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Review Article

Omics and Artificial Intelligence Addressing Host Immune Response in TB

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Abstract

Tuberculosis caused by mycobacteria(s) of the complex of *Mycobacterium tuberculosis* (MTBC) nowadays represents a problem in public health. The scenery is worsened by comorbidities and the rise in multidrug-resistant strains (MDR). Despite this, recent reports have highlighted the emergence of high-throughput alternatives to potentiate diagnostic and more effective treatment, such as omics technologies. Indeed, current Omics technologies allow a deep analysis of the dynamics of gene expression, proteins, and metabolites The gene expression profiles along with the type of blood samples versus stools and sputum can make a difference in the diagnosis because they represent a window into the molecular signature of cell tissue or organ-specific. The integration of omics data with artificial intelligence methodologies (i.e., machine learning, deep learning, big data analytics, and neural networks) can generate algorithms as a biological language model to evaluate, and predict embed numerical representation of the data generated from omics technologies addressing the host-pathogen interface. The objective of the present review is to pinpoint how the omics technologies has been contributing to the dissection and understanding on this. At the same time, emphasize the use of AI to accelerate this. This review was based on searches and data from the PubMed database from 2020 to 2025. The result was a landscape of the milestones of omics and AI in TB. These advances in both or individually can support and potentiate enormously the diagnostic and treatment in TB.

Keywords: *Mycobacterium tuberculosis*,Omics Technologies,Host Innate and Cellular Immune Response,Artificial Intelligence

Introduction

Tuberculosis (TB), is an ancient infectious disease dated from Egyptian mommies [1], caused by the etiologic agent *M. tuberculosis (Mtb)*. It represents a health problem in underdeveloped countries as well as in developed countries. It is one of the 10 leading causes of mortality worldwide caused by a single pathogen [2]. The most recent mortality registered ranged from 1 to 5 million, while approximately 10 million individuals developed active TB [1,2]. A quarter of the world's population develops latent tuberculosis with a probability percentage of 3 to 10% of reactivation [2,3]. According to recent data from WHO [1] in 2023-2024, people who develop Tuberculosis accounted for 87% of the global amount. The scenery is worse because of the emergence and increase in multi drug resistance (MDR) and super extensive drug resistance (XDR) to the first line and even second line of antibiotics [7]. On the other hand, the only vaccine against human tuberculosis is the *Bacillus Calmette Guerin*-based vaccine or BCG-vaccine, the only effective and officially approved prophylactic measure [8]. However, the BCG vaccine protect children from different forms of TB. Memory fades as they grow and, practically in adulthood, there is no immunological memory, and therefore the risk of developing active TB is high [8-11]. A hotspot in the TB vaccine (TBVAC) development is the route of administration. If the bacillus enters via the upper airways, the mucosal and the systemic immune system is activated and triggered [9-13]. However, in a recent report it has been reported that intravenous BCG vaccine administration to *Macaques rhesus* and aerosol challenge with *Mtb* have induced protective antibodies [13,14]. On referring specifically to how to potentiate the diagnosis of human TB is necessary to gain knowledge of the *Mtb* susceptibility of the host to mycobacterial infections [14,15]. The success of transmission could reflect pathogen adaptation to the host, strengthening the theory that there has been a co-evolution of the pathogen with its host at molecular and immunological level, and thus, the eradication of the pathogen is not an easy task and require the understanding and elucidation of the molecular mechanism of pathogenicity for the development and design of vaccine and immunotherapies to halt the transmission and to hamper the antimicrobial resistance [15-17]. Indeed, the *Mtb* strain genotypes could also influence the multidrug-resistant capability of the strains and, indirectly, antibiotics-based treatment [18-20]. The host genetic variability to mycobacterial infections leads to the establishment of a framework in the dissection and knowledge of the immune pathogenesis of TB [21].On the other hand, omics technologies in conjunction with immunological parameters can aid to dissect blood cells subsets that are playing a role in the host immune response against *Mtb* [5,8,22,23]. Studies using single-cell transcriptomics and T cell receptor sequencing are being contributed and highlight that all major cell clusters (mononuclear cell populations) are present in both, pleural fluid and peripheral blood of Extra Pulmonary Tuberculosis (TPE) patients [22-24]. Another contribution of the omics technologies is toward the biology of the TB infection and the host pathogen interaction, specifically referring to the bio signatures, in non-and immune cells, i.e., monocytes, and granulocytes at transcriptional, and epigenetic level (DNA methylation, and microRNA) [24,25]. Furthermore, the integration of omics technologies such as metabolomics and transcriptomics can inform us about the physiological level of the metabolites and signalization pathways at the immunological level of the host response and this can be used either as basic or applied knowledge [22,18-20]. Moreover, it can provide information about the capabilities of *Mtb* to escape and transverse the harsh, stringent, heterogeneous niches, and the microenvironment in humans, as well as the expression of virulence factors for the extra pulmonary dissemination [3,5,7,26,27]. It can provide information of the virulence factor involved in the molecular mechanism of pathogenesis, such as the analysis of the secretory system in the pathogen, the efflux bombs, the cell wall composition, in the genetic variability of the different clinic isolates which can provide valuable information of the resistance mechanism [2,6-8,27]. Overall, these technologies can aid in the identification of correlates of immune protection (biomarkers) and progression of TB disease. Along with the multi omics integration approach can be facilitated through the use of AI-based approaches, to integrate large amounts of quantitative and omics data. Artificial intelligence (AI) methodologies such as deep learning (DL)(simple interconnected units), machine learning (ML)(based on algorithms for the processing of many parameters, e.g., images, biomarkers, immunological), Big Data Analytics (BDA) and Artificial Neural Networks (ANN), might give input to the processing and analysis of the data and images to potentiate the prognostic, diagnostic, and vaccine development [22-27], of paramount importance, for the development of rational TB treatment regimens especially novel host response-directed therapeutics [22-27]. In the present review, it is pinpointed

both the advancement and development of the omics and the AI, in addressing the mechanism of TB immunopathogenesis to potentiate enormously diagnostic and prophylactic/therapeutic vaccines. Therefore, after the introduction to the three main issues, Tb, omics and AI, we pursued to first pinpoint the main aspects of the host response upon infection with *M. tuberculosis,* the main target to be deal with, followed by the milestones of omics and AI, and the implication on diagnostic and development of treatments.

The host-pathogen interaction interface in Tuberculosis

- The general hallmark of the host immune response upon *Mtb* infection is the co-existence with the host immune response that results in an inflammatory response induced by the pathogen. Several studies in the different animal models and clinical studies have proposed that there are some basic requirements for the molecular mechanism of Tuberculosis [8,14,26,27-29] that includes the molecular and cellular components of the host immune system, innate and adaptive.
- The initial molecular recognition, upon air droplet entrance and ingestion by upper airway cells, bacilli is internalized by the alveolar macrophages [14,29-34], with a molecular recognition in first term. The molecular interaction between the pathogen-associated mediated patterns (PAMPS) and the patterns of recognition receptors surface (PRRS) on antigen presenting cells (Macrophages, and Dendritic cells).
- The PAMPS on the pathogen surface such as the mycobacterial glycolipids (lipoarabinomannan (LAM), lipomannan (LM), 38-kDa and 19-kD mycobacterial glycoproteins, phosphatidylinositol mannosidases (PIM), tri-acylated or di-acylated, lipoproteins, recognized by (TLR2/TLR1) or (TLR2/TLR6) [27-29].
- The PRRS on the antigen presenting cells as -TLRs receptors located on cell membranes or intracellularly (TLRs),TLR2, TLR4, TLR9, and possibly TLR8. TLR2 can form heterodimers with both TLR1 and TLR6 [29-34]. -Receptors are the C-type lectin receptors (CTLRs) (e.g. mannose receptor): -Receptors located in the cytoplasm, NLRs, the CD207, and the IPAFs [28-34].-the cytoplasmic proteins such as the Retinoic acid-inducible gene,(RIG)-I-like receptors (RLRs),-The receptor on the Dendritic cell-specific intercellular adhesion molecule grabbing non-integrin (DC-SIGN) and Decti-1), The phagocytic receptors, such as FC-γg receptors, the complement receptors, and the scavenger receptors [29-34].

The host innate immune response upon M. tuberculosis infection

After the initial molecular interaction as pinpointed above [71,73,87-89], the recruitment of the innate immune cells at the site of infection allows control of Tuberculosis infection at very early times, maturation, migration of APC, and the expression of the costimulatory molecules, but it also allows the infected APCs to maintain an inflammatory state that is like a depot effect for clearance and elimination of *Mtb* [29,30,34,35].

