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EDITORIAL

Location Matters in Defining T Cell–mediated Immunity in Response to *Salmonella* Typhi Vaccination

Infection with *Salmonella enterica* serovar Typhi results in nearly 250,000 deaths and more than 21 million illnesses worldwide. *S* Typhi is transmitted through the fecal-oral route through contaminated food or water and therefore is a major global health problem in regions that lack the infrastructure to provide safe water and ensure adequate sanitation. Of the 2 widely used *S* Typhi vaccines, Ty21a is an oral live-attenuated vaccine that confers moderate protection against infection for several years.[1,2] Unfortunately, neither vaccine is suitable for the immunization of young children, one of the primary populations at risk for infection. Furthermore, the emergence of antibiotic-resistant *S* Typhi underlines the need for the development of the next generation of vaccines. Improved understanding of the mechanisms by which the live-attenuated Ty21a vaccine induces immunity to *S* Typhi may better inform the development of novel vaccine strategies. To date, the majority of studies regarding T cell–mediated immunity to *S* Typhi have focused on the characterization of central and effector memory T-cell populations within the peripheral blood of vaccinated individuals, whereas local cellular immunity in the intestinal mucosa has not been characterized. This lack of information regarding activation of mucosal immunity is surprising, considering that the intestine, the terminal ileum in particular, is the initial site of *S* Typhi infection. *Salmonella* invades the mucosa through specialized M cells located in Peyer patches, after which myeloid cells take up the bacteria and dendritic cells present *Salmonella* antigen to T cells.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Booth et al[3] provide a description of ileal immune cell populations in individuals receiving the oral *S* Typhi Ty21a vaccine. The investigators isolated lamina propria mononuclear cells (LPMCs) from terminal ileum biopsies of volunteers undergoing routine colonoscopies, some of whom were vaccinated with Ty21a 2 weeks prior. To compare peripheral immune cell populations with those in the intestinal mucosa, they also collected peripheral blood (PBMC) immediately before the first vaccine dose (–21 days) and at the time of colonoscopy. Analysis of LPMCs from vaccinated individuals demonstrated that the number of $CD8^+$ T cells expressing gut homing receptors was increased, suggesting that these cells were recruited from the circulation. Furthermore, the authors showed that the mucosal immune response to *S* Typhi induces the generation of $CD8^+$ effector memory (T_{EM}), central memory (T_{CM}), and $CD45RA^+$ effector memory populations subsets (T_{EMRA}); however, the *S* Typhi–specific proinflammatory response was distinct and more pronounced within the T_{EM} and T_{EMRA} populations. The investigators went on to demonstrate that Ty21a vaccination induced the generation of $CD8^+$ LPMC multifunctional effector responses, resulting in memory T cells that produced both Th1 and Th17 cytokines. In contrast, cytotoxic memory LPMCs failed to develop this multifunctional phenotype. A key finding in the study showed that each ileal memory T-cell population exhibited a unique *S* Typhi–specific response that was significantly different than that observed in $CD8^+$ T memory PBMC, which displayed a singular effector phenotype after vaccination.

Perhaps one of the most interesting findings reported was that vaccine-induced immunity to *S* Typhi is regionally compartmentalized within the intestine. Although colonic T cells were previously reported to be unresponsive to Ty21a vaccination,[4] stimulation of duodenal $CD8^+$ T cells induced single cytokine production,[4] whereas a multifunctional phenotype was observed in ileal $CD8^+$ memory T cells. These findings are particularly relevant because vaccine-induced protection against intracellular bacteria correlates with this multifunctional phenotype.[5,6] Variation in the microbiota may account for some of the regional differences observed in intestinal memory T-cell responses; however, the investigators postulated that continuous exposure to the diverse microbiota located within the ileum may contribute to the enhanced magnitude and multifunctionality of *S* Typhi–specific T_{EM} responses. Taken together, the multifunctional T_{EM} phenotype observed in the terminal ileum may represent the primary response generated in response to Ty21a-induced immunity. Moreover, the increased recruitment and retention of memory T cells in the ileal mucosa may provide a novel functional correlate to assess vaccine-mediated protection. The investigators conclude that induction of this diverse $CD8^+$ memory T-cell response may be advantageous in the development of oral vaccines against other enteric pathogens.

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Conflicts of interest
The author discloses no conflicts.

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