COMPUTATIONAL TARGET IDENTIFICATION OF PEPTIDOGLYCON METABOLIC PATHWAY PROTEIN OF MYCOBACTERIUM TUBERCULOSIS 826

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Abstract - Peptidoglycon metabolic pathway of M.tuberculosis were selected because there is a difference in eukaryotes in cell wall due to this differences that eukaryotes have not a cell wall, so to identifying the effect of M.tuberculosis on the human cell, we were selected cell wall protein of peptidoglycon metabolic pathway. The cell walls of prokaryotes are generally formed of a different molecule (peptidoglycon) to those of eukaryotes (many eukaryotes do not have a cell wall at all). With multidrug-resistant cases of tuberculosis increasing globally, better antibiotic drugs and novel drug targets are becoming an urgent need. Traditional β-lactam antibiotics that inhibit D,D-transpeptidases are not effective against Mycobacterium tuberculosis, in part because mycobacteria rely mostly on L,D-transpeptidases for biosynthesis and maintenance of their peptidoglycan layer. This reliance plays a major role in drug resistance and persistence of Mycobacterium tuberculosis (Mtb) infections. The crystal structure at 1.7 Å resolution of the Mtb L,D-transpeptidase Ldt(Mt2) containing a bound peptidoglycan fragment, reported here, provides information about catalytic site organization as well as substrate recognition by the enzyme. Together, this information provides vital insights to facilitate development of drugs targeting this validated yet unexploited enzyme.

Keywords - Peptidoglycon pathway protein, target identification M.tuberculosis

INTRODUCTION

M. tuberculosis, known as the "tubercle bacillus", was first described on 24 March 1882 by Robert Koch, who subsequently received the Nobel Prize in physiology or medicine for this discovery in 1905; the bacterium is also known as "Koch’s bacillus"[7]. Tuberculosis has existed throughout history, but the name has changed frequently over time. In 1720, though, the history of tuberculosis started to take shape into what is known of it today; as the physician Benjamin Marten described in his A Theory of Consumption, tuberculosis may be caused by small living creatures that are transmitted through the air to other patients[8].

Mycobacterium tuberculosis (MTB) is a pathogenic bacterial species in the family Mycobacteriaceae and the causative agent of most cases of tuberculosis (TB)[4]. First discovered in 1882 by Robert Koch, M. tuberculosis has an unusual, waxy coating on its cell surface (primarily mycolic acid), which makes the cells impervious to Gram staining. Acid-fast detection techniques are used instead. The physiology of M. tuberculosis is highly aerobic and requires high levels of oxygen. Primarily a pathogen of the mammalian respiratory system, MTB infects the lungs. The most frequently used diagnostic methods for TB are the tuberculin skin test, acid-fast stain, and chest radiographs[4].

M. tuberculosis bacterial colonies

TEM micrograph of M.tuberculosis.
Because TB is an infectious disease for humans, it is important to sequence the genome of the Mycobacterium
tuberculosis in order to find drugs fight against the bacteria by developing potential drug targets. Especially since Mycobacterium tuberculosis is multi-drug resistance and could cause latent infection, it is especially hard to treat and prompts scientists to research for new drug targets by looking through the Mycobacterium tuberculosis genome and gene products.

M. tuberculosis requires oxygen to grow. It does not retain any bacteriological stain due to high lipid content in its wall, hence Ziehl-Neelsen staining, or acid-fast staining, is used. Despite this, it is gram-positive bacteria. While mycobacteria do not seem to fit the Gram-positive category from an empirical standpoint (i.e., they do not retain the crystal violet stain), they are classified as acid-fast Gram-positive bacteria due to their lack of an outer cell membrane[4].

All Mycobacterium species share a characteristic cell wall, thicker than in many other bacteria, which is hydrophobic, waxy, and rich in mycolic acids/mycolates. The cell wall consists of the hydrophobic mycolate layer and a peptidoglycan layer held together by a polysaccharide, arabinogalactan. The cell wall makes a substantial contribution to the hardiness of this genus. The biosynthetic pathways of cell wall components are potential targets for new drugs for tuberculosis[2].

M. tuberculosis divides every 15–20 hours, which is extremely slow compared to other bacteria, which tend to have division times measured in minutes (Escherichia coli can divide roughly every 20 minutes). It is a small bacillus that can withstand weak disinfectants and can survive in a dry state for weeks. Its unusual cell wall, rich in lipids (e.g., mycolic acid), is likely responsible for this resistance and is a key virulence factor[6].

When in the lungs, M. tuberculosis is taken up by alveolar macrophages, but they are unable to digest the bacterium. Its cell wall prevents the fusion of the phagosome with a lysosome. Specifically, M. tuberculosis blocks the bridging molecule, early endosomal autoantigen 1 (EEA1); however, this blockade does not prevent fusion of vesicles filled with nutrients. Consequently, the bacteria multiply unchecked within the macrophage. The bacteria also carried the UreC gene, which prevents acidification of the phagosome[1]. The bacteria also evade macrophage-killing by neutralizing reactive nitrogen intermediates[5].

The ability to construct M. tuberculosis mutants and test individual gene products for specific functions has significantly advanced our understanding of the pathogenesis and virulence factors of M. tuberculosis. Many secreted and exported proteins are known to be important in pathogenesis[9].

M. tuberculosis is genetically diverse, which results in significant phenotypic differences between clinical isolates. Different strains of M. tuberculosis are associated with different geographic regions. However, phenotypic studies suggest that strain variation never has implications for the development of new diagnostics and vaccines. Microevolutionary variation does affect the relative fitness and transmission dynamics of antibiotic-resistant strains[3].

Typing of strains is useful in the investigation of tuberculosis outbreaks, because it gives the investigator evidence for-or-against transmission from person to person. Consider the situation where person A has tuberculosis and believes that he acquired it from person B. If the bacteria isolated from each person belong to different types, then transmission from B to A is definitively disproved; on the other hand, if the bacteria are the same strain, then this supports (but does not definitively prove) the theory that B infected A.

MATERIALS AND METHODS

Sequence retrieval: The complete amino acids sequences for Mycobacterium tuberculosis were downloaded from the Peptidoglycan pathway of M.tuberculosis in KEGG (Kyoto Encyclopaedia of Genes and Genomes), PDB organism of NCBI protein.

Sequence alignment: Sequence homology has been used as a rapid approach to assign biological function to these proteins. They were subjected to a BLAST p search against non redundant database with e - value inclusion threshold set to 0.001. The search was restricted to proteins from Homo sapiens sapiens through an option available in BLAST program. Then DEG (database of essentials gene) were used to search homology with Homo sapiens sapiens.

RESULTS AND DISCUSSION

The Source Organism browser is a hierarchical representation of all organisms in the NCBI Taxonomy database (Taxonomy). All organisms which have structures in the PDB are listed as active links in the browser. These organisms are the source of the individual naturally-occurring polypeptides. The PDB source organism assignment is based on author/UniProtKB specified mapping of polypeptides.

Total protein 125 of Peptidoglycan pathway from M.tuberculosis strain (826) bacteria only from PDB organism was taken. 123 Proteins from pathway when aligned with human proteins by using Blastp were found nonhomolog. These proteins are aligned with essential proteins from DEG. These 115 non homologous essential proteins of M.tuberculosis are Target proteins.

REFERENCES

8. Jump up^ "Tuberculosis History Timeline". Retrieved 2010-06-18