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Mycobacterial Lipid Exploitation using Nanotechnology for Diagnosis, Vaccines, and Biomarkers

Divya Singh*

MSc Microbiology, Kalinga Institute of Industrial Technology, Bhubaneswar, Odisha, India

Correspondence to: Divya Singh, MSc Microbiology, Kalinga Institute of Industrial Technology, Bhubaneswar, Odisha, India; E-mail: puchky.divya24@gmail.com

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Introduction

The *Mycobacterium tuberculosis* complex (MTBC) is a collection of closely related acid-fast bacilli that cause occasional interspecific infections in a variety of hosts. As the number of cases and fatalities from COVID-19 diminishes, tuberculosis (TB), the worst illness in the history of humanity, is once again the globe's number one infectious illness killer. For the first time in a decade, there were more TB fatalities, but there were also fewer diagnoses, reports, and treatments than predicted [1]. The intricacy of *M. tuberculosis*'s life cycle is one of the main barriers to TB control. However, under immunosuppressive circumstances, the infected nodule transforms into a highly contagious respiratory illness. In most people, *M. tuberculosis* infection is successfully controlled within a pulmonary granuloma, resulting in a dormant phase that can last decades or until death [2]. *M. tuberculosis* was identified more than a century ago, and tools to prevent, diagnose, and treat the disease in its many stages are lacking. On the other hand, *M. tuberculosis* is the only species associated with human tuberculosis; the closely related species, namely *M. africanum*, *M. canetti*, *M. bovis*, and *M. caprae,* are increasingly detected in human TB cases in different countries, and phenotypic studies have investigated the functional consequences of these genomic variants, including pathogen metabolism, clinical characteristics, and transmission dynamics. SNPs in the pykA gene and enogens in the MAF gene are related to the L6 preference for pyruvate as a carbon source. The observation that some sublineages of modern lineages, like L4 and L2, can be more pathogenic and infectious than ancient lineages, like MAF lineages, which are geographically restricted, can be used to support this idea. Some strains of MTBC have also been linked to significant outbreaks, while others are less virulent in specific host populations, confirming the importance of strain diversity in pathogenicity.

M. tuberculosis, which has surpassed the hepatitis C virus as the leading cause of mortality from infectious illnesses, continues to be one of the top 10 killers globally despite huge improvements in biomedical research. Huge efforts have been undertaken worldwide to control the spread of this new illness due to the enormous disease burden. In the past ten years, the use of nanotechnology in the medical management of TB has grown, particularly in the areas of early diagnosis, prevention, and therapy. It has been demonstrated that nanomaterials are useful for the quick and precise identification of TB germs. The capacity to increase medication concentrations in target organs while decreasing treatment frequency has been demonstrated by new nanocarriers, which also hold great promise for improving drug delivery. The creation of better vaccines as well as therapy regimens will depend on having an in-depth knowledge of these immune escape mechanisms, which is crucial for the prevention, diagnosis, and treatment of TB (Figure 1) [2].

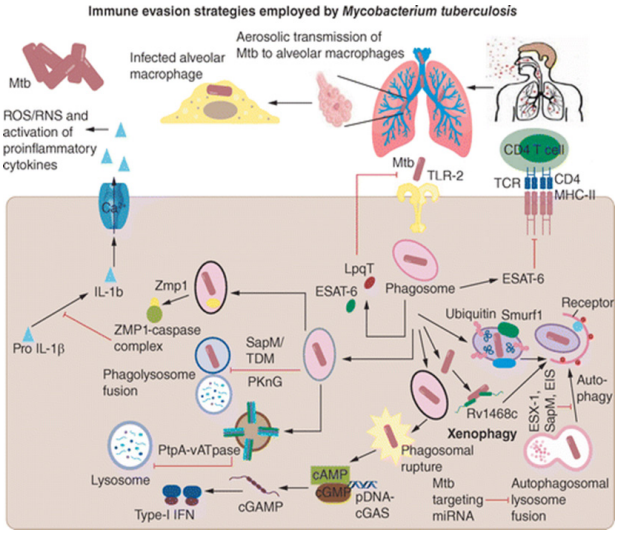

Figure 1: Manipulation and exploitation of host immune system by pathogenic *M. tuberculosis* for its advantage [2].

