Mucosal Immunology Update
Society for Mucosal Immunology
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Cover Art: BALB/c mice were adoptively transferred with CFSE-labelled, DO11.10 T cells and fed OVA. Inguinal lymph nodes were taken 20hrs after feeding and imaged by multiphoton excitation microscopy. The location of cells within the intact lymph node was measured in 21 planes per three-dimensional stack of 222 x 178 µm optical sections collected at 2.5 µm intervals between each plane progressing deeper into the lymph node from an initial depth of approximately 100 µm below the surface. The time interval between each stack was 18s. The image shown is a single plane 150 µm within an intact lymph node.

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Introduction

Dear Colleagues:

It was our pleasure to welcome more than 750 of you to the 12th International Congress of Mucosal Immunology in Boston from June 26-30, 2005. This meeting highlighted more than 500 scientific abstracts and presentations and more than two-dozen plenary speakers. The meeting was viewed as a tremendous success based upon the numbers of participants attending and the breadth of the scientific work presented. The fact that the speakers represented scientists from a wide array of disciplines emphasizes the ongoing excitement and growth in the field of mucosal immunology. We are delighted that we can present this issue of Mucosal Immunology Update, through the generosity of the numerous chairs and co-chairs of the scientific sessions, as a summary of the proceedings of many of the sessions from the Congress.

We thank you for your support of the Society of Mucosal Immunology; your participation in the recent meeting and look forward to seeing you in Tokyo in 2007.

--Sincerely,
Rick and Lloyd

IBD Pathogenesis: Summary

Co-Chairs: Ivan Fuss and Rainer Duchmann

In the opening paper, Drs. Steinhoff and Visekruna (Max-Planck-Institute for Infection Biology, Berlin, Germany) reported their data on structure and function of proteasomes in IBD patients. These were the first data to report on proteasome expression in human gut.

Proteasomes may be involved in inflammatory diseases through a variety of mechanisms. As the central proteolytic machinery of cells they cleave intracellular proteins and generate the majority of peptide antigens that bind to MHC class I. In more detail, the proteolytic active site of 26S proteasomes is housed in the 20S proteasome core complex, which again contains several α and β subunits. Stimulation with IFN-γ, an important cytokine in Crohn’s disease (CD) pathogenesis, exchanges constitutive 20S subunits for inducible proteasome subunits. This leads to the generation of different immunoproteasomes which display profoundly altered cleavage specificity. In consequence, tissue specific differences in proteasome composition could control organ specific immune responses or restrict inflammation to certain sites.

Comparing 20S proteasome subunit composition in small intestine, colon and liver, the authors showed that high amounts of proteasome immunosubunits are expressed in normal small intestine, whereas constitutive proteasome subunits are predominantly expressed in normal colon. Interestingly, there was a strong up regulation of immunosubunits in inflamed intestine of patients with Crohn’s disease, but not in ulcerative colitis.

Since the ubiquitin/proteasome pathway mediates the generation of NF-kB subunit p50 from its precursor form p105, Steinhoff and Visekruna speculated that the high content of immunoproteasomes might be linked to enhanced activation of NF-kB and that specific proteasome inhibitors might provide a new road to CD treatment.

In the second study, Silva, Menezes and Seidman (McMaster University, Hamilton, Canada) investigated the role of IL-15 in Crohn’s disease. In first experiments, they used inflamed and noninflamed tissue from pediatric intestinal resections. They showed that IL-15 did not induce secretion of IFN-γ, TNF-α or IL-2Rα into supernatants but was able to suppress Ionomycin+PMA stimulated secretion of the same cytokines from inflamed tissue. The inhibitory effect of IL-15 on Ionomycin+PMA stimulated secretion of TNF-α and IFN-γ was confirmed in further experiments using explants from rectal biopsies that had been taken from inflamed and noninflamed CD and from controls. Since IL-15 has been shown to be over expressed in inflamed CD intestine, the authors speculated that this could represent a protective mechanism against the exaggerated Th1 cytokine. This finding is surprising, since IL-15, a pleiotropic cytokine with important function for the innate and adaptive immune system, and has so far been associated with immune-stimulating rather than immune-suppressive functions.

