#26: Mucosal resident Macrophages drive Adaptive Immunity against Entero-Invasive Infection

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Intestinal mucosa represents the largest surface of the body exposed to the outer environment. Mucosal mononuclear phagocytes are an essential element of the intestinal immune system. To combat a constant exposure to dietary and microbial antigens, mucosal mononuclear phagocytes, which consist of dendritic cells (DCs) and macrophages, are able to induce immune responses against gut pathogens while maintaining tolerance to dietary and commensal antigens. However, the mechanisms behind these regulations are only starting to be unraveled. Mucosal macrophages share an antigen-presenting phenotype with DCs, but develop through a distinct pathway and acquire unique functions when compared to DCs. Mucosal macrophages are essential for maintaining tissue homeostasis but, in contrast to DCs, their role in inducing adaptive immunity, particularly against intracellular pathogens such as *Salmonella enterica* (SL), has never been examined. Thus, the goal of our study was to explore the role of macrophages in shaping adaptive immune responses to enteric infection. By combining mouse models of selective DC or macrophage depletion with entero-invasive SL infection, we found that macrophages, but not DCs, prevent mortality from SL. Accordingly, macrophage depletion accelerated systemic spread of SL, prevented production of SL-specific mucosal IgA and compromised SL clearance from the gut lumen. Induction of adaptive immune responses against SL was dependent on the antigen-presenting molecule MHC Class II (MHCII) expressed by macrophages, underlying their role in antigen-presentation. Development of mucosal tertiary lymphoid tissue (TLT), which mainly consists of B cells and fewer macrophages and T follicular helper cells (Tfh), is the hallmark of SL infection. We found that TLT development was attenuated by macrophage depletion or MHCII depletion in macrophages. Furthermore, infection drastically increased the number of macrophages in the large bowel. The enlarged pool of macrophages in the inflamed gut can be separated into three functionally distinct subsets - Nos2+ (bactericidal), Ccr7+ (MLN-migratory) and Il10+Tnfhi (resident). Intriguingly, only mucosal resident macrophages upregulated expression of Cxcl13 (encodes CXCL13, which organizes B cells in follicles) and Tnfsf13b (encodes B cell activating factor, BAFF). We thus conclude that mucosal macrophages are a driving force of SL-specific immunity, achieved through three complementary mechanisms: 1) bactericidal activity (bactericidal macrophages); 2) migrations to the MLNs followed by induction of SL-specific T cells and systemic antibody responses (MLN-migratory macrophages); and 3) induction of local protection via assembly of mucosal TLT and production of mucosal SL-specific IgA (resident macrophages).