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OR.113. The Role of the Immunoproteasome in Inflammatory Bowel Disease

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Crohns Disease (CD) and Ulcerative Colitis (UC) are characterized by intestinal infiltrates which produce and secrete a variety of proinflammatory cytokines, chemokines and proteases. The expression of these mediators is controlled by transcription factors of the NF-κB family which are activated by the proteasome. Proteasomes occur in two major forms, i.e. the constitutive proteasome (c20S) which contains the catalytically active subunits β1, β2 and β5 or the immunoproteasome (i20S) with β1i, β2i and β5 subunits. To investigate the impact of individual catalytic subunits of the proteasome, we used DSS induced experimental colitis to study the inflammatory response in control—and LMP7 KO mice, which lack the β5i subunit. LMP7 KO mice developed drastically reduced titers of proinflammatory cytokines, chemokines and neutrophil activation markers. Accordingly, the weight loss of LMP7 KO mice after DSS treatment was less pronounced and animals recovered much faster than their control littermates. Similar protective effects were also observed in DSS colitis of wt mice which were treated with proteasomes inhibitors, indicating that lack or inactivation of single immunosubunit has a drastic influence on the development of experimental intestinal inflammation. We therefore propose the immunoproteasome as suitable target for the treatment of chronic intestinal inflammation.

OR.114. TLR Signaling Mediates Mucosal Antibody Production and Plays a Crucial Role for Primary Influenza Virus Infection

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Recent studies have been revealed that Toll like receptor (TLR) is involved in development of adaptive immune response; however, exact role of TLR or RLR signal for induction of mucosal antibody responses is poorly understood. To elucidate this issue, we adopted several innate signal deficient mice (e.g., TRIF$^{-/-}$, MyD88$^{-/-}$, MyD88$^{-/-}$TRIF$^{-/-}$, and IPS-1$^{-/-}$). All groups of mice were primed with live PR8 influenza virus (H1N1; 5×10^2 PFU) via intranasal route and MyD88$^{-/-}$ and MyD88$^{-/-}$TRIF$^{-/-}$ mice showed significantly decreased levels of antigen-specific IgA antibody in the mucosal tissues and T cell proliferation compared to those of wild-type C57BL/6 mice. To further assess MyD88$^{-/-}$TRIF$^{-/-}$ mice on the susceptibility to influenza infection, protective efficacy was determined post primary (1×10^5 PFU) or secondary challenge (4×10^6 PFU, 4 weeks after primary infection with 5×10^2 PFU) with influenza PR8 virus. As a result, MyD88$^{-/-}$TRIF$^{-/-}$ mice were more susceptible to primary influenza infection compared to wild-type mice but fully protected against secondary infection when mice primed with non-lethal dose of antigen-matched virus (5×10^2 PFU). Taken together, TLR signal play an essential role for induction of mucosal IgA antibody responses and critical for protection against influenza infection, especially in primary infection.

OR.115. Colonic Macrophages in Intestinal Homeostasis and Inflammation

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Macrophages (mΦ) are abundant in the normal colon and play a critical role in inflammatory bowel disease, However they are central for accommodating commensal mirobiota and little is known about their function in the healthy gut, or how their apparently paradoxical properties are controlled. Murine colonic mΦ are heterogeneous, with two major subsets. In normal colon, >70% are F4/80+CD11b+, class II MHChi, CCR2- and fail to express TLR. These "resident" mΦ are avidly phagocytic, but are unresponsive to stimulation and have a low turnover *in vivo*. During experimental colitis, resident mΦ are replaced by rapidly turning over F4/80+CD11b+CD11clo, class II MHC++, CCR2+, TLR++ cells which produce TNFα. Small numbers of such inflammatory mΦ are present in resting colon, suggesting constant turnover of these cells even in the absence of inflammation. We propose that under physiological conditions, colonic mΦ are conditioned to be unresponsive to local stimuli such as commensal bacteria, but retain the ability to limit their penetration without causing inflammation. This regulation of resident mΦ behaviour is critical for homeostasis, but in the presence of pathogens or epithelial damage, an influx of newly recruited, potentially responsive mΦ promotes protective immunity and/or pathology.

OR.116. Molecular Chaperone Networks in the Gut: A Study on Novel Bacteria from the Intestine of TNFΔARE Mice

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Microbes play important roles in inflammatory bowel diseases (IBD), yet there is little data on gut bacteria in animal models of IBD. Because many intestinal bacteria are not cultured, we aimed at characterizing cultivable gut bacteria from TNFΔARE mice suffering from ileitis. Since molecular chaperones are evolutionary conserved and regulate immune responses, we hypothesized that surface eukaryotic-chaperone-like structures from gut bacteria influence intestinal epithelial cells (IEC) functions. We isolated bacteria from the cecum of a 25-weeks-old TNFΔARE mouse using DYNAL magnetic beads coated with mouse anti-Grp-78 antibodies. Antibody-free beads were used as control. Twenty-seven isolates were identified by 16S rRNA gene sequencing. Six strains, including five so far unknown bacteria, occurred only in samples isolated on Grp-78 antibodies. They belong to the family Coriobacteriaceae or the genera Neisseria, Staphylococcus

or Streptococcus. Based on comparative phenotypic and genetic analyses, one of the new bacteria was named *Enterorhabdus mucosicola* and classified as an equol-producing risk-group-2 bacterium resistant to colistin and ciprofloxcin. *E. mucosicola* was also isolated from the ileal mucosa of a 12-week-old TNFΔARE mouse on mucin-containing agar, hinting at possible close interactions with IEC. Taxonomic and functional description of the isolates is underway, particularly concerning their involvement in immune and cell stress responses.