MICROBIAL INFECTIONS
Wednesday, July 8

OR.93. Low-level *Helicobacter Pylori*-induced Regulatory T Cell Responses in the Human Gastric Mucosa are Associated with the Presence of Pre-malignant Pathology

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Helicobacter pylori is a major cause of peptic ulcer disease (PUD) and gastric cancer. We recently showed that PUD was associated with poor regulatory T-cell (Treg) responses in the infected human gastric mucosa (Gut 2008,57:1375), indicating that Tregs are protective. To investigate whether Tregs protect against gastric carcinogenesis, we examined the association of Treg responses with pre-malignant pathology. Gastric antral biopsies were collected from 26 Hp-infected patients attending the University Hospital, Nottingham. Biopsy Treg responses were assessed by qRT-PCR. Tissue sections were scored for gastric pathology; the density of infiltrating leukocytes (cells/sq.mm) was determined using microscopy. Comparing biopsies where atrophy or intestinal metaplasia (IM) was present rather than absent, mRNA expression levels of Treg-associated genes FOXP3, IL-10, and TGF-beta1 were significantly decreased ($p<0.05$). Median fold decreases in mRNA expression were: FOXP3 - 8.78 (atrophy); 7.45 (IM), TGFbeta1 - 1.58 (atrophy); 6.51 (IM), IL-10 - 425 (atrophy); 425 (IM). Increased IL-8 mRNA levels were associated with atrophy and IM, and correlated inversely with the Treg response. FOXP3 levels correlated with the density of leukocytes in the gastric lamina propria ($Rs=0.46$, $p=0.004$). Histological scores of cellular infiltration include Tregs; the proportion of Tregs is negatively associated with inflammation and pathology. We propose that Treg responses are protective against the development of gastric cancer.

OR.94 CCR2-dependent Intraepithelial Lymphocytes Mediate Inflammatory Gut Pathology During Toxoplasma Gondii Infection

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Mice of the C57BL/6 strain develop acute ileal inflammation following infection with the protozoan parasite *Toxoplasma gondii*. This pathology resembles many key features of human Crohn's disease, including a Th1 cytokine profile with high levels of IFN-γ, IL-12 and TNF-α, presence of pathogenic CD4+ T cells, and infiltration of gut flora into inflammed tissue. Using CCR2-/- mice, we identify a role for this chemokine receptor in pathogenesis of inflammatory pathology during *T. gondii* infection. Compared with wild-type animals, CCR2-/- mice are resistant to Toxoplasma-induced damage of the intestinal mucosa. Furthermore, lack of CCR2 was associated with low levels of CD103+ T lymphocytes in the intraepithelial compartment, Peyer's patch and lamina propria relative to wild-type animals. Adoptive transfer of wild-type, but not IFN-γ-/-, intraepithelial CD103+ T lymphocytes converted CCR2 knockout mice from a resistant to susceptible phenotype with respect to parasite-triggered inflammatory gut pathology. These results for the first time demonstrate a role for CD103+ intraepithelial T lymphocytes in pathogenesis of ileitis triggered by a microbial pathogen.

OR.95 Interleukin 23 Mediates T. Gondii-induced Immunopathology in the Small Intestine via Matrixmetalloproteinase 2 and Interleukin 22 but Independent of Interleukin 17

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Peoral infection with *Toxoplasma gondii* in susceptible C57BL/6 mice results in the development of small intestinal inflammation and massive necrosis (pan-ileitis) dependent of Th1-type cytokines. New evidence showed an important role of Th17 cells in models of mucosal inflammation. The role of Th17 cells in ileitis is unknown. We investigated the role of the IL-23/IL-17 axis in the development of *T. gondii*-induced immunopathology. IL-23 but not IL-17 was found to be essential for the development of *T. gondii*-induced ileitis. IL-23 mediated gelatinase-A (MMP-2) upregulation in the ileum of infected mice. MMP-2 deficiency protected mice from the development of *T. gondii*-induced immunopathology. Moreover, IL-23 dependent upregulation of IL-22 was essential for the development of ileitis whereas IL-17 was downregulated and dispensable. IL-22-/- mice did not develop small intestinal necrosis although they harbored the same number of parasites as both Wild-type and IL-17-/- mice. Commensal gut flora was also important in the upregulation of IL-22 in the ileum of infected mice. Interestingly, IL-22 was not exclusively produced by CD4+ T cells but also by a non-T non-B cell population in the small intestinal lamina propria. In conclusion, IL-22 and MMP-2 induced by IL-23 are key mediators of immunopathology in the small intestine.

OR.96 Cellular Prion Protein Expressed on M Cells Serves as Invasive Receptor of a Zoonotic Pathogen Brucella Abortus

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Brucella abortus is a Gram-negative bacterium causing brucellosis, one of the major zoonotic infectious diseases. Although oral infection has been implicated, the *in vivo* infection route of *B. abortus* remains to be clarified. We here report that cellular prion protein (PrP^C) is highly expressed on the apical surface of M cells and could serve as an antigen uptake receptor. Since PrP^C is reported to play an important role for internalization of *B. abortus* into macrophages, we examined whether this is also the case in M cells. Our *B. abortus* uptake assay with a ligated

intestinal loop demonstrated that *B. abortus* were selectively internalized into M cells, but not other epithelial cells. During this process, colocalization of PrP^C and *B. abortus* was evident on the apical surface as well as in the subapical vesicular structures. Internalization of *B. abortus* into M cells was greatly reduced in PrP^C-deficient mice compared to that in wild-type mice. These observations suggest that *B. abortus* invade into the host through M cells, by utilizing PrP^C on the apical surface of M cells as an invasive receptor.