**Could ‘omics’ unlock the secret of surviving TB meningitis?**

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**COMMENT**

Despite the devastating mortality among patients with Tuberculosis meningitis (TB meninigitis) little progress has been made in understanding the pathophysiology since the landmark autopsy studies of Rich and McCordick in the 1930’s 1. Even with treatment, two thirds of sufferers either die or are left with severe neurological deficits including cognitive impairment, epilepsy and paralysis 2. In *The Lancet Infectious Diseases* Arjan van Laarhoven and colleagues 3 present an elegant systems biology, or multiple “omics” approach designed to elucidate the underlying mechanisms responsible for these dire outcomes and ultimately aiming to identify new approaches to therapeutics. TB meningitis is a paucibacillary disease, with the scarcity of organisms present in the cerebrospinal fluid (CSF) responsible for the difficulty of confirming the diagnosis 4. It is clear that the damage suffered is often a consequence of the host inflammatory response to the invasion of *Mycobacterium tuberculosis* into the spinal fluid, rather than due to the bacteria themselves 5. However, recent work on the role of the LTA4H pathway has also shown that the balance is important, with too weak an inflammatory response as harmful as too strong 6. The complex interplay of different bacterial, host genetic and environmental factors demands a systems biology approach to solve the puzzle. van Laarhoven and colleagues have attempted to do this, starting with metabolomics data, combining clinical data and finally correlating with publically available data from autopsy samples and genomic data. Using this step-wise approach, they identify a novel but highly plausible player in the TB meningitis puzzle - tryptophan.

The group initially identified candidate metabolites with a discovery cohort then validated their findings in a second cohort. CSF tryptophan exhibited the largest difference among metabolites and a unique pattern, with the lowest concentrations observed in survivors and the highest in controls. The association between survival and low CSF tryptophan was validated in a second independent cohort. The addition of publicly available brain autopsy data also implicated up-regulation of a component of the tryptophan pathway in TB meningitis. Intuiting that tryptophan metabolism loci may serve as prognostic indicators, the authors then examined genome-wide association study (GWAS) data seeking gene variants associated with CSF tryptophan levels. They identified 11 quantitative trait loci (QTL) suggestively associated with CSF tryptophan level. A composite prognostic index of the 11 QTLs, plus age and gender predicted survival in a final independent validation cohort. Examination of publicly available expression data for all related loci identified 16 potential causal genes.

The resulting composite index appears to be a very strong predictor for survival from TB meningitis. However, the potential mechanisms responsible are far from clear and must be further characterised before potential adjuvant treatments can be contemplated in humans. Although it is possible tryptophan may simply be a dependent marker of the true causal mechanism the authors suggest that up-regulation of tryptophan metabolism protects by restricting growth of *M. tuberculosis* in the CSF, or that the downstream metabolites, particularly the kynurenine pathway, have a neuroprotective role. *M. tuberculosis* is not a tryptophan auxotroph and can synthesise tryptophan under stress unlike chlamydia and leishmania 7,8, but this ability may be impaired within the restricted environment of the CSF. A small molecule inhibitor of this pathway was recently proposed as an immune-dependent drug candidate for *M. tuberculosis* (9 and could potentially be tested in the rabbit model of TB meningitis. While tryptophan may be a prognostic biomarker, it remains possible that diagnosis of TB meningitis occurs too late in the majority of patients for interventions in this pathway to influence survival.

Multi-omic approaches, have huge potential to stimulate functional studies and provide novel biological insight for disease 10,11. This study is an elegant example of a much needed new approach to the problem of improving outcomes for TB meningitis patients. However, it is unfortunate the study was done in a single country, with individuals largely from a single ethnic group. It is vital that such work is replicated and validated across ethnic groups with larger cohorts before translation to therapeutic interventions are contemplated. Applying a similar approach to large studies may yield the much needed diagnostic signature for differentiating TB meningitis from meningitis of other aetiologies and sufficient understanding at the molecular level to develop rationally targeted personalized interventions.

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