UKE Paper of the Month Juli 2021

Structure and dynamics of a mycobacterial type VII secretion system

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ABSTRACT: *Mycobacterium tuberculosis* is the cause of one of the most important infectious diseases in humans, which leads to 1.4 million deaths every year. Specialized protein transport systems—known as type VII secretion systems (T7SSs)—are central to the virulence of this pathogen, and are also crucial for nutrient and metabolite transport across the mycobacterial cell envelope. Here we present the structure of an intact T7SS inner-membrane complex of *M. tuberculosis*. We show how the 2.32-MDa ESX-5 assembly, which contains 165 transmembrane helices, is restructured and stabilized as a trimer of dimers by the $MycP_5$ protease. A trimer of $MycP_5$ caps a central periplasmic dome-like chamber that is formed by three $EccB_5$ dimers, with the proteolytic sites of $MycP_5$ facing towards the cavity. This chamber suggests a central secretion and processing conduit. Complexes without $MycP_5$ show disruption of the $EccB_5$ periplasmic assembly and increased flexibility, which highlights the importance of $MycP_5$ for complex integrity. Beneath the $EccB_5$–$MycP_5$ chamber, dimers of the $EccC_5$ ATPase assemble into three bundles of four transmembrane helices each, which together seal the potential central secretion channel. Individual cytoplasmic $EccC_5$ domains adopt two distinctive conformations that probably reflect different secretion states. Our work suggests a previously undescribed mechanism of protein transport and provides a structural scaffold to aid in the development of drugs against this major human pathogen.

STATEMENT:

Our work highlights the first structure of an intact inner membrane type VII secretion system nanomachinery from the important human pathogen Mycobacterium tuberculosis. Furthermore, we describe how a thus far elusive protease component restructures and stabilizes this machinery. As type VII secretion systems are crucial pathways for virulence and nutrient uptake in Mycobacterium tuberculosis, our study provides a potential blueprint for structure-based drug design studies aimed at combating tuberculosis.

BACKGROUND:

This work was performed at the Institute of Structural and Systems Biology, in the group of Thomas Marlovits, and in collaboration with researchers from the Amsterdam University Medical Center and Vrije Universiteit Amsterdam. The Marlovits group studies the structural basis for assembly, regulation, and function of transmembrane molecular machines through a multidisciplinary approach, combining molecular biology, genetic, cellular, biochemical, and a wide range of structural tools (i.e. cryo electron microscopy).