

## A Review: History, Structure, Diagnosis and Treatment of Tuberculosis Disease

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Received Date: May 14, 2018; Accepted Date: June 5, 2018; Published Date: June 12, 2018

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### Abstract

In the present scenario, tuberculosis is of the most infectious disease which is caused when *Mycobacterium tuberculosis* gets encountered into the body. Tuberculosis being a communicable disease or transferrable disease, it is easily passed down to other person who remains in contact to the infected person by the process of inhaling air droplets carrying that particular bacteria. Tuberculosis mainly affects the lungs, but it can also affect the other organs. When this bacteria encounters in the body, the immune cells checks and control pathogen. However this disease remains latent but can become active at any time after some years when the particular immune system is weakened. If this disease is not treated at that time, then this disease can also become life- threatening illness.

**Keywords:** Tuberculosis; Mycolic acid; Mycobacterial; Immune system

### Introduction

In the present scenario, *M. tuberculosis* is infecting about one third of world's population and the disease known as Tuberculosis or TB is caused by this bacterium [1]. The disease is transmitted through aerosols, and enters the pulmonary system by inhalation [2]. Droplets are produced by other person suffering from pulmonary tuberculosis. Many children also get infected by *M. tuberculosis* due to staying close to adults suffering from TB. The disease leads to development of primary parenchymal lesions in lung which also spreads to lymph nodes. The risk of this type is mostly seen in young children. During earlier days tuberculosis disease was one the reason for many deaths especially in settings with poor sanitation and high population density [3].

Historical texts also identify this disease as "consumption" and "phthisis" which was based on clinical manifestation [4]. This Mycobacterium is also found in Egyptian mummies from 2000 B.C. [5]. Tuberculosis not only affects the lungs of the body it also affects the bones, central nervous system and many other organs of the body but this disease mainly results from the deposition of *M. tuberculosis* which are already present in aerosol droplets in alveolar surfaces of lungs. Diagnosis is done by acid fast staining in smears. So, man is constantly fighting tuberculosis since ancient times [6]. New vaccines and effective drugs are introduced in market which helps the patients to recover as early as possible. While developing antituberculosis drugs it is very much necessary to know about the physiology of *M. tuberculosis* and to know about the mechanism how it causes disease. In present scenario genes and their respective proteins are purified so as to identify new bacterial targets which can be used for creating vaccines and drugs [7].

*M. tuberculosis* is large non-motile rod shaped bacterium. The length of rod is near about 2-4  $\mu\text{m}$  and width is 0.2-0.5  $\mu\text{m}$ . They require oxygen as they cannot respire anaerobically also known as

obligate aerobe. This bacterium is a facultative intracellular parasite. It divides slowly taking approximately 15- 20 hours. These bacteria are known as acid fast bacteria as these bacteria can form acid stable complexes with acrylmethane dye when added [8] *Mycobacterium* spp. are having thick peptidoglycan layer with lipid rich layer present on outer surface of the cell which give them the property of acid fastness [9]. Cell surface of *M. tuberculosis* is having waxy coating due to presence of mycolic acid which makes this bacterium acid fast bacterium. Genomic size is 4.4 Mb having 65% GC content, it contains 3959 genes in which only 40% of genes are functional 60% are non-functional. The most important part of the bacterial genome is the genes coding for lipid metabolism [10]. There are many mycobacterial species that have been recognized as zoonoses, which are as follows:

- *M. bovis*- which essentially infects cattle, sheep, goats and deer etc.
- *M. tuberculosis*- infects primates, elephants, aquatic mammals, horses, pigs, cattle and deer.
- *M. avium*- which essentially infects pigs and poultry. Other hosts include cattle, sheep, goats, deer/antelope, marsupials, primates and horses.
- *M. paratuberculosis* -which affects a broad range of domestic and non-domestic ruminant species.
- *M. intracellulare*- which infects amphibians, reptiles, birds including domestic poultry, marsupials, primates, pigs and cattle.
- *M. chelonae*- which causes lesions in fish, reptiles, aquatic mammals, and also in primates, pigs and cattle.
- *M. fortuitum*- which is essentially linked to disease in amphibians, primates and pigs.
- *M. lepraemurium*- which is also called as the rat leprosy bacillus which essentially infects rodents.
- *M. marinum*- the causative agent of fish-tank or fish-breeder granuloma which affects people in contact with tropical fish, a causative agent of lesions in fish and molluscs.
- *M. microti* - essentially a pathogen of small rodents; also causes disease in hedgehogs and voles.
- *M. scrofulaceum* - cattle, buffaloes and pigs.

