

Protein Virulence Factors of *Mycobacterium tuberculosis* Complex: An Overview

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DESCRIPTION

The genus *Mycobacterium* is distinguished by a highly complex cell wall envelope that accounts for their cells' remarkable low permeability, as well as the distinctive differential staining procedure (known as Zhiel-Neelsen acid-fast stain), which specifically stains all members of the genera. Both of these characteristics are caused by the presence of long chain -alkyl, -hydroxy fatty acids in their cell wall. The *Mycobacterium* genus is typically divided into two major groups based on their growth rate.

Cell wall proteins

Proteomic studies of the mycobacteria cell wall have identified more than five hundred proteins in this cellular structure, including secreted cell wall proteins and lipoproteins. Cell wall proteins include Outer Membrane Proteins (OMPs) that are likely localised in the newly discovered mycobacterial outer membrane bilayer by combining the use of an algorithm entirely based on physical principles to predict *Mycobacterium tuberculosis* OMPs with biological knowledge.

ERP (Exported Repetitive Protein)

ERP (Exported Repetitive Protein) is a cell-wall-associated surface protein that is usually secreted into the culture medium and has a molecular mass of 36 kDa. Erp proteins are organised in three domains: two well-conserved N- and C-terminal domains, and a central domain containing several Pro-Gly-Leu-Thr-Ser (PGLTS) repeats that vary in number, with four repeats in *Mycobacterium leprae* and 24 repeats in *Mycobacterium xenopi*.

FBP (Fibronectin Binding Protein)

FBP (Fibronectin Binding Protein) is a protein complex composed of three proteins: FbpA, FbpB, and FbpC2, and its name is derived from their ability to bind Fibronectin (FN). This complex is commonly referred to as antigen 85 (Ag85), and it consists of Ag85A (FbpA), Ag85B (FbpB), and Ag85C (FbpC2). The fbpA, fbpB, and fbpC2 genes encode these proteins, which are located in different genomic regions: Rv3804, Rv1886c, and Rv0129c, respectively.

Mce

Mce proteins are a large group of secreted or exposed proteins that are organised in large operons. The name Mce, which stands for mammalian cell entry, refers to the first function described for the Mce proteins: It has been demonstrated that Mce1 allows mycobacteria to enter and survive inside macrophages. In mice infected *via* systemic or intraperitoneal route with this mutant, the mce1 *Mycobacterium tuberculosis* strain displayed a hypervirulent phenotype when compared to parental or complemented strains.

OmpATb

OmpATb is an outer membrane protein pore-forming protein (porin) that belongs to the OmpA family. The structure allows it to form pores with diameters of 1.4 and 1.8 nm, allowing small hydrophilic molecules such as arabinose, glucose, sucrose, and serine to pass into the cytoplasm. This porin, like other members of the OmpA family, contributes to pathogenicity. An *Mycobacterium tuberculosis* mutant in the ompATb gene had significantly lower multiplication in macrophages than the wild type, and its growth in the lungs and spleen of BALB/c mice was significantly lower than the wild type.

HbhA (heparin-binding hemagglutinin)

The major adhesin exposed at the cell's surface is HbhA (heparin-binding hemagglutinin). This protein binds sulphated glycoconjugates like heparin, promoting mycobacteria attachment to epithelial cells and fibroblasts but not macrophage-like cells. Furthermore, the protein promotes rabbit erythrocyte agglutination and induces mycobacterial aggregation.

PstA1 and PhoT

PstA1 and PhoT (encoded by pstA1 and phoT, respectively) are proteins involved in inorganic phosphate transport. Unlike pstA1, which is found in the same operon as pstC2 and phoS2 (also known as pstS3), phoT is found elsewhere in the genome. The substrate-binding protein is PhoS2, the permeases containing the Membrane Spanning Domain (MSD) are PstC2 and PstA1, and PhoT has homology to the nucleotide-binding

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domain protein, which is responsible for energy coupling to the transport system.

CaeA

CaeA, also known as Rv2224c, is a cell surface carboxylesterase. The protein functions as an esterase/lipase, preferentially hydrolyzing ester bonds in substrates with intermediate carbon chain lengths ranging from 3 to 7 carbon atoms.

CtaC

CtaC is the subunit II of the cytochrome c oxidase that is required for aerobic growth. An in silico analysis revealed that the cytochrome oxidase domain is located on the membrane's extracytoplasmic face. CtaC is predicted to be required in *Mycobacterium tuberculosis* H37Rv.