The next study by Poritz, Thompson, Boyer, Zhang and Koltun (Milton S. Hershey Medical School, Hershey, PA) aimed to identify mechanisms leading to a Stat6null phenotype. Cells with this phenotype, previously identified by the authors in patients from their familial IBD registry, are characterized by a defective Stat6 activation phenotype in response to IL-4 stimulation. Testing the hypothesis that IFN-γ causes the Stat6null phenotype by blocking Stat6 phosphorylation, they showed that EBV transformed Statnull cells were converted into Stat6high cells by addition of IFN-γ whereas anti-IFN-γ had the opposite effect. Spontaneous secretion of IFN-γ was higher in Stat6null cell lines compared to Stat6high cell lines, suggesting that they create their own Stat6null phenotype by suppressing Stat6 phosphorylation.

There is now strong evidence that inflammatory bowel disease is an immune mediated intestinal inflammatory disease that is associated with increased reactive CD4+ T cells as well as an increased humoral response. This latter aspect may be associated with an increase in autoantibodies that may bind to epithelial
cells. However, it remains unclear whether the epithelial cell derived products are recognized by such autoantibodies and are in fact involved in the pathogenic process. In work presented by Dr. Shirane, Hokama, and Mizoguchi (Massachusetts General Hospital, Boston, MA) they have identified an epithelial protein lectin, galectin-4, that specifically stimulates interleukin 6 production by effector CD4+ T cells. Surprisingly, the reactivity of CD4 T cells to the galectin-4 is only elicited under intestinal inflammatory conditions. No increase in inflammatory cytokines was evident when CD4 T cells obtained from lamina propria of normal or non-colitic animals were stimulated with galectin-4. The galectin-4 mediated production of IL-6 was found to be MHC class 2 independent and was found to directly bind the immunological synapses of CD4+ T cells. The binding and activity of galectin-4 was PKCθ-dependent. PKCθ selectively translocates to the central region of the immunological synapse and is required for the activation of such synapse-signaling cascade. PKCθ necessity was seen as evident by unresponsiveness in PKCθ-deficient animals. Since the reactivity of CD4+ T cells to galectin-4 was induced under inflammatory conditions and given the fact that galectin-4 has been shown to specifically bind to an asialo-core 1 O-glycan, these results raise the possibility that the alteration of glyco conjugates found on the immunological synapse of CD4 T cells under inflammatory conditions may confer an ability to respond to galectin-4. Quantitative PCR analysis of purified colonic LP CD4+ T cells from wild type mice and mice with acute DSS colitis and/or SCID transfer colitis were performed. It was found that members of sialy transferases (ST6 GalNAc-2, 3, 6 and ST8Sia-1, 3) that are known to be modifiers of O-glycans which are downregulated on CD4 T cells under inflammatory conditions. Therefore, the inflammatory conditions led to the exposure of Core 1 O-glycans without evidence of sialylation. Thus in conclusion, galectin-4 stimulates CD4 T cells to produce IL-6 by cross-linking lipid rafts found within the immunologic synapse under intestinal inflammatory conditions. The reactivity of CD4 T cells to galectin 4 appears to be conferred by the inflammation induced downregulation of sialylation within the O-linked oligosaccharides on these cells. This process and pathway indeed may upregulate intestinal inflammation and therefore give evidence to the biological role of lectin and/or epithelial cell derived proteins in the interaction with CD4 T cells to modulate intestinal inflammation.

