Predicting active tuberculosis progression by RNA analysis

Published Online
March 23, 2016
http://dx.doi.org/10.1016/S0140-6736(16)00165-3
See Online/Articles
http://dx.doi.org/10.1016/S0140-6736(15)01316-1

WHO's goals for tuberculosis control after 2015 are to reduce the number of deaths by 95% and the number of new cases by 90% by 2035.[1] These ambitious goals will require development of new approaches for preventing emergence of active tuberculosis from the vast pool of individuals with latent tuberculosis infection.[1,2]

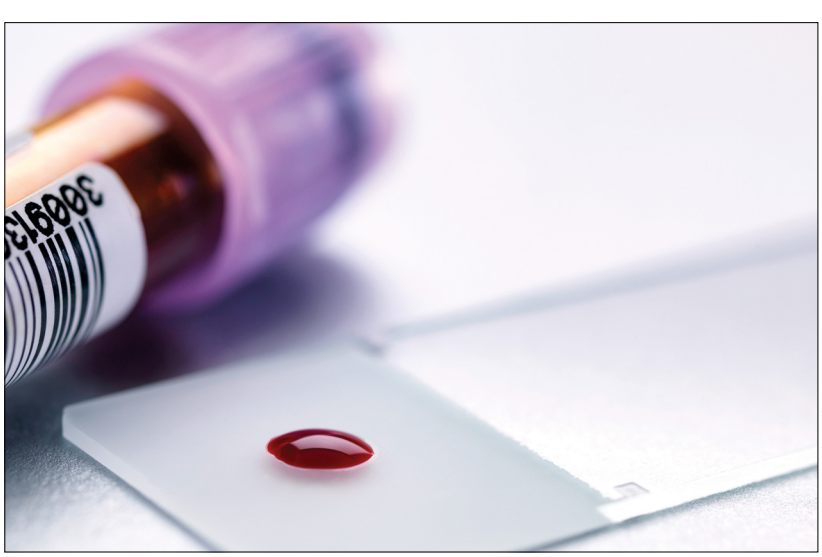
Latent tuberculosis infection describes individuals who have been infected with *Mycobacterium tuberculosis*, but in whom the infection has been contained by the immune response.[3,4] Latent tuberculosis infection is defined by tuberculin skin test or in-vitro T-cell reactivity to mycobacterial antigens. A third of the world's population have latent tuberculosis infection, but only 5–10% progress to active disease.[5] Progression is most common in the years soon after infection and in young children, those with HIV infection, people who have had renal dialysis, or those with other immune-suppressive conditions.[6] Patients who progress from latent tuberculosis infection to active disease might be symptomatic and infectious for months before tuberculosis is diagnosed. Thus, the epidemic is sustained by emergence of new cases of tuberculosis from the 2 billion people with latent tuberculosis infection and onward infection of their contacts.

Antimycobacterial drugs are effective in reducing the risk of progression from latent tuberculosis infection to active tuberculosis.[6,7] However, routine treatment of all latently infected individuals in high-burden countries is not feasible because of the large numbers who would require treatment. Additionally the prolonged courses of antimycobacterial drugs needed, the potential toxic effects of the drugs, and the danger of increasing drug resistance through inadvertent treatment of active tuberculosis cases with prophylactic rather than therapeutic regimens are prohibitive to population-level treatment.[5–7] A test that identifies individuals with latent tuberculosis infection who are at risk of progression would transform tuberculosis control, enabling targeted treatment of the population at risk.

In *The Lancet*, Daniel Zak and colleagues[8] report the results of a multicentre study investigating blood RNA expression to predict progression from latent tuberculosis infection to active disease. 6363 South African adolescents were screened by skin testing or interferon gamma release assay to identify those with latent tuberculosis infection, who were then followed up for 2 years. Sequential blood samples from 153 latent tuberculosis infection cases who either progressed to active tuberculosis or from controls who did not progress by the end of the study were analysed by RNA sequencing to identify genes that were differentially expressed between the two groups. A 16 gene signature was identified that discriminated progressors from non-progressors, which was then validated using quantitative real-time PCR, first in the adolescent cohort, and then in independent Gambian and South African cohorts of 4466 screened household contacts of sputum-smear positive cases of tuberculosis.

The 16 gene signature predicted progression to tuberculosis in the adolescent cohort in the 12 months preceding tuberculosis diagnosis, with sensitivity of 66·1% and specificity of 80·6%. In the household contact cohorts the signature had a sensitivity of 53·7% and a specificity of 82·8% for progression to tuberculosis within 12 months. Predictive performance of the signature in both cohorts decreased with increasing time to diagnosis.

The signature not only identified progression from latent tuberculosis infection to active disease; it also distinguished active from latent tuberculosis infection with high sensitivity when applied to published tuberculosis RNA expression data. As the authors first identified RNA expression differences between progressors and non-progressors using blood samples taken closest to time of tuberculosis diagnosis, it is



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not surprising that the genes comprising the signature have previously been identified as differentially expressed in tuberculosis.[9–11] The most significant finding is that expression differences were noted months before symptomatic tuberculosis developed, suggesting that progressors have an immune response typical of active tuberculosis long before diagnosis, and that latent tuberculosis infection and tuberculosis represent a continuum of outcomes in the battle between host and pathogen.

The study provides evidence that individuals with latent tuberculosis infection who progress to active tuberculosis within a year or two have a different immune response from those who remain well. Understanding the immunological differences between the progressors and non-progressors might shed light on the nature of protective immunity. Furthermore, the study suggests the feasibility of developing a test that uses transcriptional signatures to select those at greatest risk of progression for preventive chemotherapy. Such a test would represent a leap forward in worldwide tuberculosis control, enabling emergence of new cases of tuberculosis from the many people with latent tuberculosis infection to be prevented.

Despite the exciting potential, there is a long journey ahead to translate these findings into a clinically applicable test. First, translation of multigene transcriptional signatures into a test that can be used in low-resource settings requires simple, inexpensive methods for both detection and subsequent bioinformatics analysis of the expression data.[10–12] Second, sensitivity and specificity of the current signature are probably inadequate to justify its development as a test for use in high-burden countries. Since the patients studied by Zak and colleagues are likely to have had recent infection and thus higher rates of progression to tuberculosis than the general population with latent tuberculosis infection,[5,6] performance in population studies is likely to be inferior.

Despite these caveats, the findings of Zak and colleagues should encourage further research into methods to identify those with latent tuberculosis infection who will progress to active disease. The study is an important step towards developing new methods that might enable targeted treatment of latent tuberculosis infection, which is needed if the WHO goals for tuberculosis control are to be met.

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ML and MK are members of an EU funded TB vaccine consortium (TBVAC) and have worked previously on an EU funded TB biomarker study, both of which included co-authors of the research article.

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