Researchers identify bacterial mechanism for vitamin B12 uptake

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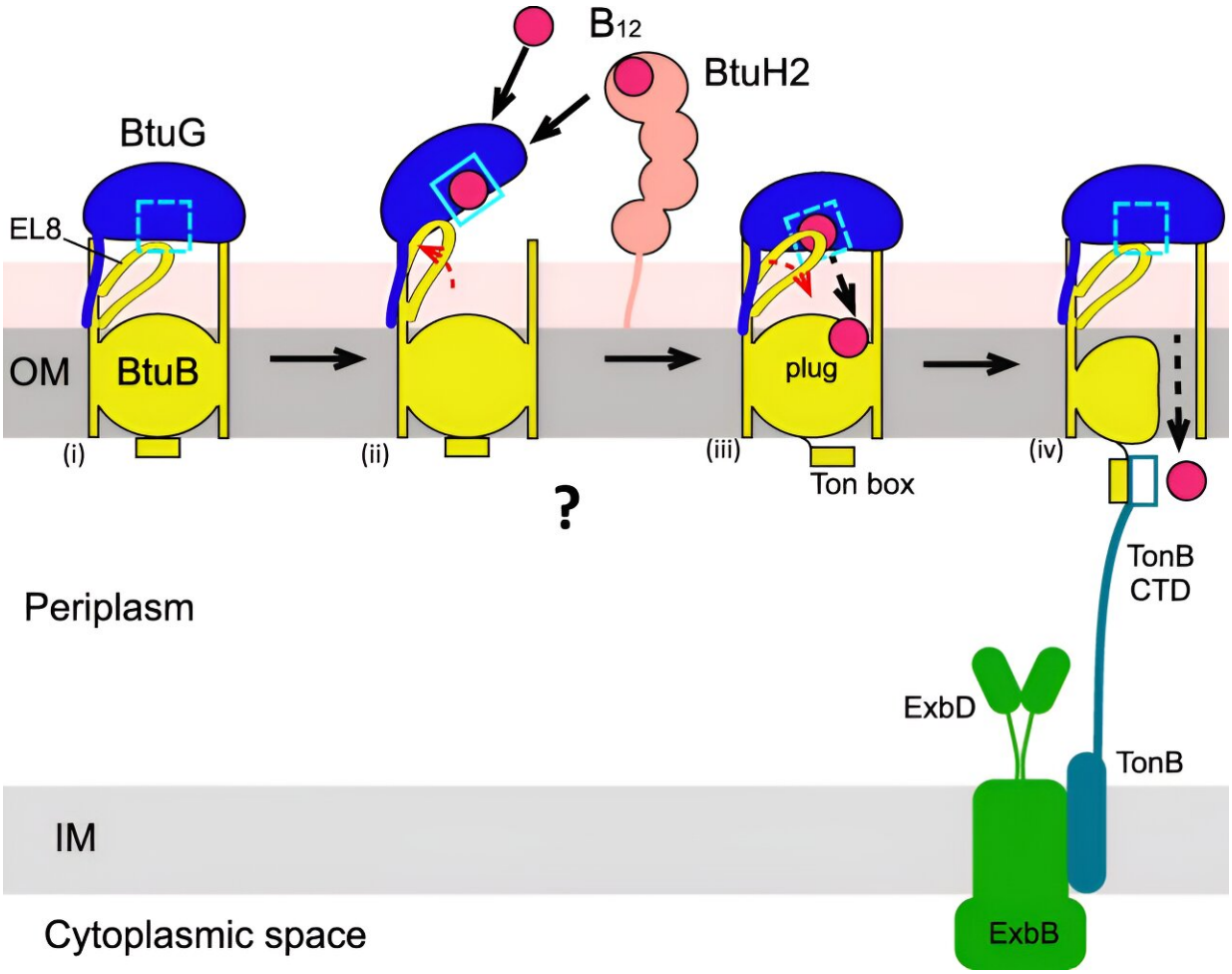

Schematic model for lipoprotein-mediated B_{12} acquisition by B. theta. Starting from the closed state in which EL8 occupies the B_{12} binding site on BtuG, the BtuBG complex opens, which might happen spontaneously or perhaps is promoted by accessory proteins such as BtuH. (ii) After opening, EL8 moves away from the B_{12} binding site, allowing acquisition of the vitamin by BtuG

from the external environment or from BtuH. (iii) Upon lid closing, EL8 act as a spring-loaded hinge to destabilize the bound B_{12}, causing its release and transfer to BtuB. Binding of B_{12} by BtuB generates allosteric changes in the plug that leads to TonB box exposure in the periplasmic space. During the final stage (iv), the C-terminal domain (CTD) of TonB binds to the TonB box and causes unfolding of the plug due to mechanical force generated by the TonB-ExbB-ExbD complex in the IM. The channel that is formed allows diffusion of the substrate into the periplasmic space. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-40427-2

A team of scientists led by Dr. Ulrich Kleinekathöfer, professor of Theoretical Physics at Constructor University in Bremen, has now discovered how B_{12} is absorbed by certain intestinal bacteria. Published in the journal *Nature Communications* at the beginning of August, the findings will serve as a basis for research on how to better fight diseases and develop better antibiotics.

Kleinekathöfer and his team's breakthrough finding, what they call "pedal-bin mechanisms," offers critical understanding for how bacteria in the intestine known as bacteroides can absorb vitamin B_{12}. This is important for human health since B_{12} cannot be produced or absorbed by humans themselves.

The scientists' name for the finding derives from its similarity to the pedal mechanism of a bucket; the proteins have a lid that opens when vitamin B_{12} is nearby, takes it in and closes again. Other bacteria do not have this mechanism.

"In this project we aimed at understanding the mode of action of the vitamin B_{12} uptake system," Kleinekathöfer said. "Although the human gut microbiome has been implicated in many aspects of human health, the uptake of small molecules by gut bacteria is poorly characterized."

Kleinekathöfer and his team believe the results can help to design antibiotics which are not being taken up by gut bacteria. Since intestinal bacteria are "good" bacteria, research is interested in ensuring that they are not killed by absorbing antibiotics. However, further research will need to first explain through which proteins the gut bacteria do actually take up antibiotics. In the future, this finding could be the basis for placing specific substances in the bacteria in order to fight diseases.

"Our simulations at the molecular level helped interpreting the results obtained by our experimental colleagues," Kleinekathöfer said. "A detailed understanding of these processes is potentially a first step in curing problems in the gut microbiome."

The research team focused on specific proteins of the bacterium, of which three variants exist. The starting point was static crystal structures of the proteins provided by scientists from Newcastle University, a cooperation partner in this project. The Constructor University team then used simulation to determine the capture process of B_{12} by the proteins. The simulations allowed the researchers to simulate several hundred thousand atoms simultaneously.

More information: Javier Abellon-Ruiz et al, BtuB TonB-dependent transporters and BtuG surface lipoproteins form stable complexes for vitamin B12 uptake in gut Bacteroides, *Nature Communications* (2023). DOI: 10.1038/s41467-023-40427-2

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