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Mycobacterial Tuberculosis Epidemiology and Pathogenesis

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Review Article

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Abstract

Mycobacterium tuberculosis (MTB) is an acid fast bacterium (AFB); it has tough cell wall and circular chromosome. It is transmitted through the airborne route and cause tuberculosis (TB). The distribution of tuberculosis is not uniform across the globe; about 80% of the population in many Asian and African countries and it is the second most common cause of death from infectious disease after HIV. Organisms deposited mainly in the upper lung zones, kidneys and bones. In persons with intact cell-mediated immunity (CMI), collections of activated T cells and macrophages form granulomas that limit multiplication and spread of the organism. The Status of CMI will determine if the patient will get active or latent TB infection.

Keywords: MTB; AFB; TB; CMI; Granuloma; Latent; Active

Introduction

Tuberculosis (TB) is an infection caused by the rod-shaped, non–spore-forming, aerobic bacterium *Mycobacterium tuberculosis* (*MTB*) [1]. Tuberculosis has recently remerged as a major health concern. Each year, approximately 2 million persons worldwide die of tuberculosis and 9 million become infected. The prevalence of tuberculosis is continuing to increase because of the increased number of patients infected with human immunodeficiency virus (HIV), bacterial resistance to medications, increased international travel and immigration from countries with high prevalence, and the growing numbers of the homeless and drug abusers [2].

Mycobacterium TB (MTB)

Description and Significance

M. tuberculosis is an acid fast bacterium (AFB), which can form acid-stable complexes when certain arylmethane dyes are added. All species of mycobacteria have rope like structures of peptidoglycan that are arranged in such a way to give them properties of an acid fast bacteria [3]. Mycobacteria are abundant in soil and water, but *MTB* is mainly identified as a pathogen that lives in the host. Some species in its *MTB* complex have adapted their genetic structure specifically to infect human populations [4].

Cell Structure and Metabolism

MTB has a tough cell wall that prevents passage of nutrients into and excreta from the cell, therefore giving it the characteristic of slow growth rate. The cell wall of the pathogen looks like a Gram-positive cell wall. The cell envelope contains a polypeptide layer, a peptidoglycan layer, and free lipids. In addition, there is also a complex structure of fatty acids such as mycolic acids that appear glossy. The *MTB* cell wall contains three classes of mycolic acids: alpha-, keto- and methoxymycolates. The cell wall also contains lipid complexes including acyl glcolipids and other complex such as free lipids and sulfolipids. There are porins in the membrane to facilitate transport. Beneath the cell wall, there are layers of arabinogalactan and peptidoglycan that lie just above the plasma membrane [5]. The *MTB* genome encodes about 190 transcriptional regulators, including 13 sigma factors, 11 two-component system and more than 140 transcription regulators. Several regulators have been found to respond to environmental distress, such as extreme cold or heat, iron starvation, and oxidative stress [6]. To survive in these harsh conditions for a prolonged period in the host, *MTB* had learned to adapt to the environment by allowing or inhibiting transcription according to its surroundings [7].

Genome Structure

MTB has circular chromosomes of about 4,200,000 nucleotides long. The G+C content is about 65% [8]. The genome of *MTB* was studied generally using the strain *MTBH37Rv*. The genome contains about 4000 genes. Genes that code for lipid metabolism are a very important part of the bacterial genome, and 8% of the genome is involved in this activity [9].

The different species of the *MTB* complex show a 95-100% DNA relatedness based on studies of deoxynucleic acid (DNA) homology, and the sequence of the 16S ribosomal ribonucleic acid (rRNA) gene are exactly the same for all the species. So some scientists suggest that they should be grouped as a single species while others argue that they should be grouped as varieties or subspecies of *MTB* [10].

Plasmids in *MTB* are important in transferring virulence because genes on the plasmids are more easily transferred than genes located on the chromosome. One such 18kb plasmid in the *MTB H37Rv* strain was proven to conduct gene transfers [11].

Immunodominant Protein Antigens of *M. Tuberculosis*

The immunodominant T cell antigens recognized by *M. tuberculosis* infected humans or animals are mostly secreted proteins, including such well-studied examples as ESAT-6, CFP-10 and the Ag85 family of mycolyltransferases, Mtb32a, Mtb9.8, Mtb8.4, TB10.4 and lipoproteins such as the 19-kDa and 38-kDa antigens [12-14]. Many of these antigens are currently being studied as components of new candidate vaccines and there is clear evidence for their presentation to T cells by the MHC class I and class II pathways. Infection with *M. tuberculosis* can generate strong immune responses against a relatively limited number of epitopes of these immune dominant secreted protein antigens early in the course of infection. This has been observed for antigens such as ESAT-6 and Ag85B, which are secreted early after infection and tend to dominate as targets of the T cell responses in experimentally infected animals or humans with naturally acquired tuberculosis. On the other hand, T cell responses to cytosolic non-secreted proteins have generally been found to be absent or weak in infected animals, although cellular and humoral responses have occasionally been reported to these [15-17].

