Gene expression signatures identify biologically and clinically distinct tuberculosis endotypes

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Abstract

Background In vitro, animal model and clinical evidence suggests that tuberculosis is not a monomorphic disease, and that host response to tuberculosis is protean with multiple distinct molecular pathways and pathologies (endotypes). We applied unbiased clustering to identify separate tuberculosis endotypes with classifiable gene expression patterns and clinical outcomes.

Methods A cohort comprised of microarray gene expression data from microbiologically confirmed tuberculosis patients was used to identify putative endotypes. One microarray cohort with longitudinal clinical outcomes was reserved for validation, as were two RNA-sequencing (seq) cohorts. Finally, a separate cohort of tuberculosis patients with functional immune responses was evaluated to clarify stimulated from unstimulated immune responses.

Results A discovery cohort, including 435 tuberculosis patients and 533 asymptomatic controls, identified two tuberculosis endotypes. Endotype A is characterised by increased expression of genes related to inflammation and immunity and decreased metabolism and proliferation; in contrast, endotype B has increased activity of metabolism and proliferation pathways. An independent RNA-seq validation cohort, including 118 tuberculosis patients and 179 controls, validated the discovery results. Gene expression signatures for treatment failure were elevated in endotype A in the discovery cohort, and a separate
validation cohort confirmed that endotype A patients had slower time to culture conversion, and a reduced cure rate. These observations suggest that endotypes reflect functional immunity, supported by the observation that tuberculosis patients with a hyperinflammatory endotype have less responsive cytokine production upon stimulation.

**Conclusion** These findings provide evidence that metabolic and immune profiling could inform optimisation of endotype-specific host-directed therapies for tuberculosis.