Microbicides innate mechanism of the host response, such as phagosome-lysosome fusion, autophagy, oxidative stress, antigen processing, inflammasome activation, antigen presentation by MHC class I, class II, and CD1 (glycolipids presentation, cross-priming) [31,32], production of nitric oxides [92] and other reactive intermediates that eventually will favor an inflammatory state to continue in a replicative state (active infection) [29,31,34]. Innate mechanisms of the host response, such as phagosome-lysosome fusion, autophagy, oxidative stress, antigen processing, inflammasome activation, antigen presentation by MHC class I, class II, and CD1 (glycolipids presentation, cross-priming) [31,32], production of nitric oxides and other reactive intermediates that eventually will favor an inflammatory state to continue in a replicative state (active infection) [29,34], while in macrophage infection, there are mainly pro-inflammatory cytokines, and the activation of the macrophages elicited several other cytokines, IL-18 and IL-12, for continuous activation of macrophages and naïve CD4+ lymphocytes, the Th (helper T cells). Th1 cells that upon activation induce the production of IFN-γ and TNF-α at the same time, macrophages produce oxide nitric (NO) [30-34] (Figure 1A), granulocyte-macrophage colony-stimulating factor (GM-CSF), chemokines (CXCL1, CXCL5, CCL2, and CCL7), antimicrobial peptides, which mediate the activation and recruitment of inflammatory cells [35,36]. In addition, the innate mechanism includes reactive O2 species and the activation of the proteasome for antigen processing [30,36-38] (Figure 1A).

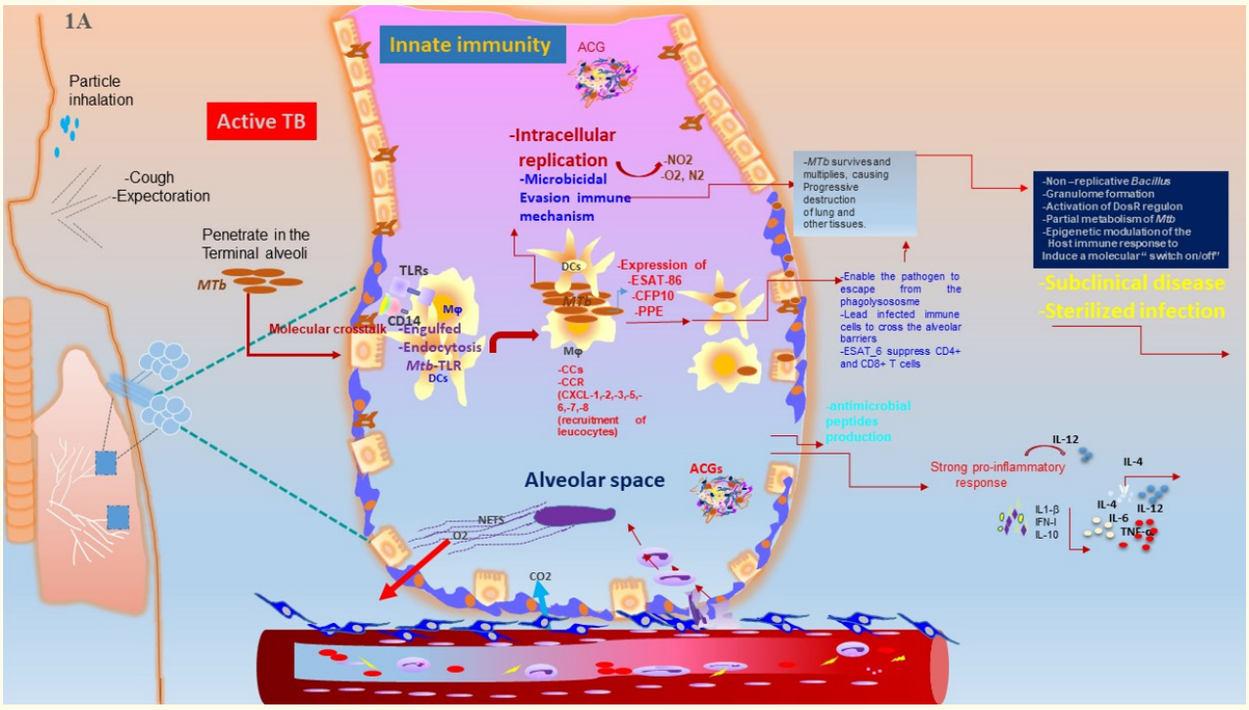

Figure 1a: Upon infection, *M. tuberculosis* enters via the upper airways as particle droplets, followed by the uptake by the alveolar macrophages, which reach the local bronchi alveolar(s) in the lung, and replicate. The recruitment of the innate immune cells at the site of infection allows in principle control of Tuberculosis infection at very early times, maturation, migration of APC, and the expression of the costimulatory molecules, microbicides innate mechanism of the host response, such as phagosome-lysosome fusion, autophagy, oxidative stress, antigen processing, inflammasome activation, antigen presentation by MHC class I, class II, and CD1 (glycolipids presentation, cross-priming), production of nitric oxides and other reactive intermediates that eventually will favor a inflammatory state to continue in a replicative state (active infection). Moreover, the production of antimicrobial peptides, such as beta-defensins and cathelicidins by the airway epithelium and alveolar macrophages, play a role not only in the bacterial elimination but also in the recruitment and activation of diverse immune cells(human {beta}-defensin-2, expressed and associated with *Mycobacterium tuberculosis* during infection of human alveolar epithelial cells. The cytokines, like the chemokines, influence the behavior of the innate cells and their recruitment of innate cells to the site of infection, linked with adaptive immunity.

The activation and the production of a set of cytokines reach and allow the differentiation of the helper T cells to T helper 17 (Th17) cells interleukin-17 (IL-17) producers [39-43].

In latency, the granuloma can sterilize the infection, becoming sclerotic and calcified, whereas in active Tuberculosis, granulomas are necrotic and have a caseous appearance. Latent bacilli coexist for survival with immune and nonimmune cells, including fibroblast and epithelial cells [18,29,30,44]. Myeloid cells continue to provide a safe, persistent, and survival niche for the establishment of the bacilli in the granuloma in the lung and tissues [18,29,30,31,34,35,44,45]. The bacilli remain quiescent in a non-replicative state [32,38] at the level of the lung, and occupies the majority of its decades-long life cycle in a state of slowed or arrested replication [1,4,7] (Figure 2B). However, the role of other targeted tissues targeted is the inducible bronchus-associated lymphoid tissue (BALT), a lymphoid tissue that contains B-cell follicles found in inflammatory lung diseases [41,45]. A recent report proposed that the proximity of BALT to the lung granuloma could influence the B cell follicles in BALT for protection against TB in addition to interferon-gamma (IFN-γ) [17-19,29]. While TNF-α is a pro-inflammatory cytokine required for an organized formation of granuloma [29,34,46] (Figure 1B). Furthermore, besides the cellular and molecular components that can be followed and detected, the dormancy regulon, and especially those dedicated to providing energy, the encoded phospholipases [46], the two-component system, Pho P, and Pho Q[47], the phosphate-binding proteins Pst1 and PstS2 [48]and the proteins encoded by operons [46,47] could be targeted [36]. Thus, the host immune response could be raised at glance by the tuberculin skin test (TST) and the delayed hypersensitivity test (DHT) to mycobacterial antigens [22,48-56]. These tests is the extent to which these might reflect or predict the likelihood of developing active disease. This possibility remains a mystery because the subtle molecular balance between the bacilli and the host interaction is such that the latent bacilli are maintained, under certain conditions, and for cell cycle replication, and is lauded to reenter the cell cycle to ensure its propagation as a species [3,7,14,28,29,35,45,46].