In complementary work by the group of Drs. Wei and Braun (UCLA David Geffen School of Medicine, Los Angeles, CA) they demonstrated that abnormal T cell reactivity plays a prominent role in the pathogenesis of immunologic disorders related to the intestine and systemic organ system. In their studies they observed that splenic T cells obtained from Gltz2 knockout mice when transferred into recipient SCID or RAG deficient animals these recipients developed evidence of systemic as well as colonic inflammation. In addition, the inflammation occurred with prolonged latency and involved skin, lymph node, lung, pancreas, as well as intestines. The granuloma formed in the skin and the intestine had many features similar to that of Crohn’s disease. Increased lymphocytic infiltration occurred within many organ systems that included the lung, pancreas, and intestine. Retransfer of whole spleen cells obtained from Gltz2 T cell recipients promoted the process of systemic inflammation in immune deficient recipient animals. Associated with the occurrence of disease in the recipient mice was marked elevations in inflammatory cytokines, particularly TNF-α. In addition, the co transfer of wild type mesenteric lymph node B cells prevented expansion of effector CD4 T cells and disease induction. The protective function of mesenteric lymph node B cells required MHC, which was thought to facilitate the expansion of such B cells under inflammatory conditions. Furthermore, cognate CD1d interaction was also required and was thought to be involved in the regulatory effect of the B cells on intestinal inflammation. It remains to be delineated but the finding suggests that B cells may be a source of interleukin-10, which was found to be elevated in diseased recipient animals and that upregulation of CD1d is associated with enhanced IL-10 production from such mesenteric lymph node B cells. Therefore this Gltz2 T cell transfer model provides a system to delineate immune effector cell and regulatory cell defects that may underlie the pathogenesis of inflammatory disorders.

Finally, in studies presented by Drs. Maul, Zeitz, and Duchmann (Charité University Medicine Berlin, campus Benjamin Franklin, Berlin, Germany) they investigated the occurrence of lamina propria CD4+ CD25+ high regulatory T cells in inflammatory bowel disease. In prior work, this group had shown in peripheral blood from patients with IBD that the percentage of CD4+ CD25 high positive cells were strongly decreased in active IBD patients compared to inactive disease. Therefore, in these studies biopsies were obtained from inflamed and non-inflamed area of the lamina propria from patients with IBD as well as inflammatory and healthy controls. T cell phenotype was analyzed by flow cytometry (CD4+ CD25 high), immunocytochemistry (CD3+ Foxp3+) as well as real-time PCR for Foxp3. They found that the percentage of CD4+ CD25 high positive T cells was increased in inflamed compared to non-inflamed mucosa of IBD patients. In correlation with these findings, an increase of the transcripts for Foxp3 could be detected in inflamed IBD mucosa compared to non-inflamed areas. Compared to lamina propria from healthy control, IBD patients with no inflammation showed no increase in the percentage of CD4+ CD25 high positive T cells or CD3+ Foxp3+ transcripts. However, the increase of CD3+ Foxp3+ T cells and/or the CD4+ CD25 high positive T cells found in active IBD lesions was significantly lower as compared to inflammatory controls. In addition, in suppressor assays these regulatory cells were found to be effective in suppressing prolifer-

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New Therapeutic Approaches in IBD: Summary
Sponsored by Japanese Society for Mucosal Immunology
Co-Chairs: Toshifumi Hibi and Daniel K. Podolsky

The pathophysiology of inflammatory bowel disease (IBD) has emerged as a puzzle containing many pieces such as diminished regulatory T cells, luminal bacterial flora, exacerbation of innate immunity and genetic factors all identified by recent advances in basic research. Based on those evidences, the keynote lecture regarding new clinical therapy against IBD was introduced by Professor Podolsky, which was entitled ‘Therapeutic adventures in IBD: explorations of mechanisms of mucosal immune response’. Those therapeutic agents include native microbiologic preparations isolated for beneficial properties, recombinant cytokines and anti-cytokines, monoclonal antibodies (mAb), antisense oligonucleotides, stem cell transplantation and cytapheresis therapy.

Tacrolimus has been shown to inhibit transcription of the early activation genes for cytokines such as IL-2, TNF-α, and IFN-γ in T cells. Ogata et al presented the results of randomized trial for oral tacrolimus therapy against refractory ulcerative colitis. The high potency and rapid onset of oral tacrolimus therapy were demonstrated, and a steroid-tapering effect was also observed. Thus the oral administration of tacrolimus represents a safe and effective treatment option for patients with refractory ulcerative colitis.

