An Insight into the Cell Wall of Mycobacterium Tuberculosis

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Abstract: Mycobacterium tuberculosis is the most successful pathogen of the present times. It operates via a very complex and indispensable cell wall that is responsible for the persistence and resistance of the bacteria inside the human host. Various kinds of lipids are present in mycobacterial cell wall, some unique to Mycobacterium tuberculosis and some present evenly in other mycobacteria as well. Since these lipids play an important role in the successful establishment of infection and are essential for pathogenesis as well they may prove to be an effective drug targets in the present scenario where the emergence of MDR and XDR tuberculosis has challenged the efficacy of current drug regime.

Keywords: Mycobacterium Tuberculosis, Cell Wall, Lipids, Mycolic Acids

1. Introduction

Mycobacterium tuberculosis, causative agent of tuberculosis, has adapted significantly to the evolutionary changes that shaped the modern Homo sapiens as well as the bacteria itself. The elucidation of tuberculosis genome by Cole et. al., had revolutionized studies on the cell wall of mycobacteria along with the modern analytical techniques such as GC-MS, HPLC, NMR etc. The cell wall of mycobacteria is the most distinguishable structure of Mycobacterium tuberculosis which separates it from other species.

Mycobacterial cell wall can be divided into two parts i.e. soluble and insoluble fraction; Treatment of Mycobacterium tuberculosis with various solvents results in the solubilization of some of the lipids, whereas some are rendered insoluble. The lipids which are solubilized easily are the free lipids that are present in the outer part of the cell wall & those which remain intact form the inner part of the cell wall. Soluble part comprises of phthioceroldimycocerates (PDIM), Sulfolipids, Cord factor, etc. Whereas the insoluble part consists of peptidoglycan conjugated with arabinogalactan which is further conjugated to mycolic acids. This association forms the backbone of mycobacterial cell wall. This dynamic structure of the cell wall of Mycobacterium tuberculosis is responsible for the persistence, resistance and an unusual impermeability barrier of the bacteria inside the human host where it combats against the various immunological stress that are induced by the human body.

In this review we have given a brief introduction about the various soluble as well as insoluble lipid fraction of Mycobacterium tuberculosis.
Insoluble Fractions

The insoluble fractions form backbone of the cell wall of the *Mycobacterium tuberculosis* and is made up of peptidoglycan, arabinogalactan, mycolic acid.

Peptidoglycan: There are three features in the peptidoglycan of *Mycobacterium tuberculosis* that distinguishes it from the *E. coli*. Apart from the normal alternate repeating units of N-acetyl glucosamine and N-acetyl muramic acid as seen in *E. coli*, *Mycobacterium tuberculosis* peptidoglycan have an extra element that consist of N-glycolylmuramic acid which is formed by the acetylation of muramic acid of the peptidoglycan with the glycolic acid. Cross linking peptide that links dimer of N-acetylgucosamine and N acetyl muramic acid in *E. coli* consist of Ala-Glu-DAP-Ala linked via Ala-DAP of the repeating units, while in *Mycobacterium tuberculosis* it consist mostly of DAP-DAP linkages. The degree of cross linking of the repeating units in *Mycobacterium tuberculosis* is about two and half times higher than the *E. coli*. This unusual cross linking in the peptidoglycan of the *Mycobacterium tuberculosis* helps in its survival against the conventional proteases.

Arabinogalactan

The arabinogalactan is sandwiched between peptidoglycan on one side and mycolic acid on the other and hence forms PAM(peptidoglycan-arabinogalactan-mycolic acid) complex. It is made up of two components i.e. arabinan and galactan that are attached to each other via a linker molecule. Arabinans are linked via an Ara(1→5)-Galfglycosidic bond togalactans which is a polysaccharide consisting of approximately 30 β(1→5) and β(1→6) Galf residues. Arabinan and galactan together forms arabinogalactan moiety.