Mycobacterial Lipids and Other Nonpeptide Antigens Of *M. Tuberculosis*

Mycobacteria produce many unique lipids and glycolipids, and some of these have been found to be specific T cell antigens that are presented by MHC class I-like CD1 molecules. In humans, there are five forms of CD1, and three of these (CD1a, CD1b and CD1c – the so-called group 1 CD1 proteins) have been shown to present mycobacterial lipids and glycolipids [18]. A major subset of human γδ T cells is well documented to be responsive to low molecular weight non-peptidic antigens produced by *M. tuberculosis* and many other bacteria. The specific antigens that have been identified are primarily intermediates produced by pathways of isoprene biosynthesis, and include isopentenyl pyrophosphate (IPP) and 4-hydroxy-3-methyl-but-2-enyl pyrophosphate (HMBPP) [19,20]. The mechanism by which such small alkyl phosphate compounds are presented to γδ T cells remains unknown, although it is believed that the known MHC and CD1 antigen presenting molecules are not involved [21].

Tuberculosis (TB)

Epidemiology Of Tuberculosis

- Roughly one-third of the world's population has been infected with MTB, and new infections occur at a rate of one per second [22]. However, not all infections with MTB cause TB disease and many infections are asymptomatic [23]. In 2007 there were an estimated 13.7 million chronic active cases and in 2010 there were 8.8 million new cases, and 1.45 million deaths, mostly in developing countries. The number of death was 0.35 million occur in those co-infected with HIV. In 2014 there were an estimated 9.6 million people fell ill with TB and 1.5 million died from the disease [24,25].
- Over 95% of TB deaths occur in low- and middle-income countries, and it is among the top 5 causes of death for women aged 15 to 44 [26].
- In 2014, an estimated 1 million children became ill with TB and 140 000 children died of TB [25].
- The Millennium Development Goal target of halting and reversing the TB epidemic by 2015 has been met globally. TB incidence has fallen by an average of 1.5% per year since 2000 and is now 18% lower than the level of 2000.
- The TB death rate dropped 47% between 1990 and 2015.
- An estimated 43 million lives were saved through TB diagnosis and treatment between 2000 and 2014 [27].

TB is the second most common cause of death from infectious disease after HIV [28]. The absolute number of TB cases has been decreasing since 2005 and new cases since 2002. China has achieved particularly dramatic progress, with an 80 percent decline in its TB mortality rate [29]. The distribution of tuberculosis is not uniform across the globe; about 80% of the population in many Asian and African countries test positive in tuberculin tests, while only 5-10% of the United States (U.S). Population test positive [30]. In 2007, the country with the highest estimated incidence rate of TB was Swaziland, with 1200 cases per 100,000 people. As of 2014, India has the largest total incidence, with an estimated 2.2 million new cases. India has more than 0.3 million deaths and economic losses of $23 billion every year [31].

In developed countries, tuberculosis is less common and is mainly an urban disease. In the United Kingdom, the national average was 15 per 100,000 in 2007, and the highest incidence rates in Western Europe were 30 per 100,000 in Portugal and Spain. These rates compared with 98 per 100,000 in China and 48 per 100,000 in Brazil. In the United States, the overall tuberculosis case rate was 4 per 100,000 persons in 2007 [24]. In Canada, tuberculosis is still endemic in some rural areas.

The incidence of TB varies with age. In Africa, TB primarily affects adolescents and young adults [32]. However, in countries where TB has gone from high to low incidence, such as the United States, TB is mainly a disease of older people, or of the immune compromised [30]. TB incidence is seasonal, with peaks occurring every spring/summer [26]. The reasons for this are unclear, but may be related to vitamin D deficiency during the winter [33].

In 2010, the estimated number of prevalent TB cases in the World Health Organization (WHO) Eastern Mediterranean Region was 1 000 000 (670 000-1 500 000). The estimated number of incident TB cases in 2010 was 650 000 (580 000–730 000), accounting for 7% of the global TB burden. Nine countries contribute 95% of the TB burden in the Region in 2010. These are Pakistan, Afghanistan, Sudan, Morocco, Somalia, Iraq, Egypt, Islamic Republic of Iran and Yemen. Pakistan alone shoulders 61% the TB burden of the Region [29].

The incidence of tuberculosis (per 100,000 people) in Egypt was 15 in 2014. Incidence of tuberculosis (per 100,000 people) in Egypt was last measured at 16 in 2013, according to the World Bank. The value for incidence of tuberculosis (per 100,000 people) in Egypt was 17 as of 2011. Over the past 21 years, the value for this indicator has fluctuated between 34.00 in 1992 and 17.00 in 2011. Incidence of tuberculosis is the estimated number of new pulmonary, smear positive, and extra-pulmonary tuberculosis cases (Figure 1).

