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ADVANCES IN *MYCOBACTERIUM TUBERCULOSIS* GENOMICS: EVOLUTION, RESISTANCE, AND DISEASE CONTROL

Lubna F. Hussein [1], Shahad Imad Hameed [1,*] and Rayaheen Mohammed Tamkeen [2]

[1] Department of Biology, College of Science, University of Baghdad, Baghdad, Iraq.
[2] College of Science, University of Baghdad, Baghdad, Iraq.
* Corresponding Author

ORCID Details
Lubna F. Hussein: https://orcid.org/0009-0004-2516-5319
Shahad Imad Hameed: https://orcid.org/0000-0001-8154-6440
Rayaheen Mohammed Tamkeen: https://orcid.org/0009-0001-2880-6626

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ABSTRACT

Mycobacterium tuberculosis complex (MTBC), a group of virtually genetically identical microorganisms, is the primary cause of tuberculosis (TB), the deadliest infectious disease in the world. Standard bacterial profiling methods like multilocus sequence typing are unable to distinguish its strains due to this severe DNA similarity and clonal reproduction. Recent developments in whole-genome sequencing of clinical samples from around the world have revolutionized our understanding of the disease. We now have a better understanding of its evolutionary path, host-level genetic dynamics, medication resistance mechanisms, and transition into an obligatory parasite. In order to show how these recent findings can improve international public health interventions and guide future research funding, this paper summarizes them.

Keywords: Antibiotic Resistance, Genome Sequencing, *Mycobacterium Africanum, Mycobacterium Tuberculosis,* MTBC.

1 INTRODUCTION

Nearly one billion people have died from tuberculosis (TB) during the past 200 years ago [1]. Tuberculosis remains the biggest infectious agent-related cause of death in people worldwide, with an estimated 10.4 million new cases and 1.7 million fatalities every year [2]. Furthermore, there is a substantial reservoir for future active TB infections due to the latent infection of 25% of the global population [3]. Several long-standing challenges continue to hinder global tuberculosis (TB) control, including the limited sensitivity of conventional microscopy-based diagnostic methods, the relatively low effectiveness of the century-old Bacille Calmette–Guérin (BCG) vaccine, and the limited availability of newer anti-tuberculosis drugs, as many of the currently used agents were developed several decades ago. [4].

Apart from outdated control equipment, other dogmas have hindered the progress of the subject. Among these is the idea that strains of bacteria drug-resistant are less viable compared to drug-susceptible variants [5]. According to a

different theory, TB bacilli are clones with no appreciable genotypic or phenotypic variations between strains [6]. Human tuberculosis is mainly associated with bacteria belonging to the Mycobacterium tuberculosis complex (MTBC). These closely related acid-fast bacilli disclose a very high grade of genetic connection, with more than 99% nucleotide sequence identity. Because genetic diversity within the MTBC is considerably lower than that observed among many other bacterial species, conventional approaches such as multilocus sequence typing (MLST) have limited ability to distinguish genetic variation among MTBC strains [7]. Consequently, there is still much to learn about the ecology and evolution of the MTBC. Current advances in sequencing of next-generation circumvent these limitations and enable detailed studies of the evolutionary mechanisms behind this variation by indexing MTBC variety over the entire genome [8].

This paper examines the evolutionary history of MTBC, with particular emphasis on when and where it emerged and how it evolved from an environmental organism into a specialized pathogen capable of infecting humans. It distinguishes between the evolution of animal-infecting and human-infecting MTBC strains. Additionally, it provides an overview of the global distribution of numerous evolutionary lineages of the MTBC and their epidemiological implications, highlighting the ecological niches these microbes occupy. The review also discusses the evolution of MTBC inside and between individuals and the effect of stringent clonality on antibiotic resistance.

1.1 Aim of this study

This review's objective is to provide an overview of these new findings and talk about how they might be used to improve TB control methods and resources.

2 METHOD OF REVIEW

A comprehensive literature search was performed to identify relevant studies addressing the genetic evolution, antimicrobial resistance, transmission patterns, and control of *M. tuberculosis*. Electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar, were systematically searched to obtain relevant and up-to-date scientific literature.

2.1 Background

2.1.1 Mycobacteria phylogeny

There are about 170 species in the genus Mycobacterium, the majority of which are environmental organisms [9]. *M. leprae*, *M. ulcerans*, and MTBC are the three main human mycobacterial diseases that fall into the slow-growers group of Mycobacterium species, which were previously separated into fast-growers and slow-growers [10]. People with weakened immune systems can potentially contract a variety of "non-tuberculous mycobacteria" (NTMs).

