INNATE RESPONSES TO INTESTINAL INFECTION
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OR.69. Regulation of the Polymeric Immunoglobulin Receptor by Different Species of Gut Commensal Bacteria

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The commensal microbiota of the human colon profoundly affects mucosal homeostasis, and alterations in its composition are associated with increased risk for inflammatory bowel diseases. Secretory IgA antibodies, which influence the composition of the intestinal microbiota, are transported across intestinal epithelial cells (IEC) by the polymeric immunoglobulin receptor (pIgR). To compare the effects of different bacteria on gene expression, the human IEC line HT-29 was stimulated with 8 bacterial species representing the 4 major phyla in the colon: Firmicutes, Bacteroidetes, Proteobacteria and Actinobacteria. Only Escherichia coli (Proteobacteria, family Enterobacteriaceae) induced expression of pIgR, the pro-inflammatory factors TNF and IL-8, and the regulatory factors A20 and MKP 1. Similar patterns of gene induction were observed when *E. coli* was added to the apical or the basolateral surface of HT-29 cells grown under polarizing conditions in Transwell® filters. By contrast to the *E. coli*-specific stimulation of IEC, all 8 bacterial species induced gene expression in the THP-1 human monocyte cell-line. These results suggest that IECs respond selectively to colonic bacteria in the intestinal lumen, whereas bacteria of all species that penetrate the epithelium have the capacity to trigger gene expression in innate immune cells in the lamina propria. Supported by NIH and CCFA.

OR.70. Helminth-induced Alternatively Activated Macrophages in Bacterial Colitis

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Epidemiological evidence indicates an inverse correlation between the incidence of immune-mediated diseases such as inflammatory bowel disease (IBD), and helminth infection. This observation has been explained as a beneficial consequence of the helminth-induced Th2 response, and has led to the testing of helminths as a potential therapy for IBD. However, our understanding of the mechanism by which helminths modulate the mucosal immune response is incomplete. We have shown recently that co-infection with the helminth Heligmosomoides polygyrus exacerbates colitis induced by the bacterial pathogen *Citrobacter rodentium* via a STAT6 dependent pathway. Investigation of the mechanism responsible for this effect revealed that the exacerbated colitis correlated with a marked increase in the number of alternatively activated macrophages in the colonic lamina propria. *Ex vivo* functional analysis of macrophages isolated from helminth-infected mice demonstrated that the ability of these cells to kill *C. rodentium* was significantly impaired. Furthermore, adoptive transfer of F4/80+ macrophages purified from heminth-infected mice resulted in exacerbation of *Citrobacter colitis* in the recipients. Thus, our results demonstrate a significant role for helminth-induced alterations of macrophage function in the immune modulation of intestinal mucosal responses to concurrent enteric bacterial infection. They also indicate that helminth-based therapies must be applied with caution.

OR.71. Th17 Cells are the Dominant T Cell Subtype Primed by *Shigella Flexneri* Mediating Protective Immunity

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The T cell response to Shigella, the causative agent of bacillary dysentery, remains poorly understood. Using a murine model of infection, we report that *Shigella flexneri* primes predominately IL-17A- and IL-22-producing Th17 cells. Th17 cells have emerged as important players in inflammatory, autoimmune, and infectious diseases. Among the unresolved questions are the lineage maintenance of differentiated Th17 cells and their role in long-term immunity to pathogens. Here, we show that the elicited *S. flexneri*-specific Th17 pool gives rise to an enhanced recall response up to 12 months after priming, suggesting the presence of a long-term memory state. Although *S. flexneri* triggers IL-17A production by γδ T cells, Th17 cells are the major source of IL-17A during infection. In IL-12/23p40° mice the priming and maintenance of Th17 cells remains intact, whereas the induction of IL-17A-producing γδ T cells is largely reduced. The clearance of primary infection was impaired in the absence of T cells, but independently of IL-17A. However, following re-infection, IL-17A produced by *S. flexneri*-specific Th17 cells becomes important to ultimately restrict bacterial growth. These findings bring new insights into the cellular response to Shigella infection and highlight the importance of pathogen-specific Th17 cell immunity for secondary immune responses.

OR.72. NOD1 and NOD2 Enhance Inflammation and Bacterial Clearance During *Salmonella Colitis*

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NOD1 and NOD2, intracellular pattern recognition molecules (PRM) that detect distinct molecular motifs from bacterial peptidoglycan, play essential roles in initiating inflammatory responses and maintaining intestinal homeostasis. Defects in these PRM are associated with several inflammatory diseases (Crohn's disease and Blau syndrome for NOD2; atopic dermatitis

and asthma for NOD1) highlighting their importance for mediating inflammatory responses. Although NOD1 and NOD2 have been implicated in modulating host susceptibility to pathogenic bacteria in several cell culture and animal infection studies, the impact of these PRM during infectious colitis is poorly defined. Using the streptomycin pre-treated mouse model of *Salmonella colitis*, the role of NOD1/NOD2 were investigated by infecting NOD1/NOD2 double knockout (DKO) mice. Overall, infected DKO mice exhibited reduced inflammatory pathology and decreased production of inflammatory cytokines (IL-1B, KC, and IL-6). Differences were primarily observed in neutrophil recruitment and goblet cell depletion. This corresponded with an increased bacteria load associated with cecal tissue at 2 and 3 days post infection. Therefore, it appears that the lack of NOD1 and NOD2 result in a constitutively weak inflammatory response that leads to inefficient clearance of bacteria from the mucosal surface.