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Review

Learning from epidemiological, clinical, and immunological studies on *Mycobacterium africanum* for improving current understanding of host–pathogen interactions, and for the development and evaluation of diagnostics, host-directed therapies, and vaccines for tuberculosis

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SUMMARY

Mycobacterium africanum comprises two phylogenetic lineages within the *Mycobacterium tuberculosis* complex (MTBC). *M. africanum* was first described and isolated in 1968 from the sputum of a Senegalese patient with pulmonary tuberculosis (TB) and it has been identified increasingly as an important cause of human TB, particularly prevalent in West Africa. The restricted geographical distribution of *M. africanum*, in contrast to the widespread global distribution of other species of MTBC, requires explanation. Available data indicate that *M. africanum* may also have important differences in transmission, pathogenesis, and host–pathogen interactions, which could affect the evaluation of new TB intervention tools (diagnostics and vaccines)–those currently in use and those under development. The unequal geographical distribution and spread of MTBC species means that individual research findings from one country or region cannot be generalized across the continent. Thus, generalizing data from previous and ongoing research studies on MTBC may be inaccurate and inappropriate. A major rethink is required regarding the design and structure of future clinical trials of new interventions. The West, Central, East, and Southern African EDCTP Networks of Excellence provide opportunities to take forward these pan-Africa studies. More investments into molecular, epidemiological, clinical, diagnostic, and immunological studies across the African continent are required to enable further understanding of host–*M. africanum* interactions, leading to the development of more specific diagnostics, biomarkers, host-directed therapies, and vaccines for TB.

1. Introduction

Tuberculosis (TB) in humans is caused by one of several genetically related groups of organisms comprising the *Mycobacterium tuberculosis* complex (MTBC). Genomic studies indicate that all MTBC species have between 95% and 100% DNA relatedness, with the same 16S rRNA.[1,2] *Mycobacterium tuberculosis* sensu stricto is responsible for a large proportion of human TB cases worldwide.[3] Other MTBC species that cause human disease include *Mycobacterium bovis*, *Mycobacterium africanum*, *Mycobacterium microti*, *Mycobacterium canettii*, and *Mycobacterium pinnipedii*.[4–6] Globally, TB continues to be a major public health

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problem and is now the most common infectious disease cause of death. The World Health Organization annual TB report for 2016 states that there were 10 million cases of active TB in 2015, with an estimated 1.5 million associated deaths.[7]

Over the past six decades, the common dogma prevailing has been that all members of the MTBC are genetically similar, with a clonal population. Thus, it has generally been assumed that the small genotypic or phenotypic differences do not translate into differences in transmission, pathogenesis, host–pathogen interaction, disease outcome, and efficacy of diagnostics and vaccines. A huge amount of resources and effort have been invested in developing new TB diagnostics, TB drugs, treatment regimens, and vaccines. Currently available diagnostics and vaccines, and those under development, have been based on this assumption. However, molecular and clinical studies combined with genomic analyses have shown important strain diversity among the different members of the MTBC.[4,8–12] Differences between lineages could affect the performance of diagnostics, treatments, and vaccines.

Available data obtained from epidemiological, clinical, and immunological studies on *M. africanum* in West Africa are highlighted in this viewpoint;[10,13] these indicate important differences in transmission, pathogenesis, and host–pathogen interactions. The need for a radical rethink to improve current understanding of host–pathogen interactions and for the development and evaluation of new diagnostics, biomarkers, host-directed therapies, and specific vaccines for TB is also discussed.

2. Geographical distribution of *M. africanum*

M. africanum was first described and isolated in 1968 from the sputum of a Senegalese patient with pulmonary TB.[5] *M. africanum* is made up of two lineages within the MTBC: MTBC lineage 5 (also called *M. africanum* West African type I) and MTBC lineage 6 (*M. africanum* West African type II).[13,14] With advances in diagnostic technologies, *M. africanum* has been identified increasingly as an important cause of human TB, causing nearly 50% of all TB cases reported in West Africa. The following country prevalence of *M. africanum* has been reported: Benin 39%, Burkina Faso 18%, Cameroon 56%, The Gambia 39%, Ghana 20%, Guinea Bissau 47%, Ivory Coast 55%, Nigeria 8%, Senegal 20%, Sierra Leone 24%.[13,15–20] *M. africanum* has also been reported infrequently among TB patients from across Europe, South America, and the USA.[21–26] It is assumed that TB caused by *M. africanum* in non-African countries is due to human migration from disease-endemic West African regions.

Recent advances in molecular technology have allowed studies on the evolution of the nature of *M. africanum* genotypes, its position within the MTBC, and its genotypic and phenotypic expression, specific clade identification, transmission patterns, infectivity, and disease expression in humans.[10–33] Whether there are significant differences between *M. tuberculosis* and *M. africanum* in their clinical presentation, epidemiology, association with migration, transmission patterns, pathogenesis, virulence, rate of progression of disease, and treatment outcomes needs to be defined.