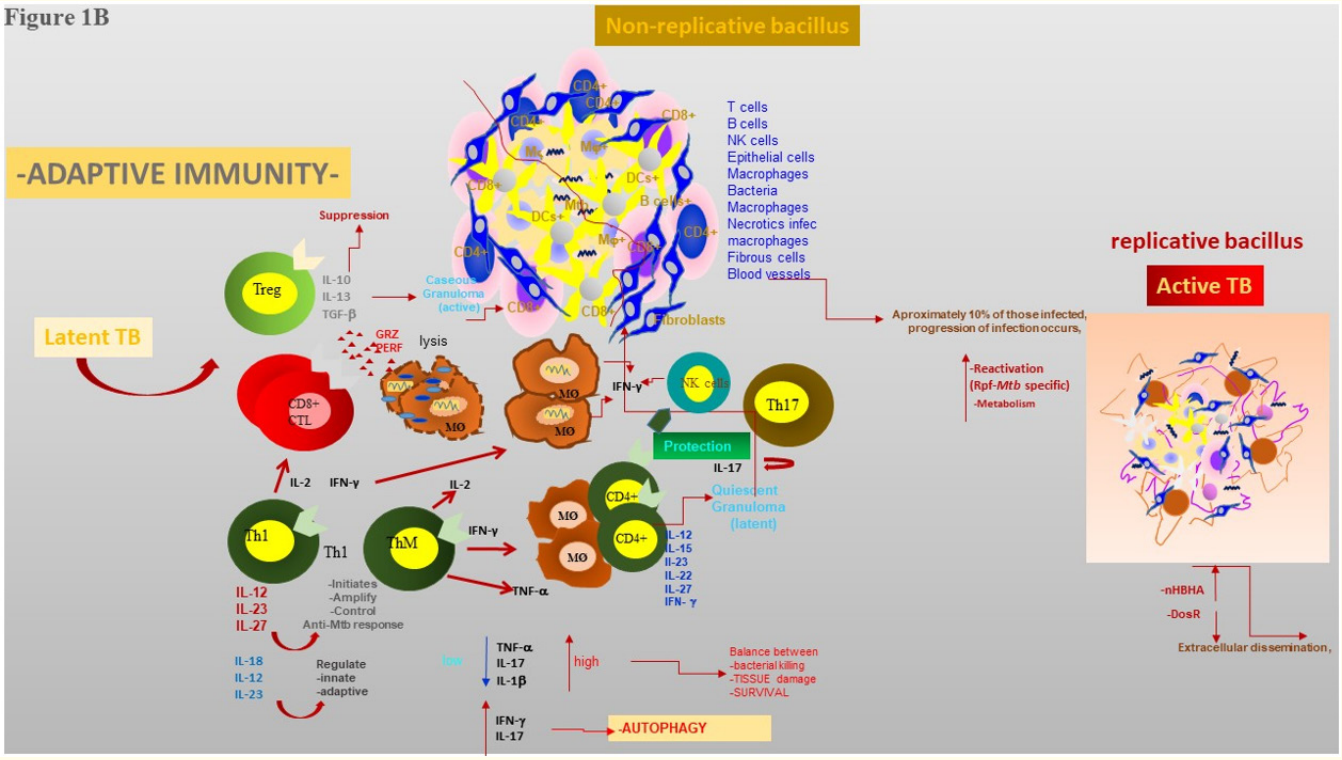

Figure 1b: The latent stage of the TB infection, is featured by the activation of the cellular response, once after the Mtb have triggered a pro-inflammatory response, with the induction of pro-inflammatory cytokines important to keep an activated state of the macrophages, and for the differentiation of the naïve CD4+T cells toward Th1, Th2, Th3, Th17. In this stage the host response is toward the balance to bacterial killing, avoid tissue damage and bacilli persistence through the formation of the granulomes. The different subsets of CD4+, the CD8+ T cells, the NK cells, the -T cells all are involved in the production of the IFN- , and other cytokines that are important to initiate, activate and control the cellular response to Mtb (IL-23, IL-27). The balance in the levels of the induction of for example TNF- , IL-17, IL-12, IL-18, are pivotal for fitness of Mtb while keeping a molecular off switch of the host response.

Omics technologies to address the host immune response to Mycobacterium tuberculosis infection

Omics technologies represent a key technological advance that have led the development of personalized medicine by providing an unprecedented amount of data enabling to dissect the molecular basis of many diseases and tracing detailed patients 'molecular signatures on a system biology scale [22-24,57]. The technologies that follow the signature and imprinting of the interaction host-pathogen, spatial, and multidimensional analysis include single-cell RNA-sequencing (scRNA-seq) and combinatorial multimodal analysis of surface proteins and cellular transcriptomics [57,58]. Examples are the cellular indexing of transcriptomes and epitopes (CITE-seq) and accessibility analyses throughout transposase-accessible chromatin (ATAC-seq) assay [46]. In terms of infectious diseases, elucidate the mechanism of pathogenicity [14,21,27,56-58] and the imprinting of the signature at the interface host-pathogen [23,24,59-63], and thus, gain insight and integrate the knowledge at the interface of the interaction that leads to disease [29,61-63].

The Human Tuberculosis study, through the perspective of One Health [1,2], consists of, 1) the unification and integration of cellular and molecular tools applied to animals [29,45,54], 2) the integration of the factors that affect the progression of the disease, 3) the identification of genetic markers, and biomarkers for diagnostic and prognostic purposes [27,29,59,61-63].

One health to integrate the "ome" host response rather than isolated features of the adaptive immune response through new generation high-throughput sequencing to obtain the complete transcriptome (RNA Ome) [63,64] or complete quantification using microarrays [65] in cells from blood samples and mucosal fluids [27,29,62-64].

The use of the multi-omics technologies allows a deep insight of several processes such as:

- The dynamics of cells and molecules, of the signaling pathways [56,57] involved in the interaction host-pathogen interface, the architecture, the topography of the immune cells in the lymphoid tissues (primary, secondary, and tertiary)
- The quantification of the repertoire of antibodies and receptor(s) in T and B cells, and
- The profile of the subset of antigen-presenting cells and lymphocytes under specific settings

The technology of the siRNA-seq analyses allows the determination of the identification and characteristics of clonal populations of T and B cells toward an antigen (a pathogen, microbial, fungi, viral to a vaccine candidate, and their association with different disease susceptibilities or states, as well as their capacity to migrate into tissues lesions [22,23,28,29,58]. A pioneer work on this has been the role of type I interferons signature in neutrophils of active TB patients [60]. A milestone in terms of new-generation Sequencing (NGS) is that millions of genomic or transcriptomic sequences can be analyzed at the same time, speeding the analysis of different organisms and different experimental and clinical settings [64-67] (Figure 2A). RNA-Seq technique allows transcriptomic profiles from cDNA libraries with the advantage of not reference genome for bioinformatics analysis, or no prior information on the transcriptome of either of the two species that are going to be analyzed [62,64] with higher levels of reproducibility [27,29,66,67]. It allows the identification of a large number of highly informative molecular markers. A set of expressed sequence tag (EST)-derived simple sequence repeat (SSR) and SNP EST-SSR and SNPs), associated with functional genes, making them applicable to adaptation studies. The identification of mutations and polymorphisms represent potential genetic markers for molecular diagnosis of human TB [14,15,21,29,60,63,68-70]. As it is outlined in Figure 2A, the contribution of each omics technology started in 1998 with the *Mtb* sequencing and the human genome sequencing (2003) allowing to unveil for one side the molecular components involved in the immune pathogenesis and for the other side, to dissect the genetic susceptibility to mycobacterial diseases (e.g., mutations in the interferon gamma receptor, MyD88, NEMO, and many other components in the pro-inflammatory pathway). From to 2015 of the use of the different omics technologies in TB mechanism of pathogenicity increased significantly, specifically at the level of epigenetics and how this is modulated by *Mtb* for success and long term survival in the lung [21,29,70].

Genomics

Since its introduction in 2010, next-generation sequencing (NGS) has become a foundational technology in genomics by providing detailed structural information about genomic variants [21,72,73]. Building on this foundation, NGS enables the detection of mutations and polymorphisms, which serve as genetic markers for the molecular diagnosis of human TB. Structural genomics supports the identification of single-nucleotide polymorphisms (SNPs) for strain typing of MTBC lineages and for determining drug resistance profiles. These applications facilitate the development of targeted diagnostic tools and inform treatment strategies in clinical research. Furthermore, to inform about how structural genomic information can influence and modulate the host-pathogen interaction, WGS using a DNA platform provides a more complete account of the genomic features of the *Mtb*-infected resistance population [64,72,73]. Moreover, using WGS analysis, several gaps are being approached: the evolving nature of drug resistance in TB, the resistance population to both first-line and second-line anti-TB drugs, and the genetic susceptibility to mycobacterial infections in humans through genome-wide studies [14,21,72-75]. Under this context, WGS-based approaches are quickly moving from research laboratories to clinical care and public health applications [64,71,76]. Thus, WHO is already using WGS for drug resistance surveillance and is scheduled to evaluate sequencing technologies for routine genotypic DST [1,76] and for accurate predictions for resistance to pyrazinamide, ethionamide/prothionamide, and para-amino salicylic acid, respectively [77-81]. The impact of this is that bona fides of NGS allow millions of genomic or transcriptomic sequences at lower time and reduced cost [77-83] (Figure 2A).

