An ER translocon for multi-pass membrane protein biogenesis

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Membrane proteins with multiple transmembrane domains play critical roles in cell physiology, but little is known about the machinery coordinating their biogenesis at the endoplasmic reticulum. Here we describe a ~ 360 kDa ribosome-associated complex comprising the core Sec61 channel and five accessory factors: TMCO1, CCDC47 and the Nicalin-TMEM147-NOMO complex. Cryo-electron microscopy reveals a large assembly at the ribosome exit tunnel organized around a central membrane cavity. Similar to protein-conducting channels that facilitate movement of transmembrane segments, cytosolic and luminal funnels in TMCO1 and TMEM147, respectively, suggest routes into the central membrane cavity. High-throughput mRNA sequencing shows selective translocon engagement with hundreds of different multi-pass membrane proteins. Consistent with a role in multi-pass membrane protein biogenesis, cells lacking different accessory components show reduced levels of one such client, the glutamate transporter EAAT1. These results identify a new human translocon and provide a molecular framework for understanding its role in multi-pass membrane protein biogenesis.

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