Discussion

As ancient as man, undoubtedly, is tuberculosis. Ancient mastodons have been shown to have diseases like TB, while Pleistocene bison have been reported to harbor *M. tuberculosis* DNA [3, 4]. *M. tuberculosis* is a very complex bacteria from a molecular standpoint, including a variety of pathogenic components, such as proteins, lipids, and glycans in their most particular forms [5, 6]. The pathogenesis of *M. tuberculosis* has been discovered to encompass all molecular types, and we can establish that the bacillus' most notable characteristic is unquestionably the peculiar waxy composition of the cell membrane. In fact, Robert Koch first announced his finding in 1882 because *M. tuberculosis*'s very oily covering considerably hindered continuous labeling for the bacilli [7]. The first successful effort to stain *M. tuberculosis* by distributing mycobacterium-infected samples on coverslips was documented in

the initial identification of the *M. tuberculosis bacillus*. Following the mounting of the samples, the coverslips were coated with aquavin solution (Bismarck brown) and submerged in a warm, basic methylene blue ethanol solution for 1 hour before being washed with distilled water. For the first time, *M. tuberculosis* could be seen as blue bacilli on a brown backdrop thanks to this method. Bacilli were either red on a blue backdrop or purple or blue on a yellow background. Ehrlich's technique was only deemed a "major development" of Koch's staining procedure by Koch himself. An inferior acid was employed for decolorization when carbolic acid (phenol) was substituted for aniline oil. Like Ehrlich's approach, the bacilli looked to be brightly colored, but the carbolifuxin solution had the benefit of being more stable than Ehrlich's aniline-fuchsin solution. Mycobacterial lipids exhibit some of the most remarkable structural characteristics, such as backbones that may reach 80 °C, polymethyl branches, or fatty esters that need particularly challenging lytic processes to cleave [8]. Lipids have been useful in the creation of diagnostics, vaccinations, and immunostimulants, among other TB control methods. One of the most useful tools in the immunodiagnosis of TB has been dubbed mycobacterial lipids [9].

Nanomedicine, Nanotechnology, and TB

One of the primary topics of interest in material science is nanomedicine, a subclass of nanotechnology and its use in medicine. The nanotechnology of biology is one of the key elements that facilitates communication between the two departments. Nanotechnology enables the creation of materials with diameters between 1 and 100 nm and customized features, such as very high surface area structures. By adjusting their size, shape, chemical content, framework, morphology, and textural qualities, their physicochemical properties may be tailored to display highly controlled biodegradation, nanoporous supports, or particle volume ratios (Figure 2) [10]. Designing substances with electrical conductivity or optical properties that are beneficial in the creation of biosensors is another use of nanotechnology. Combining these skills has led to advancements in drug delivery, diagnosis, therapy, and disease monitoring in the newly developing subject of nanomedicine in TB research [8, 11]. The creation of nanotechnology-based anti-tuberculosis medicines has drawn more attention in recent years, notably for applications in medication delivery, biosensing, and vaccines. In contrast to conventional biological sensors based on proteins, peptides, or nucleic acids known to bind people's biomarkers, including molecule targets of*M. tuberculosis* or against, vaccinations or vaccine subunits that are composed of potent immunoprotected antigens of proteins that aim to improve the therapeutic effects of anti-tuberculosis drugs.

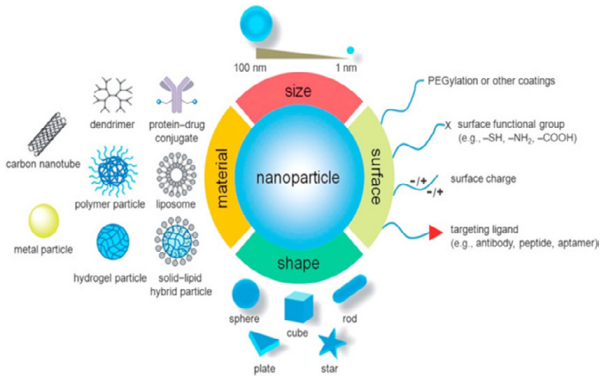

Figure 2: Types of nanoparticles and their structure [10].