Metagenomics

Next-generation sequencing (mNGS). One of the most significant milestones of metagenomics is that, despite rapid molecular methods such as PCR and LAMP, rapid advances in NGS technology

are allowing increasingly rapid and accurate sequencing of entire bacterial genomes at ever-decreasing cost, providing unprecedented depth of information [84-87]. mNGS under different settings can provide information about significant dynamic changes in the clinical manifestation of TB in the progression of the disease, and recurrent antibiotic treatment. A significant advantage of mNGS is its ability to sequence microorganisms that cannot be cultured under standard laboratory conditions. This method has improved the detection of pathogenic infections, such as Non-Tuberculous Mycobacterial (NTM) and in severe cutaneous TB cases [88-91]. In addition, similar to targeted next-generation sequencing (tNGS), mNGS enables the identification of specific pathogens in clinical samples through multiplex polymerase chain reaction (PCR) amplification or probe capture, resulting in high sensitivity and greater efficiency [92]. Indeed, it has been reported that through the use of mNGS is that it has been possible to confirm conventional metagenomics in 101 of 123 TB patients [19,85,86,88-90], with bacteriologically and clinically, supporting thus, the notion that NGS stands to revolutionize the diagnosis and epidemiological study of TB. Furthermore, to address the role of the lung microbiota in the immunomodulation of the host response in TB [84], especially in active or severe patients [85]. Thus, using BALF samples and sequencing shotgun metagenomics, it has been possible to assess alterations in the lung microbiota associated with TB infection. It has been observed that anti-TB treatment significantly affects the alpha and beta diversity in patients with PTB [85]. Moreover, determination of lung microbial signatures in cells from the upper airways provides unique features of lung microbial dynamics and clinical characteristics of TB patients, providing thus new insights for medicine of precision [19,85-90]. From the milestones, metagenomics have advanced in the last decade (Figure 2A) favoring the microbiome analysis in the host immune response to different external insults.

Epigenomics

Epigenetic processes refer to modifications in gene expression that are regulated by distinct microenvironments within the body, such as neuroendocrine alterations, oncogenic activity, and exposure to chemical substances. These mechanisms are particularly significant in the context of host-pathogen interactions during the development and progression of tuberculosis. Epigenetic regulation of host chromatin facilitates granuloma formation, thereby promoting the survival and persistence of *Mtb* [89-92]. Consequently, this intracellular pathogen has developed a mechanism to modulate and regulate the host's epigenetics, which facilitates the pathophysiology of tuberculosis and contributes to host susceptibility to the pathogen while also activating the host immune response against the invading organism, resulting in active disease. Under this scenery infected macrophages subsequently enhance their effector functions through epigenetic changes, making DNA more accessible for transcription [89-92]. Expression of these markers occurs in host-infected macrophages during pathogen recognition, phagocytosis, and degradation within the phagolysosome, activation of the inflammasome, and proteasome-mediated antigen processing and presentation [93-95]. Epigenetic studies in active disease have indicated that infected macrophages enhance their effector functions through epigenetic alterations (increased hyper-methylation of IL6R, IL4R, and IL17R) that render DNA more accessible for transcription [19,96-102]. In addition, the shift in metabolism towards glycolysis and the secretion of pro-inflammatory cytokines are effector functions that are also regulated by epigenetic modifications. This plays a crucial role in the macrophage's capacity to effectively respond to *Mtb* infection, and represent promising biomarkers for diagnostic and therapeutic strategies in infectious diseases. In addition, it has been shown that suberanilohydroxamic acid (SAHA), an FDA-approved oral drug inhibiting histone deacetylase enzymes (HDACi), can alter epigenetic mechanisms prior to the metabolic switch and enhance immune responses during *Mtb* infections [93,96,99,102]. Furthermore, modifications such as histone acetylation, changes in non-coding RNA, DNA methylation, and variations in miRNA play significant roles in the pathophysiology of tuberculosis and influence the infection's outcome [93,95]. The challenge lies in identifying the key host proteins, non-coding RNAs, or secretory proteins produced by *Mtb* that either directly or indirectly induce epigenetic modifications in the host chromatin, as a strategy to navigate and coexist with the immune response [25,26,93-98], thus promoting its survival and spread. Thus, the integration of this research with other omics technologies has facilitated the identification of various molecular genetic markers and biomarkers related to both active and latent infections (Figure 2A). To the identification and recognition of host proteins, non-coding RNAs, and secretory proteins that directly or indirectly contribute to epigenetic modifications [25,26,95,96]. In resistant individuals there is a latency stage characterized by epigenetic regulation of host chromatin that promotes the development of granulomas,

which are comprised of immune and non-immune cells.

It is a strategy to coexist with the host immune system and long-term persistence and survival of *Mtb* [93,94]. Studies conducted to study the mechanisms involved in the suppression of various immune genes, epigenetic studies included the identification of microRNAs and the analysis of regions upstream of the transcription start sites of these genes for common sequence motifs. This insight sheds light on the survival strategies of *Mtb* within infected cells, characterized by a sophisticated immune "molecular switch off" regulated by both microRNAs and Alu sequence repeat elements transposable.

Transcriptomics

Transcriptomic analysis can be conducted to investigate the spectrum of the disease, the regulation of gene expression during host-pathogen interaction, and the host immune response. This can inform about patterns and signatures to predict outcomes of the disease severity and progression, and henceforth be a tool for diagnosis and treatments [103-106]. The fundamental scientific principle of transcriptomics involves the analysis of RNA, utilizing methods such as exome sequencing and microarrays to quantify RNA transcripts in specific cells or peripheral blood during active, severe, or latent infections. This understanding provides insights into how the host's immune response is modulated during and across different stages and clinical sub-stages of *Mtb* infection. The RNA-Seq technique facilitates the generation of transcriptomic profiles from cDNA libraries, offering the benefit of not requiring a reference genome for bioinformatics analysis, even in cases where there is no prior knowledge of the transcriptome for either of the two species under investigation. Additionally, RNA-Seq does not have a maximum quantification limit and demonstrates greater reproducibility [141,145,146]. It facilitates the identification of a wide array of highly informative molecular markers [63,65,103,104]. This method allows us to explore the host-pathogen interaction through the analysis of transcripts and transcriptional signatures at the interface of systemic and mucosal compartments [103-109]. For instance, during an active or primary infection, the bacteria localize to specific sites (typically the lungs) and are associated with clinical symptoms [103,104]. The transcriptional signature can serve as a valuable tool for diagnosing and predicting the progression of active TB disease [108,109]. In terms of the host immune response, the integrated analysis of single-cell transcriptomes and T cell receptor profiling during the immune response reveals the presence of T cell exhaustion deficiencies in patients with pulmonary tuberculosis [107] in both CD4+ and CD8+ and in clonally expanded CD4+ and CD8+T cells that also expressed the cytolytic markers granzyme (GZMK) and perforin [107]. In addition, this study provided insights into the transcriptional signature associated with the type I IFN pathway in neutrophils of active TB patients compared to healthy individuals, contributing to understanding the intricate immune pathogenesis involved in active TB (Figure 1B,2A).

The transcriptome that provides insights into the non-invasive and quiescent phenotype, contrasting active infection with dormancy, reveals changes when the bacteria reach an extra pulmonary site, such as the ocular environment. The genes associated with active replication, aerobic respiration, and lipid metabolism are either significantly downregulated or show no differential expression. Thus for example, it has been reported that in AIOF (a specific cell or niche environment) exhibits a downregulation of genes from the DosR regulon, suggesting a suppression of dormancy, similar to what is observed within RPE cells [47,48,105-109].

Of note is that when *M. tuberculosis* infects human whole blood, there is suppression of gene transcription rather than activation, affecting the spatial and functional effector functions. This reveals their role in the mechanism of host immune response, such as uptake, phagocytosis, activation of the proteasome, and antigen presentation. Interestingly, when clusters of alveolar macrophages in the lung are infected, a different landscape has been observed. Instead of a transcriptional signature, an epigenetic pattern of restrictive response to infection has been found. Furthermore, through transcriptomics, it has become possible to identify immune protection correlates, particularly emphasizing the importance of cells expressing the IFN-γ receptor in protective immunity [105-109].