Mycolic Acid

Mycolic Acids are essential for the survival of *Mycobacterium tuberculosis* and consist of about 32% of the dry weight of *Mycobacterium tuberculosis*. They are β Hydroxy fatty acids consisting of an alkyl side chain with total number of carbon ranging from 60-90. There are three types of mycolic acids that are found in *Mycobacterium tuberculosis* i.e. alpha, methoxy and keto mycolic acids. Out of all three, Alpha mycolic acids are the most abundant. Mycolic acids are synthesized by the fatty acid synthase complex of *Mycobacterium tuberculosis* consisting of two system FAS I(multienzyme complex) and FAS II. FAS I enzyme is responsible for the synthesis of C20 and C26 fatty acids that are attached to CoA. Further elongation of these C20 and C26 fatty acids is carried out by FAS II system that results in the formation of meromycolate. Several other enzymes are responsible for the differentiation into α, methoxy and keto mycolic acids which are beyond the scope of this review.

**Figure 2:** Representative diagram of Peptidoglycan

**Figure 3:** Representative diagram of the structure of Mycolic acid from *Mycobacterium tuberculosis*

2. Soluble Lipids

**PDIM**(phthioceroldimycoserosates) Phthiocerol and phenolphthioceroldimycocerosateses are a group of free lipids that are present in the upper layer of the cell wall of *Mycobacterium tuberculosis*. Mycobacterium mutant lacking genes that are responsible for the synthesis of PDIM was shown severely attenuated. It is an important virulence factor of *Mycobacterium tuberculosis* which is required for the maintenance of cell wall permeability and it is specific to pathogenic mycobacteria. Structurally it is a mixture of long-chain β-diols (C33–C41) esterified by the multimethyl-branched mycocerosic or phthioceranic acids (C27–C34),mas enzyme is responsible for the synthesis of mycocerosic acid which comprises ofmethylmalonyl CoA’s(MMCOA) repeated additions. However,Phthiocerol synthesis requiresenzymes encoded by different genes i.e. ppsA-E.mmp1 are the set of genes required for the translocation of lipids to their target sites. Mmp17 is responsible for the transport of PDIM.

**Volume 4 Issue 6, June 2015**

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Sulfolipids: Sulfolipids are sulfated trehalose esters that are acylated with three or four acyl groups consisting of one saturated fatty acid i.e. either palmitic acid or stearic acid at the 2- carbon position and a combination of the hepta- and octamethyl-branched phthioceranic and hydroxyphtioceranic acids (C31–C46) at the 3-, 6- and 60- positions. pks2 and mmpl8 are the two most important enzymes that help in the synthesis of sulfolipid in Mycobacterium tuberculosis. Out of the Mycobacterium tuberculosis complex they are found only in Mycobacterium tuberculosis and hence play an important role in the virulence of Mycobacterium tuberculosis primarily at the early stage of infection. They also inhibit oxidative phosphorylation in mitochondria and inhibits the fusion of lysosome with the phagosome thereby modulating the immune response of the human host.

It has already been proved that the influx of propionyl CoA results in the increased production of sulfolipids and PDIM. So it performs dual function of a virulence factors as well as a precursor for the biosynthesis of sulfolipid and PDIM.

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3. Conclusion

The importance of the lipids in the pathogenesis and survival of Mycobacterium tuberculosis can be ascertained by the fact that gene responsible for lipidomic function of Mycobacterium tuberculosis accounts for 30% of the total genome. Lipid specifically that forms the part of the cell wall of mycobacteria are actively involved in the pathogenesis, infection & virulence and forms an indispensable part of the life cycle of the bacteria. They are even responsible for modulating the host immune responses. In many of the cases their absence renders the bacteria attenuated. This phenomenon has attracted scientists to target the various enzymes that are involved in the biosynthesis of these lipids. Importance of lipids as drug targets can prove to be achilles heel in case of tuberculosis.

4. Acknowledgement

We thank Prof. Mridula Bose for her approachability and insight, and constant support.

References