3. Clinical manifestations, transmission, and genotype studies of TB due to *M. africanum*

Several small clinical cohort studies from West Africa have evaluated differences in clinical presentation between TB caused by *M. africanum* and TB caused by *M. tuberculosis* sensu stricto.[10–12,27–33] Aerosol spread and symptoms at presentation seem similar in both. No significant associations of *M. africanum* with HIV status and chest X-ray changes have been noted. Contacts of patients with *M. africanum* infection appear to have a lower rate of progression to active TB compared with contacts of *M. tuberculosis*-infected patients.[34] A lower rate of genotype clustering for *M. africanum* compared to *M. tuberculosis* has been reported.[35] Other studies have reported that *M. africanum* West African type II has a similar rate of transmission as *M. tuberculosis* sensu stricto, although it may be associated with a lower rate of progression to disease in contacts.[36,37]

4. *M. africanum* genotype, immunological responses, and diagnostic tests

Immunological studies reported from The Gambia have shown marked differences in clinical features, immune response, gene expression, and proteins associated with inflammation between *M. tuberculosis* sensu stricto-infected patients and *M. africanum*-infected patients .[35,38,39] A number of genomic polymorphisms unique to *M. africanum* in West Africa and a study using whole genome sequencing of four *M. africanum* isolates against H37Rv,[11] have shown a number of frame-shifts and non-synonymous mutations within some functional operons, including genes associated with immunogenicity and host invasion. It was highlighted that potential differential gene expression could have implications for diagnostic tests and management algorithms in West Africa, especially when these genes are being targeted for diagnostic test purposes.

The gene product of *mpt64* is the target of three widely used rapid speciation lateral flow assays for the identification of the MTBC in culture: BD MGIT TBc Identification Test (BD TBc ID; Becton Dickinson Diagnostics, Becton, Dickinson and Company, Sparks, MD, USA); SD Bioline Ag MPT64 Rapid (SD Bioline; Standard Diagnostics, Inc., Yongin-si, Gyeonggi-do, Republic of Korea); and Capilia TB-Neo (TAUNS Laboratories, Inc., Numazu, Shizuoka, Japan). Despite the advantage of lateral flow assays, there have been reports of the failure of MPT64 tests to detect MTBC isolates, resulting in erroneous reporting of a non-tuberculous mycobacteria (NTM) diagnosis. A systematic evaluation of two commonly used rapid TB tests that detect the product of the mycobacterial *mpt64* gene compared the abundance of the *mpt64* gene product in sputum samples of patients with untreated pulmonary TB caused by *M. africanum* type II or *M. tuberculosis* sensu stricto. Ofori-Anyinam et al. compared the expression of the *mpt64* gene in sputa from *M. africanum* and *M. tuberculosis* sensu stricto-infected Gambian patients and found that the *mpt64* gene was 2.5-fold less expressed in *M. africanum* than in *M. tuberculosis* sensu stricto.[33] Thus the sensitivity of rapid tests was 20% lower for *M. africanum* cultures than for *M. tuberculosis* sensu stricto cultures.[33] A non-synonymous single nucleotide polymorphism (SNP) in the *mpt64* gene of that lineage was identified. The *mpt64* (Rv1980c) mRNA transcript was significantly less abundant in the sputa of TB patients infected with *M. africanum* type II compared to patients infected with *M. tuberculosis* sensu stricto, suggesting that the MPT64 protein may be produced at a slower rate. There also appeared to be lineage-dependent and time-specific differences in conversion to MPT64 test positivity. Thus, in West Africa, tests to identify MTBC in culture miss a substantial fraction of TB cases, and this may have direct consequences for the patients and for TB control efforts. These data have important implications for the performance of diagnostic tests and any new TB vaccine in West Africa.

5. Bugbear of current portfolio of geographically restricted TB research

Recent debates have focused on whether the currently available diagnostic tests are specific and reliable for all types of MTBC

lineage, or whether treatment or vaccine success or failure will be determined by the specific nature of MTBC lineages. Given the limited efficacy of the current TB vaccine and the recent clinical failure of the most advanced new TB vaccine candidate, novel concepts for vaccine design should be explored. Over the past 5 years, advances in molecular technologies have shown that MTBC lineages differ in their phenotypes and that they may also differ in their pathogenicity. Thus any generalizing of data from previous and ongoing research studies on TB may be inappropriate and inaccurate. The unequal geographical distribution and spread of MTBC species across Africa means that individual research findings from one country or region cannot be generalized across the continent.[13] Thus, a major rethink is required for the design and structure of future clinical trials of new diagnostic and preventive interventions. Phylogeographic studies across the African continent are now required to improve the design and interpretation of epidemiological research, translational clinical research, and evaluation trials of new interventions (rapid diagnostics, new drugs and treatment regimens, and vaccines).

6. Conclusions and the way forward

Recent phylogenomic analysis of global strains has indicated that while some lineages and sub-lineages casually referred to as generalist can infect different populations, the majority of tuberculous lineages and sub-lineages are 'specialized' to cause TB disease in distinct human populations. *M. africanum* classified into L5 and L6 seems to have specialized and remains an important cause of TB in West Africa. With the wide spectrum of MTBC lineages present across Africa, these patient cohorts provide ideal trial sites for evaluation studies . Increased investment in the study of *M. africanum* is required to further our understanding of MTBC epidemiology, evolution, and pathogenesis. The diversity within *M. africanum* must be factored into priority agendas of funders and current investments into new TB biomarkers and vaccine development. With the limited efficacy of bacille Calmette–Guérin (BCG) and the failure of the Oxford TB vaccine, novel concepts for vaccine design should be explored, such as the highly variable T-cell epitopes. Moreover, there is increasing evidence that the human-adapted MTBC has been co-evolving with the human host for a long time. Hence, studying the interaction between bacterial and human genetic diversity might help identify additional targets that could be exploited for TB vaccine development. It is important that systematic collaborative research studies are also conducted across Africa to determine the contribution of host genetics, ethnicity, or other factors in the persistent circulation of *M. africanum* in West Africa. Moreover, such studies also have the potential to help in developing host-specific adjunct host-directed therapies against both *M. africanum and M. tuberculosis* sensu stricto.[40] Whilst the infrastructure and resources for the performance of these pan-African studies have been lacking, the second European Developing Countries Clinical Trials Partnership program (EDCTP2)[41] and the EDCTP regional networks of excellence[42,43] now provide new opportunities to take forward these important studies.

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