Various factors (environmental, genetics, age, and co-infections) can influence these cells' ability to respond to IFN-γ, affecting their cytokine response capacity and, henceforth, a decreased immune response to *MTb* infection. On other hand, in comorbidities of TB and DM, transcriptional data have shown that several molecules, including lipocalin (LCN2), defensin alpha 1 (DEFA 1), and

integrin subunit alpha 2b (ITGA2B), were notably upregulated, while chloride intracellular channel 3 (CLIC3) was significantly downregulated. Moreover, interleukin 17 (IL-17) and other signaling pathways such as phosphatidylinositol 3-kinase (PI3K)-AKT, and peroxisome proliferator-activated receptor (PPAR), have been found to play significant roles in the management of post-infection with DM. Thus, the transcriptional profile can be utilized to monitor the progression of tuberculosis disease and to discover novel immune mechanisms [47,48,92,105-109].

Proteomics

In recent years, research has focused on understanding how the proteome is affected during host-pathogen interactions in TB. It has been suggested that gaining a deeper insight into how genome-encoded functions are carried out and adjusted at the proteomic level could greatly aid in the development of therapies targeted specifically at TB [109-112]. The modulation of the proteome through epigenetic alterations, commonly referred to as post-translational modifications (PTMs), these include processes like phosphorylation, particularly in proteins linked to chromosomal instability. Notably, protein acetylation (Ac), especially lysine acetylation, plays a role in regulating cellular metabolism [92,93]. Ac is recognized as a modification affecting numerous proteins, both histone and non-histone, found in various cellular compartments, including the nucleus, cytoplasm, and mitochondria, and it is involved in a range of functions from gene regulation and cell signaling to metabolism in both normal and pathological contexts [47,113-115]. A recent innovation involves the integration of diverse omics technologies to offer a comprehensive synthesis of genomic, transcriptomic, and proteomic data, ultimately elucidating functional relationships between genes and proteins [112,113]. Nevertheless, this technology faces certain constraints, particularly because proteomic data is not as plentiful as genomic data. To address these challenges, three methodologies have emerged: 1) Techniques like reverse phase protein arrays (RPPA) that enable the simultaneous collection of semi-quantitative data for a larger number of proteins in biological and clinical samples [111]. 2) This process entails the application of protein lysates to nitrocellulose, allowing for the quantification of selected proteins or phosphoproteins across multiple samples under identical experimental conditions. 3) The SOMA scan assay serves to quickly quantify a specific set of proteins, primarily aimed at identifying biomarkers for two significant purposes: facilitating preclinical and clinical drug development, and supporting clinical diagnostic applications related to various diseases and conditions [110-112]. Mass spectrometry-based proteomics (MSP) can provide insights into the quantitative status of a proteome by accurately identifying the primary chemical structures of proteins or peptides, including various post-translational modifications that may go undetected. This technology has played a significant role in deciphering cellular signaling networks, clarifying the dynamics of protein-protein interactions in numerous cellular activities, and improving the understanding and diagnosis of disease mechanisms [114,115]. Therefore, mass spectrometry (MS)-based methods have become the preferred choice over the last twenty years for reliable and nearly comprehensive identification and quantification of proteins in biological samples. One of the advantages of the MSP) is that it offers valuable information regarding the true biochemical environment of the specific cell or tissue, as it enables the quantification of small molecules [112], and it can identify the primary chemical structures of proteins or peptides that contain multiple PTMs. The limitations of discovery proteomics are currently being addressed by targeted proteomics using two methodologies, a selected/multiple reaction monitoring (S/MRS) [112] and parallel monitoring (PRM) [112]. These allow for consistent and precise quantification at low abundance levels and in complex mixtures. It is particularly effective for personalized medicine when measuring a small number of proteins across a large volume of patient samples [47,48,113]. Additionally, discovery proteomics can be utilized to explore the interactions between hosts and pathogens, particularly concerning the impact of PTMs during the interactions. This involves the use of both top-down and bottom-up approaches. Top-down proteomics examines the complete sequence of the proteins being studied, aiming to minimize any alterations to the sample. Bottom-up proteomics relies on the pre-digestion of samples (usually using trypsin) followed by the examination of peptide fragments through high-throughput analytical techniques [47,48,113]. It is crucial to gather comprehensive data on the proteins being monitored throughout the interaction, both in the early and late stages after infection, as these may serve as potential targets for specific quantification, necessary for diagnostic purposes [89-112].

On the other hand, proteomics to explore host's immune response upon in TB, offer an in-depth understanding of protein

dynamics to clarify their roles and functions in this interaction. By analyzing data computationally, various potential T and B cell epitopes were identified, which were subsequently tested *in vitro* and demonstrated immunogenicity with the ability to influence innate immune responses [15-17]. This particular protein enhances the maturation of dendritic cells by elevating the expression of activation markers such as CD80 and HLA-DR while reducing DC-SIGN expression, with this interaction being facilitated by the innate immune receptor TLR2. Mining the human proteome in TB infection has led to findings such as: 1) a protein capable of influencing innate immune responses and promoting dendritic cell maturation by enhancing the expression of activation markers like CD80 and HLA-DR, while reducing DC-SIGN expression through the innate immune receptor TLR2,2) the immunodominant *Mtb* antigen, MPT70, was found to be upregulated in macrophages infected *in vitro* in response to gamma interferon (IFN-γ) or conditions of nutrient and oxygen deprivation. *In vivo* studies indicated that the serum levels of MPT70 in tuberculosis (TB) patients revealed higher IgG reactivity or detection in comparison to healthy controls. Furthermore, the changes and immunogenic properties of the *Mtb* proteome has been reported to be linked with the dormancy survival regulator (DosR) and the resuscitation-promoting factor (Rpf) [22,29,47,48,113].

Among the proteins that contribute to the evasion of *Mtb* is Rv2626c, also referred to as hypoxic response protein 1 (HRP1) or dormancy safety regulator protein. These antigens can suppress TLR4 inflammatory signaling in macrophages by binding to the RING domain of TRAF6, thereby hindering lysine (K) 63-linked polyubiquitination of TRAF6, which affects E3 ubiquitin ligase activity [22,29,34,115]. It has been observed that this provoke a robust serum antibody response in cases of active tuberculosis. Moreover, a peptide that encompasses the C-terminal region of amino acids 123-131 has demonstrated significant therapeutic effects in a mouse model of sepsis induced by cecal ligation and puncture, targeting macrophages and effectively penetrating the cell membrane. These peptide-based treatments exhibit anti-inflammatory and antibacterial effects for sepsis management [115].

Epitope analysis of PE/PPE Rv1705, part of the five type VII secretion systems (ESX-1 to ESX-5), revealed a dominant epitope located in its N-terminal domain. Epitopes associated with a peptide TLR4 agonist RpfE-like adjuvant at the N-terminus elicit a robust helper and cytotoxic CD8+ T-cell immune response, resulting in elevated levels of IFN-γ [114-116]. This results in macrophage activation and the production of cytokines necessary for the differentiation of naive CD4+ T-cells [37,47,48,67].

Metabolomics

Metabolomics is used to examine the alterations in the body's metabolites across various conditions, which can be a significant method to determine variations in metabolites, identifying disease-related metabolic biomarkers, mechanisms behind drug action/metabolism, drug toxicity, microbial drug resistance, and the role of carbohydrate metabolism during *Mtb* infection. This might serve as indicators of the host-pathogen interaction [115,116]. These peptide-based treatments exhibit anti-inflammatory and antibacterial effects for sepsis management Metabolomics, alongside genomics, proteomics, and transcriptomics as part of systems biology, helps clarify the functionality of the genome of the pathogen in the context of host-pathogen interactions [116,117]. This approach aims to provide a better understanding of the mechanisms of drug action, drug toxicity, and microbial drug resistance. Additionally, it highlights how metabolite biomarkers can act as prognostic indicators for predicting treatment outcomes.