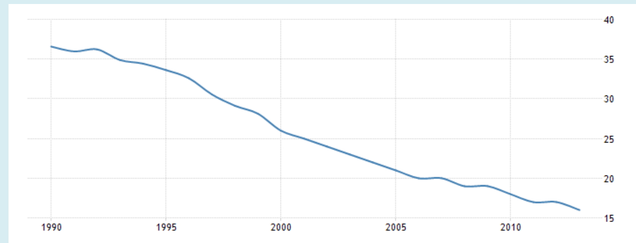

Figure 1: Incidence of TB (per 100,000 people) in years between 1990 till 2014 (34).

Ten countries had reduced their TB burden to rates below 25 per 100 000 populations in 2010, compared to only one country in 1990. The estimated number of TB deaths in 2010 was 95 000 (74 000–120 000) [34].

Transmission of Mycobacterium Tuberculosis

There are five closely related mycobacteria grouped in the M. tuberculosis complex: M. *tuberculosis, M. bovis, M. africanum, M. microti, and M. canetti* [35]. TB is transmitted through the airborne route and there are no known animal reservoirs [36]. Airborne transmission of both *M. bovis* and *M. africanum* can also occur [37].

Tuberculosis is spread from person to person through the air by droplet nuclei, particles 1 to 5 μm in diameter that contain *M. tuberculosis* complex [38]. Droplet nuclei are produced when persons with pulmonary or laryngeal tuberculosis cough, sneeze, speak, or sing. They also may be produced by aerosol treatments, sputum induction, aerosolization during bronchoscopy, and through manipulation of lesions or processing of tissue or secretions in the hospital or laboratory. Droplet nuclei, containing two to three MTB organisms are so small that air currents normally present in any indoor space can keep them airborne for long periods of time. Droplet nuclei are small enough to reach the alveoli within the lungs, where the organisms replicate. Organisms deposited on intact mucosa or skin does not invade tissue [39,40].

When large particles are inhaled, they impact on the wall of the upper airways, where they are trapped in the mucous blanket, carried to the oropharynx, and swallowed or expectorated [40].

Four factors determine the likelihood of transmission of *MTB*: the number of organisms being expelled into the air, the concentration of organisms in the air determined by the volume of the space and its ventilation, the length of time an exposed person breathes the contaminated air, and presumably the immune status of the exposed individual

[41]. HIV-infected persons and others with impaired cell-mediated immunity are thought to be more likely to become infected with *MTB* after exposure than persons with normal immunity. Also, they are much more likely to develop disease. However, they are no more likely to transmit *MTB* [42].

Techniques that reduce the number of droplet nuclei in a given space are effective in limiting the airborne transmission of tuberculosis. Ventilation with fresh air is especially important, particularly in health care settings, where six or more room-air changes an hour is desirable [43]. The number of viable airborne tubercle bacilli can be reduced by ultraviolet irradiation of air in the upper part of the room [44]. The most important means to reduce the number of bacilli released into the air is by treating the patient with effective anti-tuberculosis chemotherapy. If masks are to be used on coughing patients with infectious tuberculosis, they should be fabricated to filter droplet nuclei and molded to fit tightly around the nose and mouth. Measures such as disposing of such personal items as clothes and bedding, sterilizing fomites, using caps and gowns and gauze or paper masks, boiling dishes, and washing walls are unnecessary because they have no bearing on airborne transmission [40].

Pathogenesis of Tuberculosis

After inhalation, the droplet nucleus is carried down the bronchial tree and implants in a respiratory bronchiole or alveolus. Whether or not an inhaled tubercle bacillus establishes an infection in the lung depends on both the bacterial virulence and the inherent microbicidal ability of the alveolar macrophage that ingests it [45]. If the bacillus is able to survive initial defenses, it can multiply within the alveolar macrophage. The tubercle bacillus grows slowly, dividing approximately every 25 to 32 h within the macrophage [46]. *MTB* has no known endotoxins or exotoxins; therefore, there is no immediate host response to infection. The organisms grow for 2 to 12 week, until they reach 10^3 to 10^4 in number, which is sufficient to elicit a cellular immune response that can be detected by a reaction to the tuberculin skin test [40].

Before the development of cellular immunity, tubercle bacilli spread via the lymphatics to the hilar lymph nodes and then through the bloodstream to more distant sites. Certain organs and tissues are notably resistant to subsequent multiplication of these bacilli. The bone marrow, liver, and spleen are almost always seeded with mycobacteria, but uncontrolled multiplication of the bacteria in these sites is exceptional. Organisms deposited in the upper lung zones, kidneys, bones, and brain may find environments that favor their growth, and numerous bacterial divisions may occur before specific cellular immunity develops and limits multiplication [40].

