Researchers decipher role of triglycerides in cellular barrier of tuberculosis pathogen

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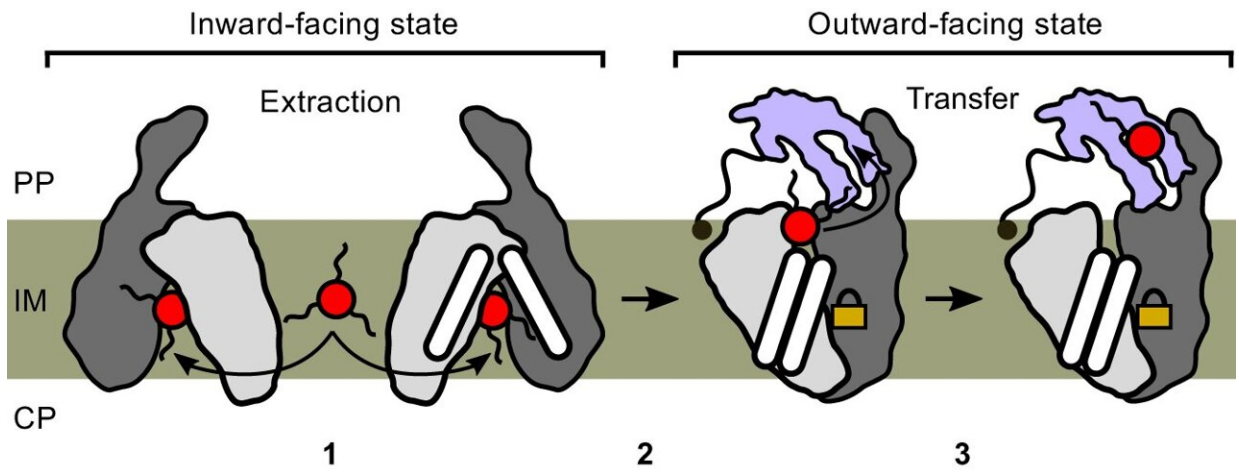

Mechanism of TAG transport by Rv1410 and LprG. LprG is colored pale lilac. (1) TAG molecule (red) enters the transporter's central cavity through lateral openings between TM5-TM8^{IN} and TM2-TM11^{IN} in the inward-facing conformation. (2) The transporter transitions from inward-facing to outward-facing state while the TAG molecule is occluded within the central cavity. The E147-R417 ion lock (symbolized by golden lock) at the bottom of the central cavity is formed and lifts TAG toward the periplasmic leaflet. (3) TM11 and TM12 periplasmic extensions shield the TAG molecule from hydrophilic periplasm while the TAG molecule relocates from the transporter's cavity to the hydrophobic pocket of LprG. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-42073-0

Tuberculosis is a severe infectious disease that claims about 1.3 million

lives annually world-wide. This dismal toll is caused by the notorious pathogen Mycobacteria tuberculosis, whose bitter success depends on its formidable cellular double barrier, which offers both protection from the host defense system and a terrain that mediates host-pathogen interactions during infection.

Understanding how to weaken this barrier by detecting how its molecular components organize and shuffle is the subject of new research. Through computer simulations, and in collaboration with the Institute for Medical Microbiology at University of Zurich, Professor Lars Schäfer and Dr. Dario De Vecchis from the Center for Theoretical Chemistry at Ruhr University Bochum, Germany, described the molecular journey of one critical component of this barrier: triglyceride.

The team of researchers describe their results in an article published in *Nature Communications* on October 13, 2023.

A molecular vacuum cleaner

Triglycerides are the form in which fat energy is stored in our tissue. "Mycobacteria also accumulate triglycerides," explains Lars Schäfer. "But in addition to store energy, these molecules are also a key component that contributes to seal their cellular barrier." This high-energy molecule needs to be transported from inside the bacterial cell (the cytoplasmic space) through the membrane, to be ultimately deposited in the mycobacterial barrier.

Until now, the precise details of this molecular journey were not known. "By teaming up with structural biologists Professor Markus Seeger and Dr. Sille Remm at Zurich, we used computer simulations to reveal how triglycerides are hunted from the transmembrane protein RV1410 that, akin to a vacuum cleaner, extracts them from the bacterial membrane via lateral portals in the protein structure."

The relay race of the Trojan horse

But how are the triglycerides ultimately transported from the membrane and deposited to the barrier? The second intermediate actor, LprG, is a periplasmic protein that is anchored to the membrane and browses its surface chasing for triglycerides. LprG has a water-repellent (hydrophobic) pocket that once paired with RV1410 creates a greasy tunnel where the "baton" triglyceride is handed off in a relay race to ultimately reach the barrier.

"We simulated the RV1410-LprG system embedded in a realistic mycobacterial membrane and describe this triglyceride-relay-race in atomistic detail," says De Vecchis. "One could think about the mycobacterial membrane as the Troy battlefield, were the scientists are trying to conquer the pathogen's ramparts by exploiting the RV1410-LprG system as the Trojan horse."

Revealing the molecular pathway of triglycerides could open new strategies to target the RV1410-LprG system, weaken the mycobacterial barrier, enhance antimicrobial permeability, and ultimately lead to more effective therapies against tuberculosis.

More information: Sille Remm et al, Structural basis for triacylglyceride extraction from mycobacterial inner membrane by MFS transporter Rv1410, *Nature Communications* (2023). DOI: 10.1038/s41467-023-42073-0

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