membrane integration: Mutation of these residues in yeast Sec61p to glycines, serines, aspartates, or lysines lowered the hydrophobicity required for integration; mutation to alanines increased it. Whereas four leucines distributed in an oligo-alanine H segment were sufficient for 50% integration, we now find four leucines in the N-terminal half of the H segment to produce significantly more integration than in the C-terminal half, suggesting functional asymmetry within the translocon. Scanning a cluster of three leucines through an oligo-alanine H segment showed high integration levels, except around the position matching that of the hydrophobic constriction in the pore where integration was strongly reduced. Both asymmetry and the position effect of H-segment integration disappeared upon mutation of the constriction residues to glycines or serines, demonstrating that hydrophobicity at this position within the translocon is responsible for the phenomenon. Asymmetry was largely retained, however, when constriction residues were replaced by alanines. These results reflect on the integration mechanism of transmembrane domains and show that membrane insertion of H segments strongly depends not only on their intrinsic hydrophobicity but also on the local conditions in the translocon interior. Thus, the contribution of hydrophobic residues in the H segment is not simply additive and displays cooperativeness depending on their relative position.

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