In persons with intact cell-mediated immunity, collections of activated T cells and macrophages form granulomas that limit multiplication and spread of the organism [47]. Antibodies against *M. tuberculosis* are formed but do not appear to be protective. The organisms tend to be localized in the center of the granuloma, which is often necrotic [48]. For the majority of individuals with normal immune function, proliferation of *M. tuberculosis* is arrested once cell-mediated immunity develops, even though small numbers of viable bacilli may remain within the granuloma [49]. Although a primary complex can sometimes be seen on chest radiograph, the majority of pulmonary tuberculosis infections are clinically and radio graphically in apparent. Most commonly, a positive tuberculin skin test result is the only indication that infection with *MTB* has taken place. Individuals with latent tuberculosis infection but not active disease are not infectious and thus cannot transmit the organism [50].

It is estimated that approximately 10% of individuals who acquire tuberculosis infection and are not given preventive therapy will develop active tuberculosis. The risk is highest in the first 2 year after infection, when half the cases will occur. The ability of the host to respond to the organism may be reduced by certain diseases such as silicosis, diabetes mellitus, and diseases associated with immunosuppression, e.g., HIV infection, as well as by corticosteroids and other immunosuppressive drugs [51,52]. In these circumstances, the likelihood of developing tuberculosis disease is greater. The risk of developing tuberculosis also appears to be greater during the first 2 year of life [53].

HIV-infected persons, especially those with low $CD4^+$ cell counts, develop TB disease rapidly after becoming infected with *MTB*; up to 50% of such persons may do so in the first 2 year after infection with *MTB* [51]. Conversely, an individual who has a prior latent infection with *M. tuberculosis* (not treated) and then acquires HIV infection will develop tuberculosis disease at an approximate rate of 5–10% per year [29].

In a person with intact cell-mediated immunity, the response to infection with the tubercle bacillus provides protection against reinfection. The likelihood of reinfection is a function of the risk of re exposure, the intensity of such exposure, and the integrity of the host's immune system. In a healthy, previously infected person, any organisms that are deposited in the alveoli are likely to be killed by the cell-mediated immune response. Exceptions may occur, but in immune competent individuals, clinical and laboratory evidence indicates that disease produced by the inhalation of a second infecting strain is uncommon. However, reinfection has been documented to occur both in persons without recognized immune compromise and in persons with advanced HIV infection [40].

Clinical Classification of Tuberculosis

Tuberculosis is divided into 2 clinically important categories:

Active Tuberculosis

In active tuberculosis (ATB) the host is infected with the bacterium that causes TB. In people with active TB, the body's immune system is unable in eliminating or corralling the pathogens. In this type of TB, TB bacterium rapidly multiplies and invades different organs of the body. A person with active TB disease may spread TB to others by airborne transmission of infectious particles when they are coughed sneezed or spited into the air [42].

Latent Tuberculosis Infection (LTBI)

Persons with LTBI have MTB in their bodies, but do not have TB disease and cannot spread the infection to other people. A person with LTBI is not regarded as having a case of TB. The process of LTBI begins when extracellular bacilli are ingested by macrophages and presented to other white blood cells. This triggers the immune response in which white blood cells kill or encapsulate most of the bacilli, leading to the formation of a granuloma [54,55]. At this point, LTBI has been established. LTBI may be detected by using the tuberculin skin test (TST) or an interferon-gamma release assay (IGRA). It can take 2 to 8 weeks after the initial TB infection for the body's immune system to be able to react to tuberculin and for the infection to be detected by the TST or IGRA within 6 weeks after infection, the immune system is usually able to halt the multiplication of the tubercle bacilli, preventing further progression [45] (Figure 2).

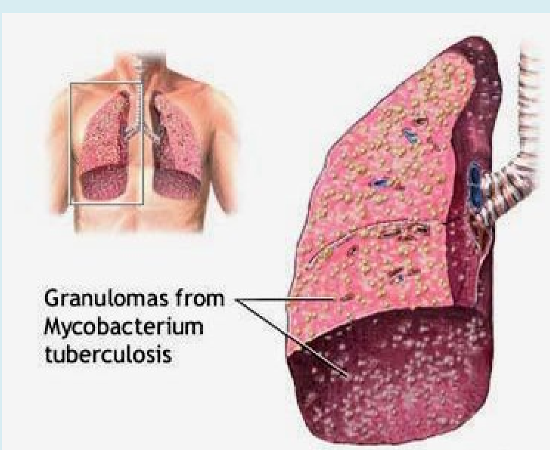

Figure 2: Latent Tuberculosis Infection (LTBI) (56).

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