Microbe Profile: *Mycobacterium tuberculosis*: Humanity’s deadly microbial foe

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Abstract

*Mycobacterium tuberculosis* is an expert and deadly pathogen, causing the disease tuberculosis (TB) in humans. It has several notable features: the ability to enter non-replicating states for long periods and cause latent infection; metabolic remodelling during chronic infection; a thick, waxy cell wall; slow growth rate in culture; and intrinsic drug resistance and antibiotic tolerance. As a pathogen, *M. tuberculosis* has a complex relationship with its host, is able to replicate inside macrophages, and expresses diverse immunomodulatory molecules. *M. tuberculosis* currently causes over 1.8 million deaths a year, making it the world’s most deadly human pathogen.
**TAXONOMY**

Phylum: Actinobacteria; Class: Actinobacteria; Order: Actinomycetales; family: Mycobacteriaceae; Genus: Mycobacterium; Species: M. tuberculosis.

**PROPERTIES**

*Mycobacterium tuberculosis* is a slow-growing, chemotrophic, non-motile, non-spore-forming, aerobic bacillus. Under optimal laboratory conditions at 37°C, *M. tuberculosis* doubles every 24 h, taking approximately 3 weeks to form buff-coloured, rough colonies on agar plates. It is visualized via the Ziehl–Neelsen acid-fast stain whereby its thick, waxy cell wall retains carbol fuschin stain in the face of acid-alcohol washes. Biochemical tests, including positive niacin production and the ability to reduce nitrate, are used to differentiate it from other mycobacteria, although these have been superseded in many cases by PCR-based analysis of specific genetic loci.

**GENOME**

*M. tuberculosis* H37Rv was the first mycobacterium to be genome sequenced [1], revealing a 4.4 Mb genome encoding 4018 genes and a high GC% content of 65.9 %. Major findings included the discovery of two large protein families with over 160 members that present conserved N-terminal domains containing either proline-glutamine (PE) or proline-proline-glutamine (PPE) and variable C-terminal domains. PE and PPE proteins have diverse functions, with distinct members playing roles in lipid metabolism, cell wall architecture and immune modulation. Over 9 % of the genome’s coding capacity is dedicated to lipid metabolism, underlining the metabolic demands for synthesis of the complex, lipid-rich mycobacterial cell wall as well as the exploitation of host lipids for *in vivo* carbon sources. Five ESX Type VII secretion systems are present and involved in secretion of PE/PPE proteins, virulence effectors, T-cell antigens and metal homeostasis. Genome-wide mutagenesis studies have identified ~600 genes that are essential for *M. tuberculosis* growth *in vitro* [2], with numerous other studies suggesting conditionally-essential genes for other conditions.

**PHYLOGENY**

*M. tuberculosis* is the type strain of the *M. tuberculosis* complex (MTBC), the group of mycobacterial pathogens that cause TB in mammalian species. The MTBC also includes the human pathogen *M. africanum*, as well as animal-adapted strains *M. microti, M. pinnipedii, M. orygis, M. mungi, M. caprae* and *M. bovis*. Comparative genomic analyses revealed low sequence diversity and clonal evolution across the MTBC, with the sequential loss of regions of difference (RD) suggesting an evolutionary scenario that places *M. tuberculosis* closest to the common ancestor of the MTBC. Whole genome sequencing of global *M. tuberculosis* populations has revealed seven major lineages with distinct geographical localization that reflect human migration patterns [3]. Estimates for the age of the most recent common ancestor of the MTBC vary from 70 000, based on genome analysis of extant strains [3], to <6000 years ago using ancient DNA extracted from Peruvian and Hungarian mummies with characteristic TB lesions.

**KEY FEATURES AND DISCOVERIES**

*M. tuberculosis* was first described as the causative agent of tuberculosis by Robert Koch in 1882 – on 24th March (now World TB Day) [4]. *M. tuberculosis* is an extraordinarily successful pathogen with a long history of afflicting humans. Disease progression is a complex process, with only a small proportion of people exposed becoming infected, and of those the majority having latent infection during which the bacteria may persist for decades in a metabolically inactive, or slowly replicating, state. Estimates are that almost 2 billion people are latently infected, providing a global reservoir of infection. Infection normally results in granuloma formation around the initial focus of infection, and can lead to caseous lesions and cavity formation in active disease. Several complex regulatory programs mediated by master genetic regulators are involved in switching into this non-replicating state that can persist for long periods of time.

During infection, the basic metabolism of *M. tuberculosis* is geared towards utilization of fatty acids such as cholesterol, and hence the glyoxylate shunt becomes important for *in vivo* survival. Although *M. tuberculosis* is a prototroph, it is likely that a range of metabolites are available to be scavenged during infection, and some acquisition systems, such as the iron siderophore mycobactin, are well characterized.

The cell wall of *M. tuberculosis* is characteristic of the mycobacteria; although classified as Gram-positive, it has a structure similar to that of Gram-negative bacteria with a second ‘outer membrane’ containing the mycolic acids – long-chain, branched fatty acids. The layer outside the cytoplasmic membrane forms a major complex, with the core comprising peptidoglycan linked to arabinogalactan, in turn linked to the mycolic acids (mAGP complex) [5]. In addition to imparting many important characteristics such as relative impermeability to antibiotics, the cell wall contains myriad immunomodulatory molecules including lipoarabinomannan, sulpholipids and phthiocerol dimycocerosate. Cord factor (trehalose dimycolate) is required for virulence and responsible for the characteristic growth of *M. tuberculosis* in culture as long, snake-like cords. The elaborate cell wall is however the Achilles heel of the bacillus, since its synthesis is the target of several frontline anti-tubercular drugs (isoniazid, ethambutol, ethionamide).

A defining feature of *M. tuberculosis* is its slow growth rate. While the metabolic reasons underlying slow growth are not fully understood, it may be due to a combination of: the presence of only a single rRNA operon; the complex...
synthetic requirements of the cell wall; nutrient uptake; and a slow rate of DNA replication.

**OPEN QUESTIONS**

Many basic questions still perplex mycobacteriologists, including:

- What were the key steps in the evolution of *M. tuberculosis* as a human pathogen?
- What pathogen factors are essential to establish latent infection and ultimate disease?
- Is the slow killing of *M. tuberculosis* by bactericidal antibiotics simply related to its slow growth, or are other factors responsible?
- What is the physiological state of *M. tuberculosis* during infection? What are the key metabolites that *M. tuberculosis* scavenges from the host?
- How can we optimally mine *M. tuberculosis* to identify novel antigens for the next generation of diagnostics and vaccines?

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**Conflicts of interest**

The authors declare that there are no conflicts of interest.

**References**


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