Temporal Transcriptomic Profile of the Human MoDC Response to Invasive non-Typhoidal *Salmonella*

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Background: *Salmonella* Typhimurium is generally responsible for localized, self-limiting gastroenteritis in humans. However, the multi-drug resistant *S.* Typhimurium ST313 pathovar has emerged across sub-Saharan Africa as a major cause of lethal bacteremia in children and HIV-infected adults. The isolate D23580 is a representative blood-stream clinical isolate from a Malawian child, and demonstrates genome degradation resembling that of the human restricted pathogen *S.* Typhi. Dendritic cells (DCs) play an essential role in the initiation and establishment of antigen-specific immune responses. Modulation of DC functions by *Salmonella* has been reported as a mechanism to avoid adaptive immunity. Studies aimed at elucidating the interaction between invasive *Salmonella* and human DCs yielded important insights, yet they are limited by population-level measurements that mask fundamental differences among individual cells.

Method: We combined single cell RNA-seq technology with fluorescent labelling of bacteria to monitor gene expression variation among otherwise seemingly identical cells with regard to the infection phenotype. We quantified the early time course of gene expression induced by *S.* Typhimurium LT2 or D23580 infection in 373 human monocyte-derived dendritic cells.

Results: A core set of genes showing consistent expression profiles in response to both strains was identified. The “core response” was type-I interferon driven, involving the NF-kB signalling pathway with concomitant chemokine production. Most of the genes associated with the “core response” were grouped into distinct modules characterized by different temporal heterogeneity profiles. A direct comparison identified several differentially expressed genes clustering in biological pathways, including antigen presentation and proteolytic processes that may elucidate the mechanisms adopted by invasive *Salmonella* to evade or hijack the host immune system.

Conclusion: To our knowledge, this is the first single-cell study carried out in human DCs to provide new insights into the molecular contest at the *Salmonella*-host interface and suggest new areas of research to understand the mechanisms of invasive *Salmonella* disease.