Celiac Disease: Summary
Chair: Nadine Cerf-Bensussan

Celiac disease (CD) is an inflammatory enteropathy induced in genetically-predisposed individuals by proline and glutamine-rich proteins (prolamines) from wheat and related cereals. Work by the groups of L. Sollid and F. Koning has firmly established the pathogenic role of adaptive immunity orchestrated by lamina propria TH1+ CD4+ T cells specific for prolamline-derived peptides presented by the HLA-DQ2.5 (or more rarely HLA-DQ8) molecules which confer the main genetic risk (figure 1). This work also demonstrated how tissue transglutaminase 2 (TG2), a ubiquitous enzyme and the target of the autoantibodies, can specifically deamidate glutamine (Q) residues within the X-Pro-Gln sequences enriched in prolamines into glutamate (E), thereby introducing a negative charge allowing efficient binding of prolamine-derived peptides to the HLA-DQ2/8 pockets (figure 1). These findings establish the link between the two main genetic and environmental factors in CD, now viewed as the best understood HLA-linked disease (1, 2). Yet, HLA accounts only for 40-50 % of the genetic risk. In addition, CD develops at very variable time points in life and with a wide clinical spectrum. Furthermore, the CD4+ adaptive response hardly explains the massive expansion of intraepithelial lymphocytes (IEL) a hallmark of CD and the origin of T cell lymphomas, a rare but most severe complication of CD (3). These observations point to additional genetic and/or environmental factors that control onset and/or expression of the disease. Recently, the complementary role of an innate immune response orchestrated by the cytokine IL-15 and induced by peptide 31-49, common to the N-termini of IL-17, a T cell-derived proinflammatory cytokine induced by IL-23, is involved in the development of some inflammatory autoimmune diseases. Cong et al investigated the role of IL-17 in the development of colitis, and they demonstrated the crucial role of IL-17 producing CD4+ T cells from C3H IL-10 knockout mice reactive to enteric (cecal) bacterial antigens induced colitis.

Expansion of B cells is commonly observed in the inflamed intestine of IBD patients as well as experimental colitis. By using DSS-induced colitis model, Shimomura et al demonstrated that the expanded B cells induced by BAFF but not the LT pathway functionally contributed to the suppression of the lethal acute colitis.

IL-12/IL23 are key cytokines that drive the inflammatory response mediated by Th1 cells. These molecules contain identical p40 subunit components. Fuss et al have shown that IL-23 in contrast to IL-12 drives T cell IL-17/IL-6 synthesis, and found that treatment with a mAb directed against IL-12/IL-23 p40 induces a clinical response/remission in Crohn’s disease patients. This therapeutic effect is due to down-modulation of p40 leading to a decrease in IL-12/IL-23 dependent cytokines. This may be related to apoptosis of cells in the Th1 pathway.

Looking back at successes in newer immunological therapeutic approaches including those 4 presentations, it is tempting - although still difficult - to develop a fundamental therapy as well as to draw conclusions about the pathogenesis of IBD by completing the puzzle.
A-gliadins but distinct from the T cell epitopes, has been suggested (4, 5). IL-15 was ascribed a key role in the loss of IEL homeostasis (6), and was also shown to arm IEL and promote their cytotoxicity against enterocytes via a pathway implicating the activating NKG2D receptor, and its ligand MIC on enterocytes (4, 7) (figure 1). These findings, summarised in the plenary session by F. Koning, were complemented by five presentations in the poster session.

Two presentations further analysed the adaptive CD4+ gliadin specific T cell response. The study of the binding register of nine gliadin T cell epitopes allowed Quiao et al in the group of L. Sollid to refine the rules of proline spacing and glutamine deamidation optimal for binding to HLA-DQ2.5. These authors also provided the first evidence that glutamate position can influence recognition by the T cell receptor. Finally, they confirmed that DQ2.2 presents most gliadin T cell epitopes less efficiently than DQ2.5, a finding that may explain why this molecule, although related to DQ2.5 is not usually associated with CD (8). The structural basis for this difference remains however to be deciphered.