The contributions of metabolomics to the characterization of tuberculosis have been significant, particularly in enhancing the understanding of *Mtb* regarding (1) metabolism, (2) growth and replication, (3) pathogenicity, and (4) drug resistance [116-119] (Figure 2A). To accomplish these various tasks and objectives, liquid chromatography tandem mass spectrometry (LC-MS/MS) in conjunction with comprehensive bioinformatics analysis has facilitated the identification of metabolites in the serum of patients with osteoarticular TB [116,117], to uncover new metabolic biomarkers for diagnosis [119]. It can also be possible to determine metabolites involved in several lipid metabolic signaling pathways, including choline metabolism, sphingolipid signaling, retrograde endocannabinoid signaling, as well as sphingolipid and glycerophospholipid metabolism [118]. To explore how metabolism is influenced during the interaction between host and pathogen in active TB, and DM [119], the multimodal metabolomics and lipid omics approach used to analyze plasma metabolic profiles revealed disturbances in lipid metabolism through the C18 metabolomics and lipid omics

Figure 2a: The timeline of the research milestones in the use of omics technologies in addressing host pathogen interaction in the context of Tuberculosis (A-C). It is pinpointed several of them, which allow to delineate the increasing usage of the single and combined omics technologies. The details of each research is delineated with the author, the year and the milestone.

assessment [119;120]. In comparison to TB alone, the comorbidity with DM demonstrated increased levels of bile acids and compounds associated with carbohydrate metabolism, along with decreased levels of glutamine, retinol, lysophosphatidylcholine, and phosphatidylcholine [120]. Additionally, arachidonic acid metabolism was identified as a potentially significant component in the pathophysiological relationship between TB and DM, and within a correlation network of the markedly altered molecules, chenodeoxycholic acid emerged as a key node. The fatty acid (22:4) was present in all major modules [119,120], while various amino acid (phenylalanine/histidine,citrulline/arginine,kynurenine/tryptophan) ratios differentiated TB from the control group. While amino acid levels (i.e., serine, glycine) and choline were lower in TB-DM than in TB alone [118-120]. All together, these findings have contributed to the discovery of new metabolite biomarkers, and to the understanding of metabolic alterations in TB-DM [116-120]. On the other hand, the combination of omics, metabolomics and lipid omics offer a comprehensive overview of the metabolic transformations linked to these infections, and autoimmune conditions [118,119]. Moreover, and of relevance is that using metabolomics and transcriptomic data from patients with PTB, and DM has suggested that the NOTCH1/JAK/STAT signaling pathway plays a crucial role [119,120]. The physiological levels of these metabolites could serve both for fundamental understanding as well as for clinical use as biomarkers for PTB in patients with DM [119,120].

Artificial intelligence and infectious disease

Artificial intelligence (AI) has been around for over 60 years. Its importance has grown with the rise of omics technologies, generating vast amounts of data and resulting in many real-world applications, particularly in medical imaging [121]. In the last

decade, the development of artificial intelligence methodologies has contributed to accelerating the processing of large amounts of data and reducing the error rate in image analysis. In infectious disease research, artificial intelligence has been used for modeling by combining machine learning, computational statistics, and information retrieval with routinely collected infectious disease surveillance data and data science [121-126]. A search in the PUBMED database currently retrieves 4,339 papers focused on the application and development of AI methods to accelerate research in this area. Infectious diseases, which the WHO cites as a major threat to individual and public health, are a key field where AI-driven tools offer significant potential [121-126] (Figure 3). This information is used to answer key epidemiological questions, such as the rate of transmission and incidence, the distribution, frequency, magnitude, the predictions and control of factors linked to human health and disease, as well as the determining factors of diseases in defined human populations.

Remarkably, AI is revolutionizing data analysis and the prediction of pathological outcomes. AI models facilitate disease diagnosis, condition classification, and risk prediction [122,123]. Integrated with systems and synthetic biology (omics technologies), AI accelerates anti-infective drug discovery, enhances the understanding of infection biology, and expedites diagnostic development [124]. The application of artificial intelligence in infectious disease research involves developing systems capable of interpreting complex datasets [122-126]. These approaches facilitate analysis at multiple biological scales, ranging from single cells to entire populations. Furthermore, AI methods integrate large-scale quantitative and omics data, thereby expanding research capabilities and driving advancements in biomedicine and biotechnology. AI has the potential to identify pathogens in different types of samples (such as fluids or solids) for accurate diagnosis [125]. This can even be more optimized through the combination of automation with AI algorithms, thus increasing productivity. Since the pandemic in 2019, in terms of imaging animal models, it has motivated rapid developments in AI and medical imaging techniques, with two main objectives: to improve patient care, but also to fill gaps that exist in clinical infectious disease research [127].

Furthermore, AI methodologies such as machine learning (ML) and big data analytics (BDA) algorithms can be applied for analyzing diverse datasets. Thus, for example, ML can be applied and addressing in several key areas, such as outbreak prediction, pathogen identification, and drug discovery, while the combination of ML and BDA can aid in the prediction of for example the performance of antigens as vaccine candidates, the feasibility of subunit antigen vaccine, at the same that be helpful in the subunit vaccine design, discovery and characterization [128]. ML and DL can be focused for a better management of human infectious diseases and clinical research, in terms of laboratory diagnostic that includes, -Digital culture plate reading,-Malaria diagnosis,-Antimicrobial resistance profiling, -Clinical imaging analysis (e.g. pulmonary tuberculosis diagnosis) [129] -Clinical decision support tools (e.g., sepsis prediction, antimicrobial prescribing), -and public health outbreak management (e.g. COVID-19) [129]. Besides, AI can address Clinical validation, such as, research with translational potential, and -drug discovery and microbiome-based interventions.

Artificial intelligence and Tuberculosis

From the 4339 paper related to the role of the AI in infectious disease, 1186 are related to AI and TB [126-130]. In Figure 2 it is depicted selected milestones of AI in TB research. Thus, the application of artificial intelligence to Tuberculosis has been explored since the development of algorithms, with the performance starting around 2012. Since then, it has become one of the system biology languages with impressive results. Artificial intelligence (AI) has become the most novel and powerful bioinformatics tool in the research of almost any field of science. The current potential of Artificial Intelligence (AI) in infectious disease resides in that it has transformed the landscape of prognostic, diagnostic, and TB treatment. The integration of AI tools, such as machine learning (ML) and natural language processing (NLP), trained with vast amounts of clinical data, including genomic, transcriptomic, and imaging data [126-128], can enhance our ability to identify at-risk populations, predict drug resistance, identify novel mutations, optimize treatment regimens, predict disease outcomes, and tailor therapeutic interventions [66,67,105,129-131]. It can enhance our ability to identify at-risk populations, predict drug resistance, identify novel mutations, optimize treatment regimens,

predict disease outcomes, and tailor therapeutic interventions [132-134]. Indeed, AI tools, such as artificial neural networks (ANN)(neural networks, connectionist models to solve complex patterns of data without previous knowledge of the distribution of the data), fuzzy logic (to facilitate expression through natural language labels and bring us closer to that natural treatment of language when attempting to qualify and quantify within the development of information systems), genetic algorithms, DL and artificial intelligence simulation (AIS), have become a promising alternative that can aid clinicians and researchers to augment efficacy and specificity in the diagnostic test in different types of samples and in computer-assisted diagnosis for chest imaging radiology [135,136] (Figure 3). Since current diagnostic tests, e.g., Tuberculin skin test (TST), interferon gamma release (IFN-γRes), biomarkers and the gold standard assay can only differentiate infected individuals from healthy ones but cannot discriminate between latent TB (LTBI), and active TB infection (ATB), it has been proposed that the application of machine learning (ML) in diagnosis [137] could aid in a more effective differential diagnosis of healthy and LTB patients. Once optimized and validated, it can be amenable to large-scale screening everywhere [137]. AI machine learning can be combined with several other methodologies, such as NGS, PET-CT (Positron Emission Tomography (PET) scan and a Computed Tomography (CT) (a combined assay of detection of radiotracers –PET., and the image test scan-CT., to evaluate organ and tissue function and thus to detect clinic manifestations of disease much faster than other image methods. To track diseases, e.g., neurodegenerative, cancer and cardiac conditions. The X-pert or the Gene X-pert MTB/RIF assay, a PCR assay for the detection of rifampicin resistance worldwide in patients with HIV-associated, smear-negative tuberculosis. The determination and identification of blood biomarkers, can aid and potentiate the TB diagnostic and treatment as well [138]. The line probe assay (LPAs), based both in PCR and electrophoresis in gel, and is an assay for the detection of MDR rifampicin and isoniazid (INZ) and for the detection of another species of mycobacteria from sputum or medium cultures [1,2].