Nonetheless, the human-adapted MTBC differs in that it is a required human sickness with neither animal or environmental reservoirs. Unlike many other diseases where transmission and virulence are unrelated, [11], the MTBC must also cause disease to spread across individuals [12].

Through incremental adjustments to the intracellular environment, MTBC transformed from an ambient Mycobacterium to a professional pathogen, increasing its potency.

The capacity to viable inside free-living protozoa, such as amoebae, which consume ambient bacteria, has been suggested as a crucial stage in this process [13]. This capacity may therefore have contributed to the MTBC's ancestor's ability to infect and proliferate within mammalian macrophages, which is a crucial aspect of MTBC pathogenicity [14].

A vital phase in the evolution of tuberculosis was the emergence of efficient host-to-host transmission. In humans, *Mycobacterium tuberculosis* is primarily transmitted through airborne respiratory particles released by infected individuals, particularly during coughing. Some theoretical research has proposed that the controlled use of fire by early human populations may have influenced the evolution of tuberculosis transmission by increasing close social contact around communal fires, and exposing individuals to smoke-related respiratory damage, potentially creating conditions that favored infection and transmission [15].

What genetic changes enabled the MTBC progenitor to develop into a professional pathogen? According to research comparing the genomes of the closely linked Nontuberculous Mycobacteria species *M. marinum* and *M. kansasii* with the MTBC, genome reduction happens when new genes are acquired by horizontal gene transfer (HGT) and genes that are not required for a pathogenic life style are eliminated [16].

The MTBC's 4.4 Mb genome is shorter than the 6.6 Mb and 6.4 Mb genomes of *M. marinum* and *M. kansasii*, respectively [17, 18]. Since diverging from *M. marinum* and *M. kansasii*, the MTBC ancestor has simultaneously gained several hundred genes through HGT [19-22].

Furthermore, pathogenic mycobacteria have higher frequencies of the PE and PPE protein families, which are distinguished by conserved N-terminal domains and varied C-terminal regions [23].

Only pathogenic mycobacteria such as *M. leprae, M. marinum, M. ulcerans*, and the MTBC, belong to the Proline-Glutamate (PE) polymorphic guanine cytosine rich sequence (PE_PGRS) protein subfamily of the PE and PPE protein families [24]. When combined, these findings show that the whole virulence and potential for human transmission of the MTBC cannot be explained by a single genetic characteristic.

Rather, numerous genomic loci's epistatic interactions and coordinated transcriptional regulation appear to be the cause. It's interesting to note that the MTBC differs from the majority of other bacteria in that it has a disproportionately high number of genes related to the toxin–antitoxin system [25], Clinical strains have been shown to exhibit differential regulation of certain of these Toxin–antitoxin (TA) systems are involved in a variety of biological processes in bacteria. Their influence on gene regulation, bacterial growth, and cellular persistence suggests that these systems may also contribute to the regulation and survival of the pathogenic life cycle of the *M. tuberculosis* complex [25, 27].

2.1.2 Comparative analysis with *Mycobacterium canettii*

The evolution of the *M. tuberculosis* complex as a specialized human disease-causing has been investigated by comparing it with *M. canettii* and other Smooth Tubercle Bacilli (STB), these organisms are considered the closest known phylogenetic links to MTBC [28]. So far, less than a hundred STB strains have been identified, all of which come from TB patients with ties to the Horn of Africa, especially Djibouti.

Apart from the fact that several strains of STB were discovered from Europeans living in Djibouti, The children appear to be more susceptible to active TB caused by STB, nothing is known about the epidemiology of STB [29]. To yet, there have been no reports of STB transmission from person to person.

All of these epidemiological findings point to the presence of an impulsive pathogen in the environment [30]. The STB genomes have substantially higher nucleotide sequence diversity and are 10–115 kb larger than the MTBC genome [31].

For example, there can be up to ~65,000 SNP differences between STB strains [31], while MTBC strains differ from one another by a maximum of ~2,000 SNPs [32]. Crucially, persistent HGT is associated with a portion of the variation in STB [28, 31]. Thus, like other mycobacteria [33], but unlike the MTBC, HGT plays a significant part in the STB's continuous evolution.