Tye-Din et al, in the group of RP Anderson, have performed an impressive screen to delineate the hierarchy and sequences of all HLA-DQ2-restricted T cell epitopes within the 105 gliadins and 112 glutenins found in the common wheat breed *T. aestivum*. Using a library of more than 2000 20-mer peptides, and an IFN-γ Elispot assay, they screened the peripheral blood T cell response of 100 patients on a gluten-free-diet after a 6 days gluten challenge. After confirmation by a second round of screening, they conclude that peptide A-gliadin 57-73 (part of the 33 mer initially described by Shan et al (9)) is dominant in 50% of the patients, and suggest that 110 bioactive peptides (which can be reduced to 41 9 mer-core motifs) elicit some weaker responses with a hierarchy highly conserved between individuals. These findings might ultimately help to focus strategies aiming to diagnose or prevent wheat toxicity on a relatively small number of sequences.

Presentation of the work of BenAhmed et al by N. Cerf-Bensussan investigated a long standing hypothesis in CD, a defect in local immunoregulation, and provided evidence of a possible role of IL-15. These authors showed that IL-15 can block the Smad3-dependent transcription pathway of TGF-β. IL-15 acts by up-regulating phospho-c-jun, which impedes binding of Smad3 complexes to TGF-β target genes. Blockade of Smad3, necessary for the immunoregulatory effects of TGF-β, might therefore promote and/or perpetuate the CD4+ gliadin-specific response. More generally, these data point to a novel mechanism through which IL-15 might participate to the pathogenesis of inflammatory diseases. Further work is however needed to delineate the mechanisms that lead to IL-15 overproduction in CD, and the exact role of gliadin 31-49 peptide.

CD triggering by intestinal infections has also been a long standing hypothesis. Hammarström et al investigated the role of bacteria. They observed adherent rod-shaped bacteria belonging to several Gram positive species in the jejunum of 35% patients with active CD and 20% patients on a gluten-free-diet. In CD patients, staining of goblet cells by lectin Ulex europaeus agglutinin I (UEAI) was decreased or absent, pointing to changes in the nature of glycocalyx/mucous layer (10). It remains however unclear whether these changes occur prior to disease onset or result from inflammatory changes which fail to fully subside after gluten-free-diet.

Clemente et al from the group of A. Fasano studied the mechanism which enables T cell epitopes to get inside the lamina propria. They suggest that as yet undefined peptides within gliadin might induce the release of zonulin, thereby provoking cytoskeletal rearrangements and impairing paracellular permeability. Precise characterisation of zonulin, a protein described by this group (11), will however be necessary to delineate its contribution to CD and to the passage of peptides across the epithelium.

![Figure 1](image_url): Hypothetical scheme summarizing current data on the pathogenesis of celiac disease. Additional questions addressed during the session are indicated on the left part of the scheme.
Infections of the Intestine: Summary

Co-Chairs Dirk Haller and Beth McCormick

Rotaviral infections are a major cause of intestinal inflammation and diarrhea. Sarah Blutt from the laboratory of M. E. Conner at the Baylor College of Medicine in Houston evaluated the role of innate signaling mechanisms for the induction of rotavirus-induced polyclonal B cell activation in various animal models. Interestingly, the generation of rotavirus-specific IgA responses and rotavirus-induced B cell activation in CD40-CD40L deficient mice remained normal, suggesting T cell independent co-association of B cell responses. In contrast, TLR4-deficient mice failed to mount an appropriate B cell response upon rotavirus infection, suggesting an important role for this pattern recognition receptor in triggering B cell activation. Finally, the infection of B cell-activating factor (BAFF) mutant mice failed to induce rotavirus-specific B cell activation. These interesting findings support the hypothesis that innate signals participate in triggering B cell co-stimulation in order to mount effective rotavirus-specific defense mechanisms.

