INFLAMMATION
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OR.25. Sheepish B Cells in Mouse Colon for Defense Against Enteric Microorganisms

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Although intestinal IgA-plasma cells have been studied vigorously, far less attention is made on intestinal IgM(+) B cells. We herein describe a previously unidentified IgM(+) B cell population that normally presents in colon and expands in the context of inflammation. The IgM(+) B cells were recruited from both transitional and recirculating B2 cells but not from B1 cells even in the absence of organized lymphoid tissues such as Peyer's patches. Interestingly, the colonic IgM(+) B cell subset was able to develop in antigen/BCR-independent manner. Indeed, frequency of somatic hypermutation in BCR, which increases during exposure of B cells to high affinity antigens, was significantly low in colonic IgM(+) B cells as compared to splenic IgM(+) B cells. Interestingly, colonic IgM+ B cells produced large amounts of IL-12p70 and they were required for the defense against enteric pathogenic bacteria. Although such antigen/BCR-independent B cells have been discovered in sheep since 1995, it has generally been explained as a specific phenomenon seen in sheep. Our data together with recent publications clearly confirm that antigen-independent "sheepish B cells" also exist in both mice and humans. In addition, our study suggests that the sheepish B cells are primarily responsible for the defense against enteric microorganisms through production of IL-12p70.

OR.26. Intestinal Tolerance is Converted to Autoimmune Enteritis Upon PD-L1 Blockade

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A role for the B7 family member, PD-L1, in regulating tolerance to self-antigens of the small intestine has not been previously addressed. Here, we investigated the role of PD-L1 in CD8+ T cell tolerance to an intestinal epithelium-specific antigen using the iFABP-tOVA transgenic mouse model, in which ovalbumin is expressed as a self-antigen throughout the small intestine. Using adoptive transfer of naïve OVA-specific CD8+ T cells, we show that loss of PD-1: PD-L1 signaling, by either antibody-mediated PD-L1 blockade or transfer of PD-1-deficient T cells, leads to considerable expansion of OVA-specific CD8+ T cells and their differentiation into effector cells capable of producing pro-inflammatory cytokines. A fatal CD8+ T cell-mediated inflammatory response develops rapidly against the small bowel causing destruction of the epithelial barrier, severe blunting of intestinal villi, and recruitment and activation of myeloid cells.

This response is highly specific since immune destruction selectively targets the small intestine but not other organs. The molecular mechanism by which OVA-specific effector CD8+ T cells destroy their enterocyte targets is currently being defined. Our results indicate that loss of the PD-1: PD-L1 inhibitory pathway breaks CD8+ T cell tolerance to intestinal self-antigen, thus leading to severe enteric autoimmunity.

OR.27. Role of Lamina Propria Macrophages in the Regulation of Both Th1 and Th17 Immunity in Inflammatory Bowel Diseases

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Intestinal antigen-presenting cells are considered critical in maintaining the balance between the response against harmful pathogens and the induction of tolerance to commensal bacteria and food antigens. Herein, we focused on a unique "inflammatory" macrophage subset, which co-expressed the macrophage (Mφ) marker CD14 and the DC-marker CD209, in human intestinal lamina propria (LP)Mφ. The LP Mφ subset markedly increased in LP of Crohn's disease patients, and isolated this subset produced robust IL-23 in response to commensal bacteria. The LP Mφ subset induced proliferation of naïve CD4+ T cells as well as monocyte-derived DCs, and expressed retinoic acid (RA) synthetic enzymes retinal dehydrogenase (RALDH)2 and retinol dehydrogenase (RDH)10, which induced expression of gut homing receptors on T cells in RA-dependent manner during antigen presentation. Moreover, the LP Mφ subset evoked the differentiation of IFN-γ+ (Th1) and IL-17+ (Th17) cells. In contrast to the effect on naïve T cells, the LP Mφ subset promoted the production of IFN-γ, but not IL-17, by memory CD4+ T cell in LP via IL-23. These observations highlight the involvement of the LP Mφ in the enhanced Th1 and Th17 differentiation at the inflammatory site of inflammatory bowel diseases, particularly in Crohn's disease.

OR.28. Reduction of Dietary Iron and Systemic Iron Replenishment Inhibit the Development of Chronic Ileitis in TNFΔARE/WT Mice Targeting Endoplasmic Reticulum Stress Mechanisms in Intestinal Epithelial Cells (IEC)

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Endoplasmic reticulum (ER) stress in IEC contributes to the development of chronic intestinal inflammation. Our aim was to characterize the role of dietary and systemic iron on the regulation of ER-stress in experimental ileitis. Histological scoring (0–12) revealed that iron-low fed TNFΔARE/WT mice (score 2.30+/-0.76) were almost completely protected from the development of severe ileal inflammation in contrast to iron-adequate fed TNFΔARE/WT mice (score 8.30+/-0.91). This suggests a pathological role for luminal enteric iron in chronic

ileitis. Systemic iron replenishment of iron-low fed TNFΔARE/WT mice by intraperitoneal injections (90 µmol iron/week) did not reverse the protective effect of iron-low feeding (score 1.67+/-0.20). Western blot and immunohistochemical analysis from inflamed (iron-adequate) versus non-inflamed (iron-low) primary IEC and ileal tissue sections revealed down-regulation of ER-associated stress mechanisms, including the expression of the glucose regulated protein (grp)-78. Chromatin-immunoprecipitation analysis identified XBP-1 and NRF-2 recruitment to the grp-78 promoter in the murine small IEC line Mode-K after stimulation with TNF and iron, confirming a mechanistic link between iron and ER-stress signaling. This study clearly demonstrates the protective effect of low dietary iron and systemic iron replenishment on chronic experimental ileitis in TNFΔARE/WT mice targeting iron as an essential modulator of ER-stress in the intestinal epithelium.