Typhoid and Paratyphoid Fever – Comparative Analysis of Molecular Immune Profiles and Disease Pathogenesis

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Background: Enteric fever caused by *S.* Typhi and Paratyphi A affects millions of humans every year. While *S.* Typhi predominates globally, *S.* Paratyphi is increasingly recognised in endemic areas. Little is known about the host response to *S*. Paratyphi A or whether it differs from those to *S.* Typhi.

Methods: In a human challenge model of paratyphoid infection, clinical data and samples were collected before and after challenge to study molecular response profiles and cellular immune responses. Using computational analyses we dissected longitudinal transcriptional responses and related these to clinical and molecular metadata. Incorporating data from our previous typhoid challenged participants we further sought to identify pathogen-specific molecular patterns.

Results: Computational analysis of whole blood transcriptomes showed dynamic regulation of gene expression as early as 12 hours after *S.* Paratyphi A ingestion. These response patterns were similar to those seen with typhoid, with early responses occurring independently of the subsequent disease profile, characterized by strong IFN-related signatures, and cytokine signalling highlighting IFN-γ, CXCL10 and TNF-α activity. Interestingly, marked differences during acute infection were observed in clinical and microbiological outcomes; these could be related to subtle differences at the transcriptional level during acute disease. Other similarities with typhoid responses include the significant dysregulation of transcriptional signatures seven days after *S.* Paratyphi A challenge seen in participants not developing infection. Computational analyses identified several non-diagnosed participants with strong transcriptional signatures consistent with enteric fever indicating that, while remaining clinical and microbiologically inconspicuous, these individuals had responses triggered by systemic pathogen exposure.

Conclusions: This is the first detailed description of the molecular events leading up to acute paratyphoid fever. While overall similarities were observed at the molecular level, detailed computational analysis has yielded insights into how subtle variations may result in differences of clinical phenotype during acute disease.