Evaluating T Follicular Helper Cell Responses to Typhoid Vaccines

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Background: Vi-polysaccharide vaccines have been available for more than two decades and provide moderate protection against typhoid disease. Despite this, these vaccines are not widely used in endemic countries. As a T-independent antigen, Vi-polysaccharide is poorly immunogenic in young children, has a short duration of protection and lacks booster responses with antigen re-exposure. Vi-conjugate vaccines overcome these limitations by inducing T-cell dependant responses, which are required to evoke immunological memory. We assessed subsets of circulating T follicular helper cells in humans, after immunisation with a Vi-polysaccharide or Vi-tetanus toxoid conjugate vaccine.

Methods: Twenty-five healthy participants enrolled in a clinical vaccine trial measuring the efficacy of Vitetanus toxoid conjugate and Vi-polysaccharide vaccine versus a control conjugate vaccine were selected for in-depth immuno-profiling. Vaccination-associated T follicular helper (Tfh) cell response was evaluated with flow cytometry before vaccination, and 7, 10 and 28 days after vaccination. The generation of a memory B cell response was quantified by ELISpot analysis, and anti-Vi antibody responses measured by ELISA. Antibody functionality was assessed using a serum bactericidal assay (SBA).

Results: There was a significant induction of PD1+CCR6-CXCR3-CXCR5+CD4+ T cells in participants who developed an anti-Vi antibody response following vaccination. This Th2-like TfH subset has been identified as a quiescent precursor to cells with capacity to provide B cell help. The expansion of this rare TfH population correlated positively with changes in anti-Vi antibody titre as well as the functionality of antibody response, as measured by SBA. PD1+CCR6-CXCR3-CXCR5+CD4+ T cell induction was also shown to positively correlate with changes in the frequency of circulating antigen-specific memory B cells after vaccination.

Conclusion: Detailed immuno-profiling has implicated PD1+CCR6-CXCR3-CXCR5+CD4+ T cells as key drivers of specific and functional immune responses to vaccination against *S.* Typhi. The identification of this TfH subset following glycoconjugate vaccination may represent an important correlate of long-lived immunity and potentially protection.