Natural Killer (NK) cells are important in triggering antigen-independent acute responses to infections. Samuel Lundin from Goteborg University reported that NK cells from the gastro-intestinal mucosa display a predominant CD8- phenotype. In contrast, CD8+ NK cells from the peripheral blood cells constituted at least half of the total NK cell population. Interestingly, CD8+ but not CD8- NK cell populations from the peripheral blood did respond to Helicobacter pylori stimulation.

The reason for the selective enrichment of CD8- NK cells in the gastro-intestinal mucosa and their potential role in contributing to innate defense mechanisms against H. pylori infections remains yet to be determined.

Intestinal infections with enteropathogenic microorganisms may have a profound impact on the induction systemic immune responses to dietary antigens. Onyinye Iweala from the laboratory of C. Nagler-Anderson at the Massachusetts General Hospital in Boston investigated the role of Th1-polarizing Citrobacter rodentium- and Helicobacter hepaticus-induced acute/chronic infections on OVA-specific immune responses in C56BL/6 mice. Similar to previous observations from this research group with Th2-polarizing enteric helminth infections, C. rodentium- and H. hepaticus primed OVA-specific T cell activation towards a Th1 phenotype. These results clearly suggest that acute and asymptomatic chronic infections of the gut direct antigen-specific systemic immune responses to dietary components towards Th1 or Th2 phenotypes.

Cholera is a prevalent world-wide disease and is caused by the Gram-negative bacterium Vibrio cholera. Verena Olivier from the laboratory of K. Satchell, Northwestern University, presented new work which utilized an adult mouse model to analyze the host response to an intestinal infection of V. cholera. This organism colonizes the upper intestine and along with the virulence factor, cholera toxin (CT), secretes three cytotoxic proteins: i) repeat-in toxin (RTX), ii) the hemagglutinin/protectase (HAP), and iii) hemolysin (HLY). This team of investigators determined that adult mice colonized with wild-type EL Tor O1V resulted in a dose dependent lethality. Infecting mice with mutant strains of...
V. cholerae revealed that CT and HLY likely play a major role with respect or lethality, while HAP appears to be of minor importance. Next, organ burden was assessed following a meticulous time course of V. cholerae infection. One interesting observation was that infection with a multi-toxin mutant V. cholerae strain colonized very efficiently early on (3-6 hrs) but the infection was cleared after 48 hrs. The ability to clear the infection is probably due to the stimulation of innate immunity by TNF-alpha, since this cytokine is high following infection with the multi-toxin mutant but considerably lower in the wild-type infected mice. Taken together, these results suggest that the toxins are modulated by the innate response in mice inoculated with the wild-type strain to avoid clearance from the intestine.

Human Salmonella infection, especially typhoid fever is a highly infectious disease with significant morbidity and mortality. The innate immunity of the gastric mucosa is the first line of defense against Salmonella infection. Charmere Coon and investigators from the laboratory of S. Bao, University of Sydney, evaluated the role of granulocyte macrophage colony stimulating factor (GM-CSF) in gastrointestinal immunity in response to antigenic challenge with S. typhimurium. Employing a mouse model of human typhoid fever in which wild type (WT) and GM-CSF knock-out (KO) mice were infected with S. typhimurium, these investigators determined that WT mice exhibited gross pathological lesions, which were significantly reduced in GM-CSF KO mice. In addition, samples of liver and spleen from WT but not GM-CSF KO mice demonstrated a substantially greater inflammatory cell infiltrate, consisting largely of neutrophils/macrophages. Inflammatory granulocytes in the affected tissues also demonstrated a gradual increase following challenge. Furthermore, the increased concentrations of TNF-alpha, IL-12, IL-18, and IFN-gamma in KO mice as compared to WT mice following infection with S. typhimurium may reflect the presence of compensatory mechanisms in the absence of GM-CSF. Thus, GM-CSF appears to play an important role in the pathogenesis of salmonellosis.

