



CLINICAL AND BIOLOGICAL PROFILE OF *MYCOBACTERIUM TUBERCULOSIS* (MTB) - A REVIEW

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ABSTRACT

Tuberculosis, MTB, or TB is a common, and in many cases lethal, infectious disease caused by various strains of mycobacteria, usually *Mycobacterium tuberculosis*. Tuberculosis typically attacks the lungs but can also affect other parts of the body. It is spread through the air when people who have an active TB infection cough, sneeze, or otherwise transmit their saliva through the air. Most infections are asymptomatic and latent, but about one in ten latent infections eventually progresses to active disease which, if left untreated, kills more than 50% of those so infected. *Mycobacterium tuberculosis* (MTB) is a pathogenic bacterial species in the genus *Mycobacterium* and the causative agent of most cases of tuberculosis (TB). 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. The aim of present article is to provide in depth knowledge about *Mycobacterium tuberculosis* and to study entire clinical and biological profile of *Mycobacterium tuberculosis*.

Keywords: Tuberculosis, MTB, TB, *Mycobacterium tuberculosis*, *Mycobacterium*.

INTRODUCTION

Tuberculosis, MTB, or TB is a common, and in many cases lethal, infectious disease caused by various strains of mycobacteria, usually *Mycobacterium tuberculosis*¹ (Fig.1, Fig.2 and Fig.3).



Figure 1: *Mycobacterium tuberculosis* (M. tuberculosis bacterial colonies)

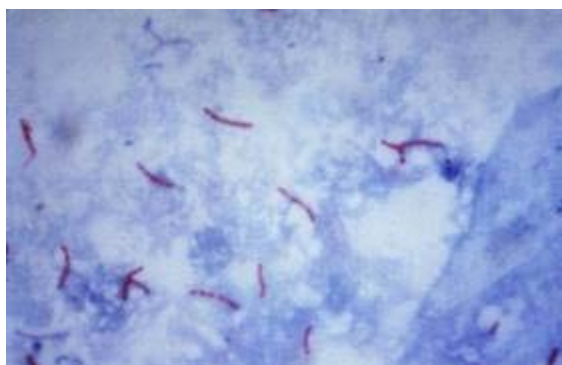


Figure 2: *Mycobacterium tuberculosis* (Ziehl-Neelsen Stain)



Figure 3: TEM micrograph of *Mycobacterium tuberculosis*

Tuberculosis typically attacks the lungs but can also affect other parts of the body. It is spread through the air when people who have an active TB infection cough, sneeze, or otherwise transmit their saliva through the air². Most infections are asymptomatic and latent, but about one in ten latent infections eventually progresses to active disease which, if left untreated, kills more than 50% of those so infected. The classic symptoms of active TB infection are a chronic cough with blood-tinged sputum, fever, night sweats, and weight loss. Infection of other organs causes a wide range of symptoms. Diagnosis of active TB relies on radiology as well as microscopic examination and microbiological culture of body fluids. Diagnosis of latent TB relies on the tuberculin skin test (TST) and/or blood tests. Treatment is difficult and requires administration of multiple antibiotics over a long period of time. Social contacts are also screened and treated if necessary. Antibiotic resistance is a growing problem in multiple drug-resistant tuberculosis (MDR-TB) infections. Prevention relies on screening programs and vaccination with the bacillus Calmette–Guérin vaccine.

An Introduction about *Mycobacterium tuberculosis*

Mycobacterium tuberculosis (MTB) is a pathogenic bacterial species in the genus *Mycobacterium* and the causative agent of most cases of tuberculosis (TB). 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, so 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. The *M. tuberculosis* genome was sequenced in 1998^{3,4}.

Patho-physiological features of *Mycobacterium tuberculosis*

M. tuberculosis requires oxygen to grow. It does not retain any bacteriological stain due to high lipid content in its wall, and thus is neither Gram-positive nor Gram-negative; hence Ziehl-Neelsen staining, or acid-fast staining, is used. 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.

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. 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 phagosome⁵. The bacteria also evade macrophage-killing by neutralizing reactive nitrogen intermediates⁶. 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 of *M. tuberculosis*. Many secreted and exported proteins are known to be important in pathogenesis.

Strain Variation

M. tuberculosis comes from the genus *Mycobacterium*, which is composed of approximately 100 recognized and proposed species. The most familiar of the species are *M. tuberculosis* and *M. leprae* (leprosy). *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. Micro evolutionary variation does affect the relative fitness and transmission dynamics of antibiotic-resistant strains. 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.

Until the early 2000s, *M. tuberculosis* strains were typed by pulsed field gel electrophoresis (PFGE)^{7,8}. This has now been superseded by variable numbers of tandem repeats (VNTR), which is technically easier to perform and allows better discrimination between strains. This method makes use of the presence of repeated DNA sequences within the *M. tuberculosis* genome. There are three generations of VNTR typing for *M. tuberculosis*. The first scheme, called ETR (exact tandem repeat), used only five loci⁹, but the resolution afforded by these five loci was not as good as PFGE. The second scheme, called MIRU (mycobacterial interspersed repetitive unit) had discrimination as good as PFGE^{10,11}. The third generation (MIRU2) added a further nine loci to bring the total to 24. This provides a degree of resolution greater than PFGE and is currently the standard for typing *M. tuberculosis*¹².

Hyper-virulent Strains

Mycobacterium outbreaks are often caused by hyper virulent strains of *M. tuberculosis*. In laboratory experiments, these clinical isolates elicit unusual immunopathology, and may be either hyperinflammatory or hypoinflammatory. Studies have shown the majority of hyper virulent mutants have deletions in their cell wall-modifying enzymes or regulators that respond to environmental stimuli. Studies of these mutants have indicated the mechanisms that enable *M. tuberculosis* to mask its full pathogenic potential, inducing a granuloma that provides a protective niche, and enable the bacilli to sustain a long-term, persistent infection.

Microscopy

M. tuberculosis is characterized by caseating granulomas containing Langhans giant cells, which have a "horseshoe" pattern of nuclei. Organisms are identified by their red color on acid-fast staining.

Genome

The genome of the H37Rv strain was published in 1998. Its size is 4 million base pairs, with 3959 genes; 40% of these genes have had their function characterized, with



possible function postulated for another 44%. Within the genome are also six pseudogenes.

The genome contains 250 genes involved in fatty acid metabolism, with 39 of these involved in the polyketide metabolism generating the waxy coat. Such large numbers of conserved genes show the evolutionary importance of the waxy coat to pathogen survival. About 10% of the coding capacity is taken up by two clustered gene families that encode acidic, glycine-rich proteins. These proteins have a conserved N-terminal motif, deletion of which impairs growth in macrophages and granulomas¹³. Nine noncoding sRNAs have been characterized in *M. tuberculosis*, with a further 56 predicted in a bioinformatics screen¹⁴.

History

M. tuberculosis, then known as the "tubercle bacillus", was first described on 24 March 1882 by Robert Koch, who subsequently received the medicine for this discovery in 1905; the bacterium is also known as "Koch's bacillus". 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.

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