Biosensors for TB diagnosis

Almost all protein antigens used in vaccine production as well as useful diagnostic antigens including Ag85B, the MPB83 antigen, the lipoglycan molecule, and lipoarabinomannan have all been studied as reagents for diagnosis [12]. An appealing method is the identification of biomarkers released by host cells, particularly in point-of-care settings where biosafety facilities are inadequate and bacterial sample safety is a concern (Figure 3) [10]. Numerous pro-inflammatory indicators have been researched as disease markers since chronic lung illness and inflammation are the most typical symptoms of active TB. Preliminary and comprehensive evaluations revealed that numerous indicators were necessary to produce a reliable diagnosis. One of the most precise molecular interactions known in biology is how antibodies recognize antigens. The ongoing production of *M. tuberculosis* antigens during active TB results in antibody responses that have a high potential for diagnostic utility but are of limited benefit for disease management. An antibody signature has been particularly linked to active TB infection. Antibody reactions against the bacilli can be a characteristic of tuberculosis.

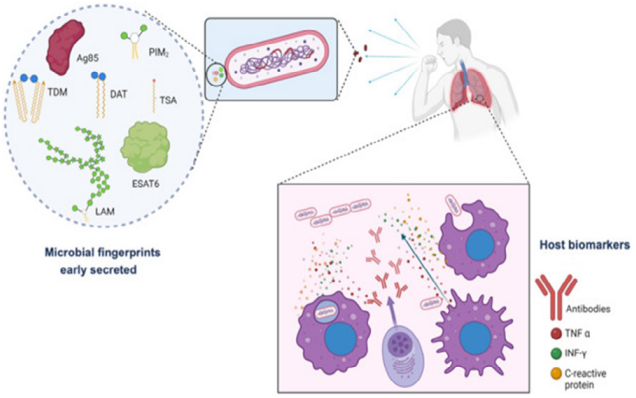

Figure 3: Biosensors to diagnose active TB cases are based on the identification of either molecular fingerprints secreted early on by the pathogen (proteins, lipids), or biomarkers secreted by host cells during an active infection, such as inflammation-associated mediators or antibodies [10].

Not Including Mycolic Acid Components

The pathogenicity, physiology, and overall gene regulation of *M. tuberculosis* are all significantly influenced by the two-component PhoPR system [13]. Genes located in the pks2 and msl3 gene clusters, which produce the enzymes necessary to produce sulfolipids and diacylrehalose/pentacylrehalose, respectively, were elevated by PhoPR. Lipid analysis supported our findings, demonstrating that the phoP mutant lacked all three lipids [14]. Although recent studies have emphasized the significant importance of other components, especially lipomannan and lipoarabinomannan (LM and LAM), which are also implicated in host immunomodulation, acid resistance has historically been mostly attributed to the waxy structure of the cell wall outer layer. to respond In *M. smegmatis*, ablation of branched -1,2-mannosyltransferase (MSMEG_4247) causes an accumulation of unbranched LAM and the total absence of LM and AF-negative bacteria [15]. This strongly implies that modifications to LM/LAM structures may impact the integrity of cell walls and AF staining. The matching *M. tuberculosis* mutant, on the other hand, exhibited no deficiencies in AF staining, indicating that LM and LAM had little impact on AF staining in *M. tuberculosis*.

Conclusion

Lipids have been recognized by *M. tuberculosis* as a crucial molecular marker of bacteria. At various phases of the immune response and antigenicity, *M. tuberculosis*'s very abundant and structurally distinctive lipid-containing molecules are involved in cell identification, activation, and suppression. Studies on lipids, however, are much worse because the quest for anti-tuberculosis medications has been ignored for decades. Working with hydrophobic bioactive substances entails time-consuming procedures and strategies, which can be difficult to scale up. *M. tuberculosis*, it is quite likely that the ZN-negativity of dormant mycobacteria results in an underestimation of the bacterial burden, which has significant consequences for both TB diagnosis and clinical epidemiology. *M. tuberculosis* may have significant effects on chemotherapy and vaccine development in addition to aiding in the better identification of the bacillus' latent forms. The recent discovery of multi-stressor *in vitro* granuloma models, which cause *M. tuberculosis* to enter a state resembling rest, may make this conceivable.

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