Continuing with the theme of salmonella infection, Vijay-Kumar and his colleagues from A. Gewirtz's laboratory, Emory University, presented new information regarding flagellin as a pathogenic determinant in a novel mouse model of salmonellosis. These investigators found that in BALB/c mice, levels of aflagellated S. typhimurium (fliC-/fliB-) were two-fold higher as compared to the wild-type in both the cecum and colon. Interestingly, the aflagellate mutant induces substantially more mucosal pathology in the host as indicated by substantially higher increases in the PMN markers, MPO and elastase. The aflagellate strain also induced greater tissue damage as compared to the wild-type strain. Taken together, these investigators conclude that the host immune response is responsible for both mucosal inflammation and tissue damage in this Salmonella model. Although the precise role of TLR5 needs further elucidation, such data suggest that TLR5 may serve an important role in bacterial clearance, thereby ultimately protecting the host from greater challenge.

**Helicobacter Pylori Infections: Summary**

**Chair: John Nedrud**

Dr Lycke (Gothenburg) opened the session with a provocative presentation suggesting that contrary to expectations, the presence of IgA antibodies may actually be detrimental to clearance of *H. pylori* in mouse models. He and his colleagues generated IL-10 x IgA double knockout mice, which exhibited greater gastritis and lower bacterial numbers than either wild type or single knockouts in both naive-infected and immunized-challenged mice. Dr. Lycke used these results to argue that T cell peptide epitope vaccines that would not induce IgA responses might be an effective approach for *H. pylori* vaccination.

In another presentation from Gothenburg, Samuel Lundin and colleagues evaluated the *in vitro* *H. pylori* stimulated peripheral blood and gastric lymphocyte responses from gastric cancer patients and control pancreatic cancer patients or *H. pylori* seropositive but asymptomatic individuals. They observed an inverse correlation between IL-10 and IFN-gamma production by both CD4 and CD8 T cells in these groups with gastric cancer patients exhibiting high IL-10 and low IFN-gamma responses while the opposite effect was seen in control individuals. It was suggested that the high levels of IL-10 in gastric cancer patients might reflect a diminished anti-tumor response.

In another human study, Dr. Trejbo (Mexico City) reported on TLR4 polymorphisms in a group of 339 *H. pylori* infected individuals with differing disease status. The majority of individuals exhibited a Thr/Thr genotype at position 399, but 5% exhibited the Thr/ Iso genotype and 0.3% exhibited Iso/Iso. The latter two genotypes were distributed disproportionally in patients with metaplasia (odds ratio 1.6) gastric cancer (OR 1.7) and peptic ulcer (OR 2.0) suggesting that TLR4 polymorphisms may be associated with disease severity.

Dr. Sutton and colleagues (Melbourne) reported results of investigations on the relationship between the epithelial cell surface mucin, Muc1 and *H. pylori* infections in mice. Muc1 was shown to be expressed in both antrum and fundus of wild type mice and Muc1 negative mice exhibited higher *H. pylori* colonization. Enhanced colonization was more pronounced in male than female Muc1 negative mice, which also displayed
more gastritis than male Muc1 negative animals. Since these effects were not observed with H. felis infection which does not bind to the epithelium, Dr. Sutton suggested that the presence of Muc1 may inhibit H. pylori binding and colonization, but that in female mice the absence of Muc1 may be compensated for by increased gastritis.

Dr. Khamri (London) used surfactant protein D (SP-D) negative mice to investigate the role of this collectin, on H. felis infections of mice. Previous results had shown that SP-D is expressed in gastric tissues and can agglutinate H. pylori. SP-D deficient mice exhibited a higher a bacterial load and lower numbers of PMN's and reduced H. felis induced splenic proliferation compared with wild type animals. Dendritic cell uptake of H.felis was also enhanced by SP-D. These results suggested that SP-D may play a role in the innate and adaptive immune responses towards gastric Helicobacter infections.

