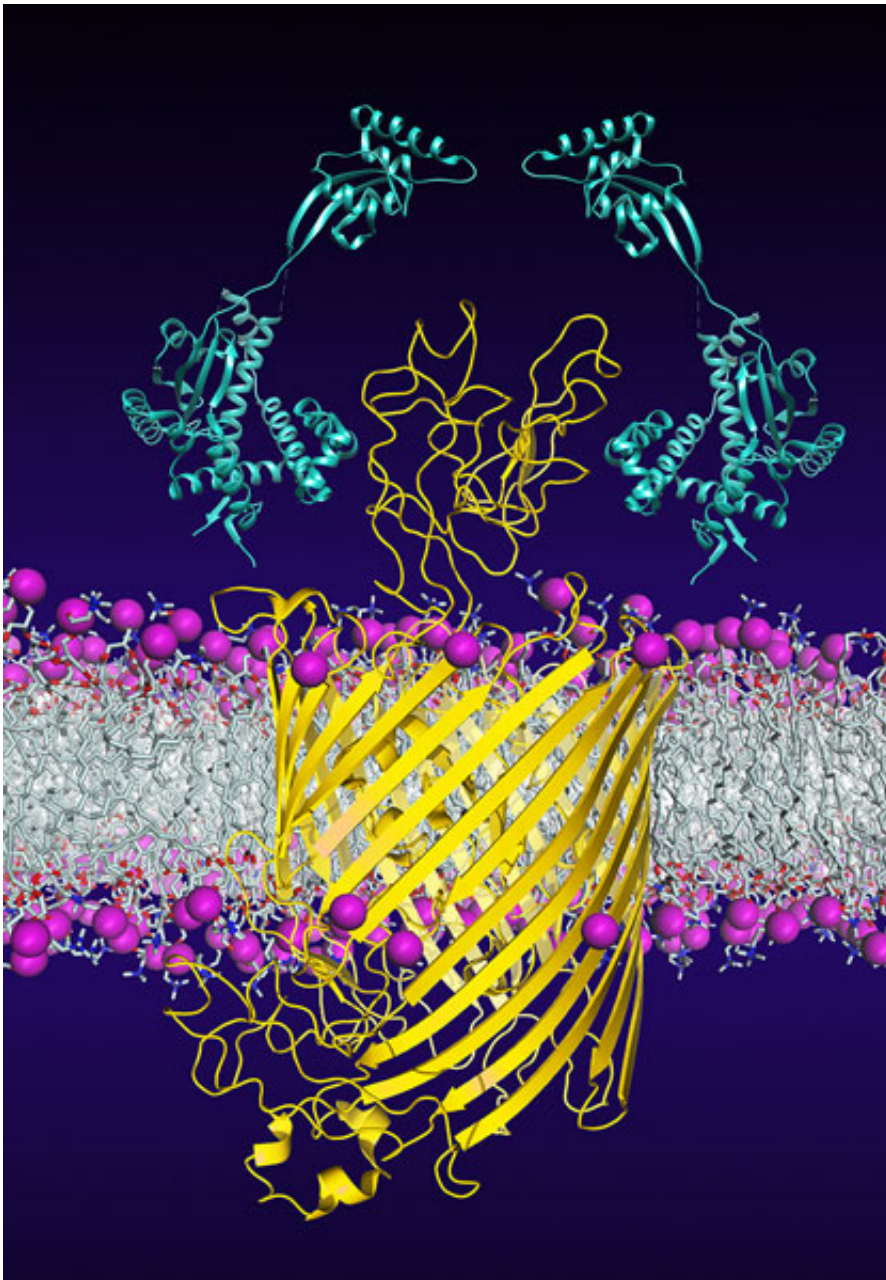


Molecular bodyguards for immature membrane proteins

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Chaperones (light blue) promote the insertion and folding of the bacterial membrane protein FhuA (yellow). Credit: University of Basel, Biozentrum

During their formation within the cells, many proteins rely on the assistance of molecular protectors, so-called chaperones. They help the proteins to fold correctly and thus ensure the right final structure. The roles of chaperones in membrane protein folding have long remained unclear. Researchers at the Biozentrum, University of Basel, and at ETH Zurich have now shown how chaperones stabilize an immature bacterial membrane protein and guide it in the right folding direction, thus protecting it from misfolding.

Their study was recently published in *Nature Structural & Molecular Biology*.

Cellular machines continuously produce long polypeptide chains, the proteins. In order to properly fulfill its cellular function, a [protein](#) must however first adopt its correct spatial structure. In each cell there are molecular helper proteins called chaperones. They take care of the immature proteins to help them in the folding process and thus preventing errors. The scientists led by Prof. Sebastian Hiller from the Biozentrum, University of Basel, and Prof. Daniel Müller from the Department of Biosystems Science and Engineering (D-BSSE), ETH Zurich in Basel have discovered how two chaperones in the gut bacterium *E. coli* protect the [membrane](#) protein FhuA during transport and assist its insertion into the membrane.

Chaperones help insertion of membrane protein

Countless proteins, which transport nutrients and signaling molecules, are embedded in the [outer membrane](#) of bacteria. One of these

membrane transporters is the protein FhuA. Via this protein, the bacteria take up vitally important iron but also antibiotics. But how does the very large, barrel-shaped FhuA protein reach the outer membrane intact? The scientists from the Biozentrum and the D-BSSE have investigated this process more deeply.

In order to reach its goal in the outer membrane, FhuA uses the help of several chaperones. Using structural analyses and single-molecule force spectroscopy, the researchers have now elucidated how these two chaperones stabilize the immature protein and prevent misfolding. "This process is extremely dynamic," says Hiller. "Under the protection of the chaperones, within a millisecond, FhuA constantly changes its structure. It thus explores energetically favorable conformations which enable the stepwise insertion and folding of individual protein segments into the membrane." With the insertion of the final protein segment, FhuA acquires its mature and functional barrel structure. Left unprotected, FhuA would fold incorrectly and finally aggregate.

Protein chaos without chaperones

Chaperones are significantly involved in the formation of functional proteins. They play an important role in the correct folding of soluble proteins and furthermore are necessary for the insertion of [membrane proteins](#) into the bacterial outer membrane. Because several organelles in plant and animal [cells](#) are of bacterial origin, chaperones also protect their membrane proteins in a similar manner and assist during membrane insertion. The new findings are consequently of great relevance also for diseases caused by misfolded proteins such as Alzheimer's, Parkinson's or cystic fibrosis.

"It has been known for a long time that chaperones protect other proteins from misfolding and encourage them to fold correctly. Now, our work has succeeded in demonstrating - for the first time in biological

membranes - how chaperones support the [membrane proteins](#) that are key to pharmaceutical research," explains ETH Professor Daniel Müller. Until recently, these could almost only be investigated using artificial environments. However, this meant that there was barely any understanding of how proteins fold into a cell's membrane.

"To give a loose analogy, until now it was like putting a cow on a sheet of ice in order to investigate its natural behaviour and then observing surprising reactions," says Müller. "We now have a better understanding of how the cell incorporates its molecular machines into membranes so that they can perform their versatile duties."

More information: Johannes Thoma, Björn M Burmann, Sebastian Hiller & Daniel J Müller, Impact of holdase chaperones Skp and SurA on the folding of β -barrel outer-membrane proteins, *Nature Structural & Molecular Biology* (2015), [DOI: 10.1038/nsmb.3087](https://doi.org/10.1038/nsmb.3087)

Provided by University of Basel

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