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ABSTRACT SUPPLEMENT

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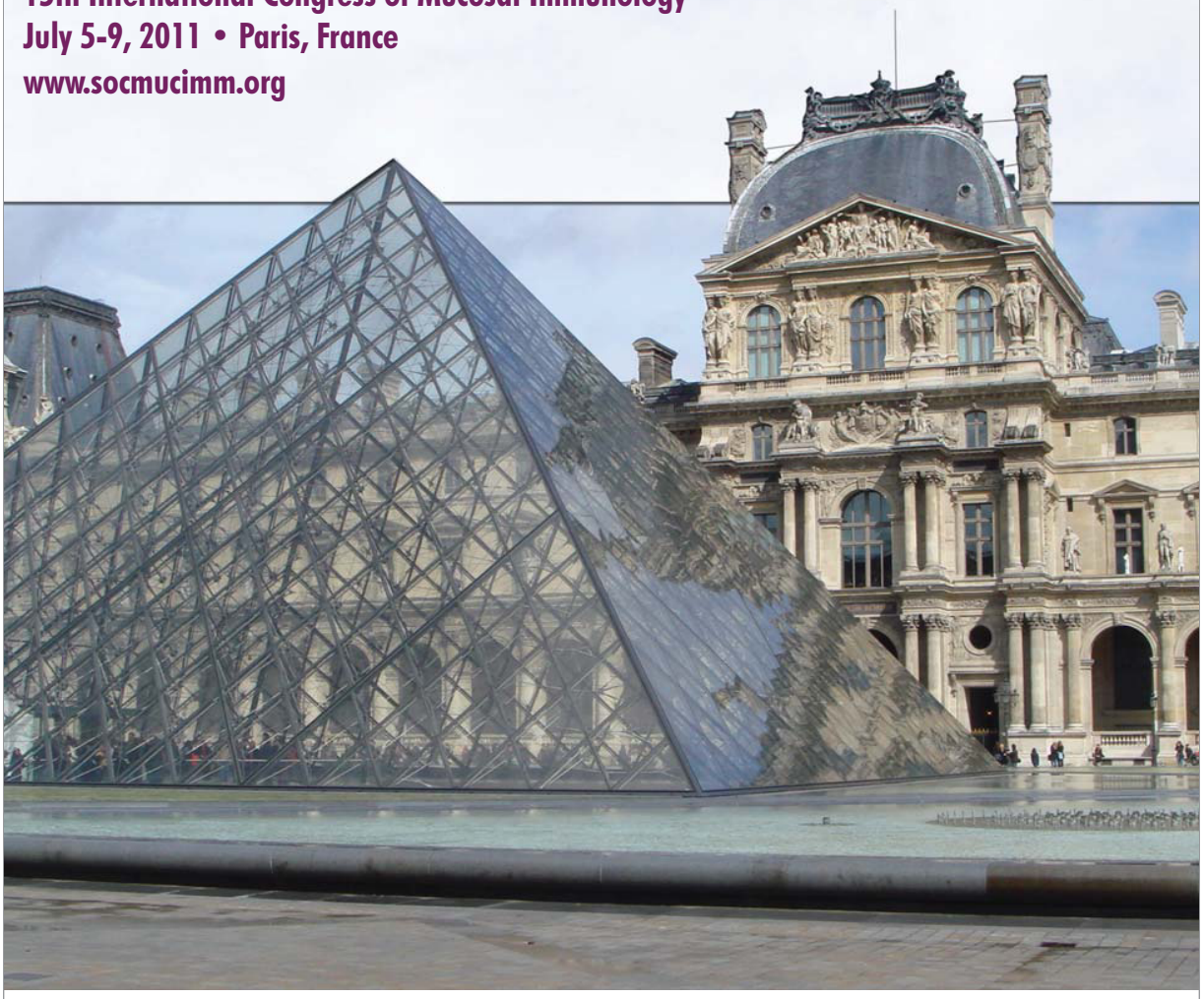