- *M. xenopi* - amphibians and pigs.

*M. tuberculosis* infection involves inhalation of tubercle bacilli as droplets when they are released in the atmosphere due to coughing or sneezing of infected persons and taken-up by the alveolar macrophages [11].

## History of Tuberculosis

Tuberculosis is one of the oldest disease which was also reported in ancient times. *M. tuberculosis* has killed more than any other microorganism. Genus Mycobacterium has originated from last 150 million years ago [12]. In present scenario many techniques are coming in the field of molecular genetics which allow good estimate of the time of origin of mycobacteria, this estimation uses the mutation rate of *M. tuberculosis* [13]. Modern members of *M. tuberculosis* complex include *M. africanum* and *M. canettii* as well as *Mycobacterium bovis*, which all emerged from a common African ancestor about 35,000-15,000 years ago [14]. The modern strains of tuberculosis have originated about 20,000-15,000 years ago [15]. Strains of *M. tuberculosis* which are seen in day to day life are in East Africa [16]. The known mutation rate indicates diversity of *M. tuberculosis* strains originated between 250 and 1000 years ago [17] and these bacteria came in existence in East Africa. This is why East Africa is known as the home for tubercle bacilli. In Egypt skeletal abnormalities of tuberculosis were seen in Egyptian mummies, which were characteristics of the Pott's deformities. DNA of *M. tuberculosis* was amplified from the tissues of Egyptian mummies which showed the sign of skeletal disease. Skeletal bones can be kept for thousands of year.

Earlier disease tuberculosis was known with the word *Sanskritam* (Sanskrit) and in ancient Indian scriptures tuberculosis was referred as *Yakshma* (meaning wasting disease). In English literature the word consumption has been used to describe tuberculosis, so the word tuberculosis is derived from the Latin word *tubercula* (meaning "a small lump"). In year 1553 "Fracastorius" believed that tuberculosis was a contagious disease. In 1720, Benjamin Marten concluded that tuberculosis was caused by species which were minute wonderful living creatures. In 1882, Robert Koch announced the discovery of tubercle bacillus. After this *M. tuberculosis* was known as the organism which causes disease known as tuberculosis and hence 24th March is celebrated as "World Tuberculosis Day" throughout the world. Wilhelm Conrad Roentgen discovered the X-rays and facilitated radiographic visualization, which showed tuberculosis in living persons. In mid 1940 drugs like streptomycin, para-amino salicylic acid (PAS) and isoniazid were used in effective treatment of tuberculosis. In 1970s tuberculosis started spreading in India which created public health problem. Initially it was thought that some 10,000 to 25,000 years ago mycobacterial pathogen was transferred from livestock to human beings and mycobacteria adapted to new environment in new host and *M. tuberculosis* evolved from it. Later it was found that *M. bovis* causes tuberculosis in cattle [18].

## Cell wall of *M. tuberculosis*

*M. tuberculosis* cell wall is characterized by complex structure caused by chemical composition which is very different from other bacteria [19]. This complex structure of cell wall makes the organism resistant to many drugs [20]. The cell wall of mycobacteria is composed of inner layer and outer layer [21]. Outer layer contains lipids and proteins [22]. Inner layer consists of peptidoglycan,

arabinogalactan, mycolic acid which is covalently linked to form a complex structure which extends from plasma membrane from outer layer to mycolic acid [23]. Mycolic acid is long chain fatty acids that are covalently bound to arabinogalactam peptidoglycan co-polymer [24]. Peptidoglycan forms the backbone of cell wall.

