Tuberculosis (TB) persists in the human population by a delicate balancing act involving the induction of lung pathology for a long enough time to ensure that a coughing host transmits viable bacterial progeny to a new susceptible host. By any metric, *Mycobacterium tuberculosis* is a grand master at host manipulation, which has allowed it to successfully parasitize humans for all our recorded history. Despite the fact that up to a quarter of the world’s population have immunoreactivity to tuberculosis antigens and are classified as latently infected, recent evidence suggests that most of the roughly 10 million new cases each year (World Health Organization, 2021) have progressed to active disease within 1–2 years after bacterial exposure (Behr et al., 2021). In fact, the historically binary classification of latent TB infection (LTBI) and active pulmonary TB (APTB) vastly understates the existing clinical heterogeneity among both groups, since the IFN-γ release assay implies clinical TB status indirectly and relies on cytokine release after antigenic T cell stimulation and, by itself, does not allow for the important clinical distinctions of incipient, or subclinical, TB from LTBI in which the pathogen has been eliminated or APTB (Davies and Pai, 2008; Drain et al., 2018; Kendall et al., 2021). Incipient TB reflects infection with viable *M. tuberculosis* that has not yet resulted in clinical symptoms or signs, radiographical abnormalities, or microbiologic evidence of infection (Fig. 1) but is very likely to progress over time to APTB without intervention. Subclinical TB disease is due to *M. tuberculosis* infection that is not associated clinically with TB-related symptoms or signs, despite radiographical abnormalities that may be detectable or microbiologic evidence of disease (Fig. 1). Importantly, while chemoprophylaxis in LTBI individuals represents an effective strategy for prevention of disease and transmission, it has proven extremely difficult to identify the individuals at the highest risk of disease progression and who would benefit the most from early treatment intervention.

Host gene expression profiling in peripheral blood of TB patients has yielded a path forward to unbiased diagnostic approaches. The application of transcriptional blood signatures to understand host responses unique to active TB disease was pioneered by O’Garra and colleagues over a decade ago and revealed type I IFNs as key drivers of inflammation during APTB (Berry et al., 2010). These findings have since been confirmed and extended with transcriptional signatures representing powerful complex biomarkers with promise to diagnose and predict active disease progression and treatment outcomes (Singhania et al., 2018; Warsinske et al., 2019; Mendelsohn et al., 2020; Mulenga et al., 2020). However, the complex and clinical heterogenous nature of LTBI presentations and early events after exposure (Fig. 1) have largely evaded transcriptional profiling to date for one obvious reason. Known exposure and establishment of infection is exceedingly uncommon even in prospective cohort studies.

Recent work has sought to identify and transcriptionally and clinically characterize individuals early after known exposure. Tabone et al. (2021) took advantage of the fact that close contacts (referred to as household contacts) of newly diagnosed patients with active disease are at high risk for the development of disease at a known time, and followed this prospective cohort to observe and categorize diverse clinical outcomes. This allowed the authors to interrogate the very earliest events in the interaction of the human immune system with the pathogen, highly elusive in conventional retrospective or cross-sectional clinical studies. Other studies have investigated differentially expressed genes in progressing TB patients, but most prior studies have employed only a binary classification of subjects as LTBI or APTB. Most of these analyses distinguish LTBI from APTB but have little or no overlap with each other in terms of component genes. The largest of

---

**VIEWPOINT**

**Signature required: The transcriptional response to tuberculosis**

Clifton E. Barry II and Katrin D. Mayer-Barber

The majority of humans infected with *Mycobacterium tuberculosis* never experience clinical symptoms or signs, but predicting those who will remains out of reach. Here, we discuss recent studies that reveal patterns and pathways that determine who is at highest risk for progression.

---

**Tuberculosis Research Section, Laboratory of Clinical Immunology and Microbiology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD.**

**Inflammation and Innate Immunity Unit, Laboratory of Clinical Immunology and Microbiology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD.**

Clifton E. Barry II: cbarry@niaid.nih.gov.

This is a work of the U.S. Government and is not subject to copyright protection in the United States. Foreign copyrights may apply. This article is distributed under the terms of an Attribution-Noncommercial-Share Alike-No Mirror Sites license for the first six months after the publication date (see http://www.rupress.org/terms/). After six months it is available under a Creative Commons License (Attribution–Noncommercial–Share Alike 4.0 International license, as described at https://creativecommons.org/licenses/by-nc-sa/4.0/).
the prior studies involved a cohort of >6,000 adolescents who were characterized as being latently infected by virtue of showing T cell reactivity to TB antigens (Zak et al., 2016). That study derived a 16-gene signature of TB risk that was significantly associated with progression from LTBI to APTB.

In contrast, Tabone et al. (2021) collected peripheral blood and monitored the transcriptional responses in TB contacts as they developed incipient and subclinical disease before the development of full-blown disease after known exposure to the pathogen. This identified the 30 most highly differentially expressed gene signatures for each APTB group, yet only 7 genes of the prior 16-gene signature of TB risk identified by Zak et al. (2016) were included. A 10-gene (TB10) signature was developed after comparison with other common pulmonary complications, and the diagnostic performance of the TB10 signature significantly outperforms any prior published diagnostic TB signatures.

Understanding who is at the highest risk for developing clinically symptomatic disease, and therefore most likely to continue transmission, would allow resources to be focused on the chokepoint of the evolutionary strategy of this pathogen. Treating all asymptomatic LTBI patients as is currently recommended has a long history of difficult implementation, since as many as 10 LTBI patients need to be treated currently to prevent a single case of new disease. Since estimates are that a quarter of the entire human population have immunoreactivity to TB antigens, the task of prophylaxis based on current testing is overwhelming. In addition, the low risk of disease often translates into poor compliance in practice, and prophylaxis fails. Approaches such as this study are promising to fundamentally alter the risk calculus at the individual patient level, making prevention a much more viable option.

References

Behr, M.A., et al. 2021. Am. J. Respir. Crit. Care Med. https://doi.org/10.1164/rccm.202011-4239pp
Berry, M.P., et al. 2010. Nature. https://doi.org/10.1038/nature09247
Davies, P.D., and M. Pai. 2008. Int. J. Tuberc. Lung Dis. Drain, P.X., et al. 2018. Clin. Microbiol. Rev. https://doi.org/10.1128/CMR.00021-18
Kendall, E.A., et al. 2021. Am. J. Respir. Crit. Care Med. https://doi.org/10.1164/rccm.202006-2394PP
Mendelson, S.C., et al. 2020. Lancet Respir. Med. https://doi.org/10.1016/S2213-2600(20)30045-X
Mulenga, H., et al. 2020. *PLoS One*. https://doi.org/10.1371/journal.pone.0237574
Singhania, A., et al. 2018. *Nat. Immunol.* https://doi.org/10.1038/s41590-018-0225-9
Tabone, O., et al. 2021. *J. Exp. Med.* https://doi.org/10.1084/jem.20210915
Warsinske, H., et al. 2019. *PLoS Med.* 16:e1002786. https://doi.org/10.1371/journal.pmed.1002786
World Health Organization. 2021. https://www.who.int/news-room/fact-sheets/detail/tuberculosis
Zak, D.E., et al. 2016. *Lancet*. https://doi.org/10.1016/S0140-6736(15)01316-1

Barry and Mayer-Barber Journal of Experimental Medicine

The transcriptional response to tuberculosis

https://doi.org/10.1084/jem.20211665