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Importance of *Salmonella* Typhi-specific CD8+ T cells in typhoid fever immunity in a human challenge model

Stephanie Fresnay[1], Monica A McArthur[1], Thomas C Darton[2], Claire Jones[2], Claire S Waddington[2], Christoph J Blohmke[2], Brian Angus[2], Myron M Levine[1], Andrew J Pollard[2] and **Marcelo B Sztein[1]**
[1]University of Maryland, USA
[2]University of Oxford, UK

Salmonella enterica serovar Typhi (*S.* Typhi) is a human restricted pathogen which causes significant morbidity and mortality, particularly in developing countries. A better understanding of the immune responses which result in protection from *S.* Typhi infection is imperative for the development of improved attenuated vaccines. Recently, a controlled human infection model was re-established in which participants received ~10^4 cfu wild-type *S.* Typhi (Quailes strain) orally. 20 participants were evaluated for their cell-mediated immune (CMI) responses. *Ex vivo* PBMC isolated before and up to 28 days after challenge were exposed to 3 *S.* Typhi-infected targets, i.e., autologous B lymphoblastoid cell-lines (B-LCL), autologous blasts and HLA-E restricted AEH B-LCL cells. CMI responses were evaluated using 14-color multiparametric flow cytometry to detect simultaneously 5 intracellular cytokines/chemokines (i.e., IL-17A, IL-2, IFN-γ, TNF-α and MIP-1β) and a marker of degranulation/cytotoxic activity (CD107a) in distinct T cell memory subsets. Pre-challenge production of IFN-γ, TNF-α and MIP-1β by *S.* Typhi-specific CD8+ multifunctional T effector memory (T_{EM}) following exposure to *S.* Typhi-infected targets were higher in most participants who develop infection. Early decreases were observed in both *S.* Typhi-specific integrin α4β7-and integrin α4β7+CD8+ TEM cells after challenge, suggesting a potential for these cells to home to mucosal, as well as to extra-intestinal sites. Higher baseline *S.* Typhi-specific CD8+ T_{EM} responses also correlated with delayed typhoid diagnosis. No changes in these responses were found in NoTD participants after challenge. These studies demonstrate that *S.* Typhi-specific CD8+ baseline responses correlate with clinical outcome in humans challenged with wild-type *S.* Typhi, and provide novel insights into the protective immune responses against typhoid disease that will aid in the selection and development of new vaccine candidates.

Biography

Stephanie Fresnay is a Postdoctoral Fellow in the Cellular Immunology Section of the Center for Vaccine Development at the University of Maryland, USA. She is a Co-Investigator for the clinical trial entitled "Understanding Typhoid Disease: Development of a *Salmonella* Typhi Challenge Model in Healthy Adults" and has published in the *Journal of Translational Medicine*. She is also the co-author of several papers investigating regulatory T cells and antigen presenting cells function after challenge with wild-type *S.* Typhi as well as the co-author of a study characterizing *S.* Typhi, *S.* Paratyphi A and *S.* Paratyphi B cross-reactive CD4+ T cell responses elicited following vaccination.

sfresnay@hotmail.com
sfresnay@medicine.umaryland.edu

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