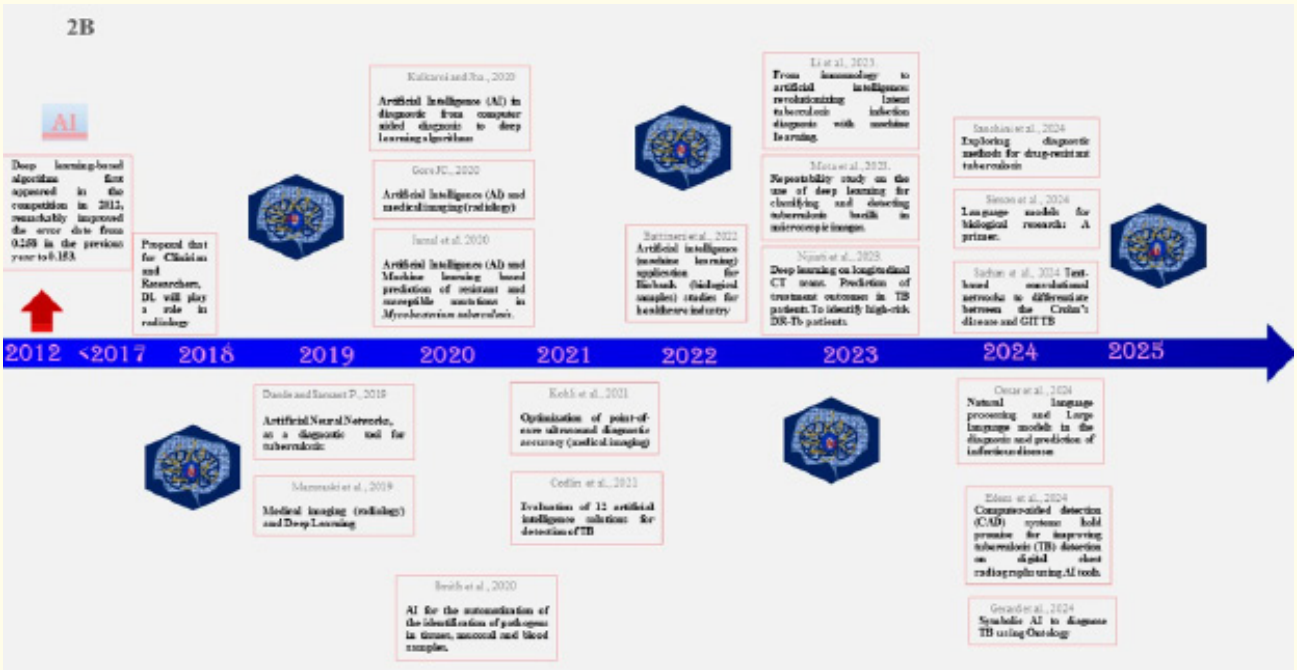

Figure 2b: As depicted for omics technologies, despite that AI started to be used sixty years ago, in recent years, the application and the use of AI through the three main methodologies, deep learning (DL), machine learning (ML) and Big Data analytics (BDA) are being applied as prediction, evaluation, validation, differentiation in diagnostic and to improvedimmunotherapies based on the host immune response.

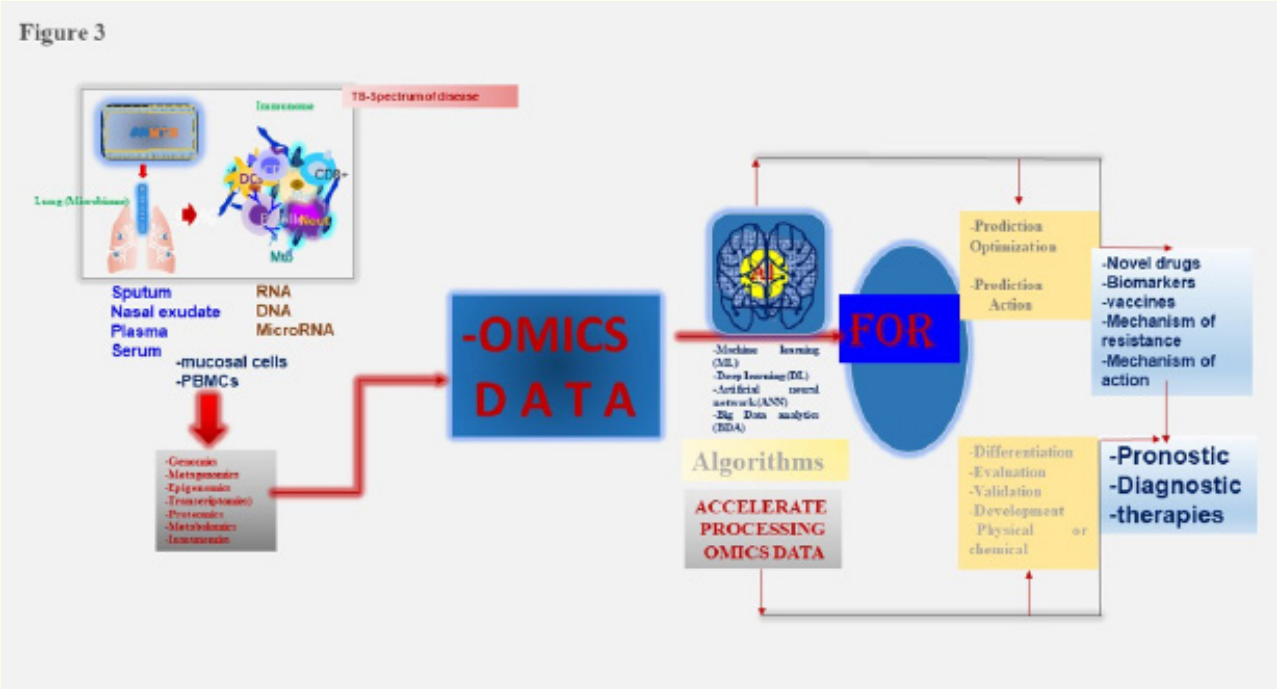

Figure 3: The interaction host-pathogen in the context of the immune pathogenesis of the TB disease can be addressed using omics technologies in conjunction with artificial intelligence. As outlined in figure 1 the milestones of the omics technologies have required the development of a biological language to interpret in active or latent TB infection, and the subclinical stages, the expression of genes, proteins, and metabolites in tissues, organs, and fluids can be determined using omics technologies. This molecular information that can be the source and a input for IA algorithms, to predict, to evaluate basic and applied investigations for example, on the different types of mycobacterial drug resistance [(MDR), single-drug resistance (SDR), and extensive drug resistance (XDR)]. AI through different methodologies, deep learning, machine learning, Big data analytics, and neural networks to approach mechanisms of resistance, the genetic variability in the host response to TB infections, the bio signature at the level of the epigenome, proteome, transcriptome, metabolome. The signature that allow biomarkers determinations for diagnostic and treatment.

AI can contribute to global health in two main aspects, one is in chest radiography, covering from simple computer-aided diagnosis systems to more advanced deep learning algorithms [139] (Figure 3). The other is in the capacity of AI-based technologies to discriminate EPTB and Crohn's disease (CD). This can be done through the use of multiple parameters, which results in increasing sensitivity and accuracy versus traditional models. Moreover, a test library of chest X-ray (CXR) images blindly re-read by two TB clinicians developed with different levels of experience and then processed by 12 CAD software solutions [140]. A disadvantage of this software is that the majority of the CAD software showed significantly lower performance among participants with a past history of TB. Another weakness was that the radiography equipment used to capture the CXR image was also shown to affect performance for some CAD software. Despite this, it is indicated that TB program implementers now have a wide selection of quality CAD software solutions to utilize in their CXR screening initiatives [140].

How to have a snapshot to decipher the dynamics, the profile of the innate and adaptive immune responses, under the external stimuli, pathogens, and their association with other diseases, with other physiologic states at specific tissue and mucosal compartments. To these challenges, novel technologies such

as multi-omics technologies have become a revolution that generates thousands of data to interpret them and to understand what is happening in health and disease [131,132]. Furthermore, multidimensional analyses generate such an amount of data that the lack of appropriate language to interpret can lead to misunderstanding of what is happening at the interface of the host-pathogen interaction and in the dynamics of a population of cells in a specific tissue environment. Therefore, a type of biological model language that has become very popular is the AI, which can be a valuable tool to evaluate what is happening in a particular experimental condition in a tissue-specific environment using language models. AI can learn complex patterns within sequences (amino acids in a protein, nucleotides in genes [131,132] and interactions, such as the Immunological pathways. Indeed, AI is an artificial neural network that can capture the interaction of amino acids in a protein, signaling pathway, or gene expression patterns across long sequences [131,132]. Another example is single-cell gene expression data formulated sequentially by creating a sequence in which genes appear in the order of their RNA expression levels in a cell. As the language model processes the input sequence, it internally computes an embedding, a numerical representation for data analysis and visualization, and fine-tuning the data relevant to the desired goal. The input allows a direct prediction approach, which is the simplest, the language model is given inputs and used as is to make predictions. The transfer of learning, in which pre-training on a larger dataset, provides the model with a fundamental understanding of the data, enabling more efficient learning of the new objective during fine-tuning with novel data. A model that has already been trained (pre-trained) on the data and is offered further trained (fine-tuned) on new data [119-124,131-133].