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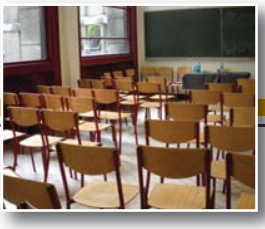

expressed by cells within the intestinal epithelium, where they may act to regulate local concentrations of Nod ligands to promote intestinal homeostasis. We hypothesize that PGLYRP2 contributes to enteric immune homeostasis, at least in part through the modulation of Nod1/2 signaling. Our preliminary data indicate that PGLYRP2-deficient mice have reduced pathological changes (lower pathological scores and less visible colonic inflammation) as well as reduced level of IL-17 producing CD4+ T cells 7 days after infection with Citrobacter rodentium. Together, our work will shed light on the mechanisms by which these innate immune proteins induce immune control, ultimately leading us to identify novel therapeutic targets for the treatment of inflammatory bowel disease.

T.105. Critical Role of ER Chaperone Grp78 for the Maintenance of Intestinal T Cell Homeostasis

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Defects in the endoplasmic reticulum (ER) stress associated mechanisms were recently implicated in the development of inflammatory bowel disease (IBD). We previously demonstrated in the TNF$^{\Delta ARE/+}$ mouse model for Crohn's disease-like ileitis that aberrant expression of ER chaperone Grp78 sensitizes intestinal epithelial cell (IEC) death. This is attributed to an aberrant cytotoxic CD8αβ+ IEL phenotype preferentially accumulating in the epithelium. In this study, we characterized the role of ER stress associated mechanisms that contribute to intestinal T cell homeostasis in TNF$^{\Delta ARE/+}$ mouse. We identified a critical activity of Grp78 as T cell intrinsic factor that mediated CD8αβ+ IEL homeostasis in TNF$^{\Delta ARE/+}$ mice. Heterozygous Grp78$^{-/+}$ mice revealed an attenuated granzyme B-dependent cytotoxicity of CD8αβ+ T cells against IEC, suggesting a critical activity of Grp78 in maintaining a cytotoxic phenotype. A deficient granzyme B production was associated with a defect in IL2-mediated proliferation of Grp78$^{-/+}$ CD8αβ+ T cells. Adoptively transferred Grp78$^{-/+}$ CD8αβ+ T cells showed a decreased frequency to accumulate in the intestine of RAG2$^{-/-}$ recipient mice. This suggests that Grp78 intrinsically controls intestinal T cell homeostasis and promotes uncontrolled CD8αβ+ IEL cytolytic activity against IEC that may further exacerbate disease manifestation in chronic intestinal inflammation.

T.106. The Role of Gammadelta T Cells in Progress of Colorectal Adenocarcinoma

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The role of gamma-delta T cells (dg T cells) in gut epithelium on colorectal adenocarcinoma has not been clarified yet. In this study, the T cells in human colorectal carcinoma tissues were analysed by immunological staining using monoclonal antibodies. Transformation of epithelial cells and progress of colorectal carcinoma in knockout mice were also examined. The results of these experiments were (1)gd T cells were decreased inside colorectal carcinoma tissues comparing with normal colorectal epithelium. The decrease of gd T cells was significant in highly-moderately differentiated cancer tissues. (2)The ratio of gd T cells in epithelium which is distant from cancer tissues were higher than that in marginal epithelium. (3)Aberrant crypt foci were observed in every mouse strains 1-1.5 month after AOM-administration. The number of ACF was highest on gd T cell-knockout mice. (4) Colorectal adenocarcinoma was observed only on gd T cell- knockout mice 5-9 months after AOM-administration. These results suggest that gd T cells play a role in suppression of progress of colorectal adenocarcinoma.