In particular, transconjugants displaying mosaic genomic pattern that resembles the outcome of eukaryotic meiosis are produced by distributive conjugal transfer, a recently identified process of HGT [34], has recently been shown in (STB) [35, 36]. Comparative genomic analyses of (MTBC), (STB), and nontuberculous mycobacteria (NTM) have identified differences in genes associated with metabolic functions. For example, the CobF gene, which is believed to participate in cobalamin (vit. B12) biosynthesis, is lacking from (MTBC) but has been detected in Smooth Tubercle Bacilli, *M. kansasii* and *M. marinum.* This genetic difference suggests that the MTBC may rely on acquiring vitamin B12 from its host rather than synthesizing it independently, unlike several other mycobacterial species [37].

On the other hand, STB, *M. marinum*, and *M. kansasii* lack the gene pe_pgrs [33], It produces a protein that is exported with potent immunomodulatory effects [38]. This is one instance of a genetic region linked to pathogenicity in of the M*ycobacterium tuberculosis* complex [31]. A recent research found that a rise in virulence in a shared ancestor of the MTBC is associated with a change of the mycobacterial cell surface [39].

These comparative studies collectively demonstrate that the MTBC's virulence and transmission determinants are composite and more complex of numerous interplaying factors, Additionally, these bacterial elements interact with numerous host variables, leading to a variety of host preferences among the various MTBC members as well as varying infection and illness consequences [40].

2.1.3 Adaptation and host tropism

The MTBC evolved into a number of human-adapted lineages as well as lineages that are adapted to different domestic and wild mammals after the MTBC progenitor was established as a professional pathogen. In this sense, adaptability refers to the virus's capacity to cause illness, effectively infect, and spread in its primary host species [11].

Periodic overflow episodes into other host organisms do not maintain the entire life cycle, particularly the dissemination to secondary hosts. It is important to differentiate between maintenance and spillover hosts .The two main causes of tuberculosis in humans are *M. africanum* and *M. tuberculosis sensu stricto* [41].

These MTBC members that have adapted to humans can be further classified into seven evolutionary lineages: *M. tuberculosis sensu stricto* includes L1, L2, L3, L4, and L7, L5 and L6 are typically referred to as *M. africanum* - West Africa (WA)1 and (WA)2. The human-adapted Mycobacterium tuberculosis Complex has a significant geographical patterns of population distribution with some lineage having a high degree of geographical restriction and others existing globally [32].

The most common lineages in the world are L2 and L4, L2 predominating in East Asia. L1 and L3 are primarily found in areas near Indian ocean. While L7 is virtually solely present in Ethiopia, L5 and L6 are extremely limited to West Africa. Many variables are thought to have influenced the contemporary phylogenetic dissemination of the human restricted MTBC members.

2.2 Future perspectives

In order to comprehend the evolutionary processes and host adaptations of the *Mycobacterium tuberculosis* complex (MTBC), future research should concentrate on whole-genome sequencing and comparative genomic techniques. Clarifying their ecology and evolution requires a focus on genomic sampling from regionally restricted human lineages and animal-adapted MTBC members. Further research is required to determine how various genomic loci and regulatory mechanisms impact virulence and phenotypic diversity, especially with reference to host adaptation-related areas such as PE/PPE and PE_PGRS protein families. Future research should examine the relationship between resistance-associated alterations and bacterial fitness in order to better understand antimicrobial resistance at the genetic level. Last but not least, extending genomic research to underrepresented people and areas is crucial to improving our knowledge of MTBC variety and evolution and supporting the creation of more effective tuberculosis-control and diagnostic methods.

3 CONCLUSION

Using whole-genome and genomic sequencing methods, the biological and evolutionary processes of the *Mycobacterium tuberculosis* complex (MTBC) have progressed. Evidence reveals that genomic alterations, including gene loss and horizontally acquired genetic regions, contributed to MTBC's appearance as a specialized human pathogen. Comparative genomic analyses with related mycobacteria, like *M. canettii*, clarify its transformation from an environmental organism. Despite MTBC's overall clonality and limited nucleotide diversity, its lineages display notable biological and epidemiological diversity, influenced by genomic heterogeneity and host adaptation. Variations in pathogenicity and host tropism arise from the interplay of bacterial genetic factors and host traits. Overall, genomic techniques offer a framework for understanding MTBC evolution, population structure, and antibiotic resistance, potentially improving tuberculosis control strategies through integrated genetic and epidemiological data.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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