DL in enhancing TB diagnosis through the classification and detection of TB bacilli in microscopic images. The systematic review outlines various DL techniques used to assist in automating sputum smear microscopy, which traditionally relies on manual counting and is prone to human error [129] explored multiple studies, identifying DL methods such as convolutional neural networks (CNNs) and their ability to significantly improve the accuracy and efficiency of TB diagnosis. These techniques, applied to Ziehl–Nielsen-stained images, offer a promising solution to address the limitations of traditional microscopy, making TB diagnostics more accessible and reliable, especially in resource-limited settings. Furthermore, prediction model for drug resistance has been developed [113,129,133,137,138] developed models for predicting resistance in the genes coding for target proteins affected by first-line TB drugs. These models use various sequence and structural features of single nucleotide variations (SNVs) to capture the impact of mutations. The study focuses on mutations in key genes such as *rpoB*, *inhA*, *katG*, *pncA*, *gyrA*, and *gyrB* that are associated with resistance to drugs like rifampicin, isoniazid, pyrazinamide, and fluoroquinolones. The models were developed using several ML algorithms, including naïve Bayes, k-nearest neighbor, support vector machine, and artificial neural network, achieving an average accuracy of 85% across all examined genes [134-141]. In another study it has been emphasized the importance of accurate and rapid diagnostics to manage MDR-TB and XDR-TB strains [133]. It is proposed that a combination of phenotypic and molecular DST methods to tackle challenges such as resistance to new drugs, hetero resistance, and low-level resistance mutations. For this aim, three DL-based prediction models (PMs) using longitudinal CT images were developed to TB treatment outcome [134-139].

On the other hand, the use of natural language processing NLP, and large language models (LLMs) in the diagnosis and prediction of infectious disease highlights how these technologies can extract valuable insights from large volumes of unstructured clinical data, such as electronic health records (EHRs). Thus, to support early diagnosis and personalized treatment strategies discuss how LLMs can be trained on vast amounts of EHR data to predict disease progression and identify high-risk patients. This approach can be particularly useful in TB-endemic regions, where resources for extensive testing may be limited [113,131,133,136,142,143].

Discussion

The host-pathogen interaction in particular referring to the interaction of the M. tuberculosis at the interface of the epithelial and mucosal surfaces offer the possibility to study and to dissect the molecular mechanism of pathogenesis that can be approached at different scales, molecular and cellular (Figure 1A-B). The host immune response at this first line of defense plays a key role that involves to the antigen presenting cells of the innate immune response, macrophages, dendritic cells, neutrophils,

NK cells[27;28]. One activated this response that also involves to the complement system, there is a connection with the adaptive immunity, in which the B and T cells iNKT, and the gamma delta lymphocytes respond to the infection producing products for the differentiation and homing of subsets of lymphocytes to distal mucosal sites. One of the question pinpointed by several authors, is how MTB inducing a state of molecular off/Switch to overcome the host immune response and survive? [27,30,48]. At which level is the regulation, epigenetic, transcriptomic, proteomic? From the milestones depicted in Figure 2A, it is clear that the use of the different omics has been step by step along and in conjunction with the development and advancements of devices and equipment to have better resolution, precision and mode of interpretation of the data. In other words, approaching the epigenetics of the interaction host-pathogen did not limit to the use of the metabolomics as a diagnostic test or the transcriptomics. The limitation that reside in one of the other omics technology might be the compartment analyzed, the methods used to obtain the sample, the sensibility of the equipment, the technique and the methodology. By the scientific part depends enormously how close we can study and analyze the interaction and the living of *Mtb* in the host, specifically with the innate and adaptive immune cells [30,35,36,38]. All this before can be traduced in biomarkers of the spectrum of the *Mtb* disease (active, clinic sub stages, latent). Biomarkers translated as metabolites, as proteins, glycoproteins, lipids, transcription factors, downstream key genes of the pro-inflammatory response, or anti-inflammatory response, methylation patterns, autophagy, ubiquitination, and many more molecular components that has been analyzed since the first approaches using omics technologies (Figure 2A). Moreover, the cross talk with the microbiome at the lung can also give a cue in the immunomodulation of the host response against TB. In addition, the genetic variability plays a key role in the fate of the infection and in the host susceptibility to the TB infection. Overall the milestones described in figure 2A either in omics technologies focused in TB shed light in the efforts to understand and how is being approached the success of MTB for long term survival and evasion of the host immune response [16-18]. Finally, how the development of algorithms can aid to the omics analysis, can aid in different ways, not only in speeding the analysis of the images but in the speeding the processing of data, evaluation of clinic test *in vivo* and *in vitro*, the animal models (Figure 2B), favoring thus, importantly, the establishments of models of prediction either of the host-pathogen interaction as well as behaviors of drugs/candidate vaccine, the adjuvants, or enhancers of the immune response (Figure 3) [16-18,48]. Taking in account what it has been pinpointed above, it is noteworthy to mention that current present in diagnostic and treatments that New guidelines concerning TB diagnostics and a corresponding operational handbook included recommendations for targeted next-generation sequencing. These guidelines recommend the use of the uridine lateral flow lipidoarabinomannan (LF-LAM) assay [1] for adults and adolescents with HIV,conducting molecular tests on respiratory specimens and stool samples in children,and simultaneously utilizing molecular tests on respiratory samples, stool, and the LF-LAM assay on urine from children living with HIV. Many studies with pipelines for TB treatment encompass translation studies from *in vitro* to *in vivo* performance in animal models such as zebrafish embryos. In the treatment guidelines for individuals with MDR/RR-TB have been incorporated a new 6-month treatment regimen that includes bed aquiline, delamanid, and linezolid, along with either levofloxacin or clofazimine, or a combination of both. Six new tuberculosis vaccines are in phase III clinical trials as of August 2024, demonstrating safety and efficacy [1-3]. In terms of the development of candidate's vaccines and delivery systems, small-molecule chemical libraries can effectively identify chemo types active against tuberculosis through phenotypic whole-cell-based assays [46-48,60,90,161,80,114]. The application of mycobacteriophages when effectively formulated in Nano-vehicles targets resistant strains, including MDR, XDR, or slow-growing mycobacteria [67,80,95,115]. Additionally, innovations in micrometric and Nano metric drug delivery methods, such as colloidal (both vesicular and particulate) carriers. Despite that for a global TB drug development pipeline, the DST [4-6] and the incorporated urine drug susceptibility test (UDST), identify active TB with precision, and is accessible in low-income nations, these studies can be complemented with different omics, among them, metabolomics, proteomics, for medicine of precision [1,2].

Conclusions

The omics technologies, translating structural genomics information into molecular signatures (transcriptional, proteomic, epigenetic, metabolomics) as profiling patients phenotypes and

genotypes (immune genetic disorders associated to mutations (expressed as single nucleotide polymorphism) leading to a medicine of precision to a personalized medicine, with implication in novel immunotherapies. In the pursuit of accelerating the development of new targets for diagnostic and preventive treatments, it is well recognized that bioinformatics tools can play a significant role. This has been demonstrated in recent years through the application of AI to streamline and expedite data analysis and processing. Artificial intelligence which started sixty years ago has become a smart tool that can speed up the analysis of big data, process data thorough machine learning and deep learning, in cases in which huge amount of such in epidemics, pandemics be necessary. It addition it can also be predictive of novel drugs, biomolecules, predict even action mechanism and even host response to external stimuli. The multiple diverse task of AI in conjunction with the omics technologies is to accelerate the input of processing, evaluation, modeling and prediction of the outcomes of the host pathogen interaction in Tuberculosis. The current present is that WHO is being try to harness from AI tools to obtain the maximum benefit in keep under control the outbreaks of *M. tuberculosis* infection in different geographical TB endemic regions.

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Conflicts of Interest

The authors declare that they don't have conflict of interests.

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