T.107. HIF-dependent Effector T Cell Regulation in Inflammatory Bowel Disease

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During inflammatory bowel disease the inflamed mucosa becomes hypoxic due to increased metabolic demand and a paucity of available oxygen. Stabilization of hypoxia-inducible factor (HIF) occurs within the cellular milieu of the inflamed intestine and directly affects the leukocyte transcriptome. However, the effect of hypoxia-dependent signaling pathways on effector T cell function, critical for IBD pathogenesis, is poorly defined to date. To address this we isolated murine CD4+ T cells subsets and exposed them to ambient hypoxia *in vitro* (1% O2; 6h). Of note, hypoxia markedly repressed expression of the transcription factor Tbet (Tbx21; 55-fold), the master regulator of CD4+ TH1 T cells. In addition, these transcriptional findings were mirrored at the protein level after 48h. In a proof of principal *in vivo* experiment, mice exposed to whole body hypoxia (10% O2; 24h) displayed suppressed splenic Tbet+ effector T cells. Furthermore, pharmacological stabilization of HIF attenuated all indices of experimentally induced colitis while conversely, selective T cell-HIF-1α deletion exacerbated disease compared to WT counterparts. Based on these preliminary studies, we hypothesize that mucosal T cell-HIF stabilization serves to attenuate experimental IBD by repressing TH1 effector function.

T.108. Study of the Mechanisms Exerted by Fructooligosaccharides from Yacón in an Intestinal Infection Model

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Fructooligosacharides (FOS), obtained from Yacón roots, have a prebiotic effect when used as a dietary supplement. We studied if FOS from Yacón can prevent enteric infection against salmonella typhimurium and the mechanism involved. BALB/c mice were divided into 4 groups: normal control, Basal (45 days with FOS-340mg/kg/day), infection control (IC-without FOS administration) and treated group (TG-45d with FOS+s. typhimurium); IC and TG groups were challenged at days 15, 30 and 45 with s. typhimurium. Translocation to liver and spleen, total and specific s-IgA, IgA+, TLR4+, CD206+, IL6+, TNFα, IFNγ and MIP 1α + cells were analyzed after challenge. We found protection only at 30 days of FOS administration with an

increase in the total s-IgA but not in the specific s-IgA levels for TG compared with IC group. In TG as regard IC group the N° IgA+, TLR4+, CD206+, IL6+ and MIP 1α+, TNFα and IFNγ cells were increased. We demonstrate that FOS from Yacón roots prevent s. typhimurium infections up to 30 days of administration through non-specific immunity with increased total s-IgA, expression of TLR4 and CD206 receptors and IL6+ and MIP1α + cells, that would improve immunological barrier mechanisms against s. typhimurium infection.

T.109. The Immunomodulatory Drug FTY720 Prevents Clearance of Citrobacter Rodentium Infection in Mice

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Background: The sphingosine-1-phosphate (S1P) agonist FTY720 prevents lymphocyte migration to sites of pathology and has shown great efficacy in both human and animal models of autoimmunity and transplantation. However, its clinical use may increase the risk of opportunistic infections, particularly in the gastrointestinal tract. We investigated the impact of FTY720 treatment in the Citrobacter rodentium model of colitis. Methods: Mice were gavaged with vehicle or FTY720 (3mg/kg) for 6 days pre-infection. Post-infection dosing was continued every 2nd day up until day 12 (D12). Mice were culled on D8 (peak-infection) and D14 (late infection/clearance). Throughout the study faecal viable counts were enumerated. At necropsy, immune cell phenotyping was performed on blood (FACS). C. rodentium colonisation was detected using bioluminescence imaging (BLI). Colons were weighed and measured and splenic CFUs were enumerated. qRT-PCR and immunofluorescent staining was performed. Results: FACS confirmed peripheral blood lymphopenia in FTY720-treated animals. CFU counts and BLI revealed inability of FTY720-treated mice to clear the infection by D14 in contrast to vehicle-treated animals. Results were supported by clinical and histological signs of colonic inflammation. Gene expression analysis revealed a deficient host immune response in drug-treated mice. Conclusion:Treatment with FTY720 impairs the mucosal immune response to bacterial infection.