## Role of mycolic acid in cell wall of *M. tuberculosis*

Mycolic acids are made-up of long alkyl side chain and hydroxyl fatty acid. Mycolic acids can be characterized as methoxy or keto mycolic acids. Mycolic acids are cis-dicyclopropyl fatty acids. Mycolic acid can be divided in two classes depending on structure, which are as follows:

- i) Length of terminal alkyl group
- ii) Number of methylene groups between cyclopropane rings and carboxyl group [25].

## The immunology of tuberculosis

*M. tuberculosis* (*Mtb*) infection is followed by adaptive immune responses in comparison to other infections [26]. Present studies have shown that *Mtb* possess unique ability to establish infection while delaying onset of adaptive response by 2-3 weeks. Genetically engineered animals are used as they are having T-cell receptors which are specific for *Mtb* antigens, and responses are seen in lymph nodes of lungs and *Mtb* infected cells are transported from lungs to lymph node [27]. The mechanism which is involved in *Mtb* presenting cells to naive T- cells is still unknown [28]. *Mtb* can stop the migration of cells from lungs to lymph nodes. Also, formation of central caseous necrotic lesions involves extracellular *Mtb* [29]. *Mtb* is capable of persisting inside the host cells by different immune evasion strategies:

- Inhibiting phagosome maturation
- Inhibiting autophagy
- Inhibiting apoptosis
- Egression in cytosol
- Blocking up of MHC antigen processing and presentation
- Inhibition of IFN $\gamma$ - receptor signaling

This helps *Mtb* to evade host defence system [30]. When *Mtb* starts depositing into the lungs in the initial phase, different types of immune cells including macrophages are recruited at early phase of response to infection which results in the formation of granulomas. These granulomas are the highly dynamic structures from which cells can show rapid influx and efflux. After innate immune response, adaptive immune system gets activated and T lymphocytes start infiltrating granuloma. This forms large solid granuloma where *Mtb* are located centrally. If there is no control of infection then regions of granuloma become necrotic and further caseous formation occurs [31]. Granuloma starts liquefying and gets discharged in the airways. This is the stage at which the tuberculosis has become contagious. Vaccines are essential to get protection from TB [32].

## Diagnosis of tuberculosis infection

- **Latent Tuberculosis:** Latent phase infection can be diagnosed by tuberculin skin test or through interferon gamma release assay (IGRA).
- **Active Tuberculosis:** Methods which are used to diagnose the active phase tuberculosis are through sputum microscopy and by

culturing. A new technique based on molecular diagnostic approach using sputum is called as Xpert MTB/RIF assay.

- **Drug Susceptibility Testing:** First line drug susceptibility test is performed using liquid culture system which requires 4 to 13 days for the result. Early result within 24 hours can be achieved by molecular line probe assay and within 2 hours using Xpert MTB/RIF assay gives the result for rifampicin resistance [33].

## Prevention of tuberculosis

**1. Bacillus Calmette Guerin (BCG) vaccine:** Bacillus Calmette Guerin (BCG) vaccine is most widely used vaccine for tuberculosis. It can protect against severe forms of tuberculosis in children [7]. It is made from the live attenuated *M. bovis* BCG strain of bacterium. This strain is related to *M. bovis* strain which causes TB in cattle [34].

**2. Drug resistance tuberculosis (MDR-TB):** Drug resistance in tuberculosis disease is one of the major problems being faced in combating tuberculosis. MDR stands for multi drug resistant which is defined as disease which is caused by mycobacteria resistant to two most effective antituberculosis drugs isoniazid and rifampicin. These drugs are used as first line treatment of tuberculosis [35].

**3. Drug resistant tuberculosis (XDR-TB):** XDR-TB stands for extensive drug resistance which develops resistance to two most important drugs isoniazid and rifampin as well as to one member of fluoroquinolone family and also to one of the injectables (capreomycin, amikacin or kanamycin) [35].

## Conclusion

The disease Tuberculosis is the airborne disease which is caused by *M. tuberculosis* which affects lungs and the symptoms which are seen are cough, fever, chest pain. The vaccine which is named as Bacillus Calmette Guerin has been resulted as one of the most effective treatment for preventing the person from tuberculosis. Many antibiotics of different levels are being used to treat tuberculosis. So as to protect the body against encountering of such bacteria, different new technologies are being used for developing the vaccines against tuberculosis.

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