Clonal analysis of Salmonella-specific effector T cells reveals serovar-specific and cross-reactive T cell responses

To tackle the complexity of cross-reactive and pathogen-specific T cell responses against related Salmonella serovars, we used mass cytometry, unbiased single-cell cloning, live fluorescence barcoding, and T cell–receptor sequencing to reconstruct the Salmonella-specific repertoire of circulating effector CD4+ T cells, isolated from volunteers challenged with Salmonella enterica serovar Typhi (S. Typhi) or Salmonella Paratyphi A (S. Paratyphi). We describe the expansion of cross-reactive responses against distantly related Salmonella serovars and of clonotypes recognizing immunodominant antigens uniquely expressed by S. Typhi or S. Paratyphi A. In addition, single amino acid variations in two immunodominant proteins, CdtB and PhoN, lead to the accumulation of T cells that do not cross-react against the different serovars, thus demonstrating how minor sequence variations in a complex microorganism shape the pathogen-specific T cell repertoire. Our results identify immune-dominant, serovar-specific, and cross-reactive T cell antigens, which should aid in the design of T cell–vaccination strategies against Salmonella.

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