T.110. γδ T Cell Subsets Differentially Modulate αβ T Cell Responses to Enteric Virus Infection

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Intestinal γδ T cells may play an important role in modulating innate and adaptive immune responses to enteric viruses. We evaluated γδ T cell subset (CD2+CD8-, CD2+CD8+ and CD2-CD8-) responses to rotavirus infection (frequencies, tissue distribution, TLR2, TLR3, TLR9, IFN-γ, IL-10, TGF-β and FoxP3 expression) in gnotobiotic pigs. We also studied cytokine-producing profiles of the three subsets and their influence on αβ T cell proliferation and cytokine production in sort-purified cocultures. Rotavirus infection induced a significant expansion of the intestinal CD2+CD8+ subset and significant increases in frequencies of FoxP3-expressing CD2+CD8+ γδ T cells in ileum, spleen and blood whereas the CD2+CD8- subset showed the highest increases in TLR2, TLR3 and TLR9 expression in ileum of gnotobiotic pigs. The CD2+CD8- subset had significantly increased frequencies of IFN-γ expression postinfection in pigs and significantly enhanced IFN-γ production by CD4+ T cells in the cocultures. The CD2+CD8+ subset produced significantly higher levels of IL-10 than CD8- subsets and significantly enhanced IL-10 and TGF-β production by CD4+ and CD8+ αβ T cells *in vitro*. Thus, the CD2+CD8- subset contributed to anti-viral immune responses by promoting CD4+ T cell proliferation and IFN-γ production. The CD2+CD8+ subset exerts regulatory T cell function in maintaining and restoring intestinal homeostasis upon enteric virus infection.

T.111. Activation of B Lymphocytes in the Gut Associated Lymphoid Tissue of Weaned Mice After Intragastric Inoculation of Shiga Toxin-producing Escherichia Coli

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After intragastric inoculation of E.coli O157:H7 Stx+ strains (125/99)in mice, we observed an early decrease of B lymphocytes (BLym) percentage (%) in Peyer's patches (PP), with a simultaneous increase in mesenteric lymph nodes (MLN) compared to controls: mice inoculated with a E.coli O157:H7 Stx- strain (605/03) or PBS (Ctrl). We aim to further study the BLym activation and trafficking. Flow cytometry analysis showed BLym activation in 125/99- and 605/03-inoculated mice: at 12 h post-inoculation as an increased CD69+ BLym % from PP(mean±SD,n) (Ctrl=31.3±2.3,3; 605/03=43.1±4.5,3; 125/99=50.3±10.8,3; $p<0.05$), and at 24 h as a decreased CD62L MFI in Blym from MLN (Ctrl=1.6±0.2,2; 605/03=0.6±0.2,3; 125/99=1.2±0.1,3; $p<0.005$; the same tendency was observed for TLym, and for B and TLym from PP. After 12 h of i.v. injection of allogenic CFSE+Lym only 125/99-inoculated mice showed an increased % of B220+CFSE+ BLym in MLN(Ctrl=12.6±0.8,4; 605/03=13.1±2.7,2; 125/99=14.7±1.9,4; $p<0.05$). Additionally, 125/99- and 605/03-inoculated mice showed an increased % of IgA+-BLym in PP(Ctrl=10.21±3.5,10; 605/03=13.6±2.6,15; 125/99=15.6±3.1,11; $p<0.05$), but only 125/99-inoculated mice showed an increased % of IgA+-BLym in NLM(Ctrl=5.9±1.7,5; 605/03=6.5±1.8,7; 125/99=8.00±1.2,11; $p<0.05$).Although both E.coli strains induced GALT activation, our results suggest that only the Stx-producing strain was able to induce trafficking of BLym and to increase IgA+BLym in MLN.

T.112. Effect of Toll-like Receptor-2 (TLR-2) Deficiency on Transcriptomic Profile in DSS-colitis

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