**Lymphocyte Homing: Summary**

**Co-Chairs: Per Brandtzaeg and Leo Lefrancois**

Dr. Per Brandtzaeg gave an introduction emphasizing that mucosal immunology should aim at development of vaccines and immunotherapy for humans. Homing is central to this theme but many open questions remain. Two issues are currently confusing this field: lack of adherence to a well-defined terminology; and important species differences (Fig. 1). In contrast to humans, mice have a self-renewing gut-homing population of T-independent IgM+ B1 cells in their peritoneal cavity, which may switch to IgA+ cells either in that compartment or in the lamina propria (LP). In T cell-deficient mice, or after knocking out CD40, these B1 cells may overpopulate LP and disturb the interpretation of the real-life situation. Direct homing studies cannot be performed in humans. Brandtzaeg's group has therefore used a marker B cell from tonsils that by non-classical switching to the IgD+IgM- mucosal (J-chain+) phenotype provides a signature for dissemination of primed B cells from human nasopharynx-associated lymphoid tissue (NALT) and allows characterization of the employed homing molecules. These studies have demonstrated a remarkable compartmentalization of the mucosal immune system, which is important for vaccination strategies (Johansen et al. Blood 2005;106:593-600). SMI has now approved a recommended nomenclature for the various mucosal inductive and effector sites (Brandtzaeg & Fabst, Trends Immunol. 2004;25:570-7).

Dr. A.M. Williams from the Univ. of Bristol, UK, reported that neonatal antigen exposure shapes the intestinal T-cell receptor (TCR) repertoire and MadCAM expression. At birth, the intestine is sterile and contains few T cells. Their recruitment and retention after antigen exposure is influenced by endothelial MadCAM-1 that binds α4β7+ lymphocytes. In the gut of conventionally housed mice (CHM), CD3+ T cells were found to increase with age. In germ-free mice (GFM), T cells decreased with age in the small but remained constant in the large intestine. In CHM aged 6 d, the TCR repertoire analyzed by CDR3 spectratyping was polyclonal but became oligoclonal post-weaning. In GFM, the TCR repertoire was mainly oligoclonal at all time points. In CHM, MadCAM-1 expression peaked at weaning, then decreased with age. In GFM, MadCAM-1 expression was reduced compared with CHM and was not influenced by age or weaning. The authors concluded that in the absence of bacteria, MadCAM-1 expression is low, T cells leave the intestine, and the TCR repertoire is less complex.

Dr. I. Kochetkova replaced B. Barsczewska from Montana State Univ., Bozeman, MT, and described activation of L-selectin and β7 on B cells after intranasal immunization with cholera toxin (CT). Nasal immunization is known to stimulate robust antibody responses in regional lymph nodes (LN). The size of both NALT and LNs was markedly reduced in L-selectin-deficient (L-Sel−) mice. ELISPOT analysis revealed that CT-specific and total IgA antibody-forming cells (AFCs) were increased in LNs of L-Sel− compared with L-Sel+ mice. Experiments performed to block activated homing molecules showed that B-cell dissemination from NALT both regionally and to Peyer’s patches (PPs) were L-Sel-dependent. By contrast, using the PP-derived B cells, migration to NALT and intestinal LP was mostly α4β7-dependent, but to the nasal passages mostly L-Sel-dependent. These data suggested that the immunization site influences differentially homing-receptor activation on primed B cells.

Dr. K. Suzuki from the Center for Allergy and Immunology, Yokohama, Japan, described two distinctive pathways for...
It has been described that intestinal DCs synthesize retinoic acid (RA, a vitamin-A metabolite), which is necessary and sufficient to induce gut tropism in T cells. In addition, intestinal DCs or RA were found to induce \( \alpha 4 \beta 7 \), CCR9 and small-intestinal homing potential in B cell-derived plasmablasts. Consistently, mice depleted of vitamin A showed a selective decrease in the proportion of \( \alpha 4 \beta 7 \) memory B cells and in the number of IgA-secreting cells in the small intestine. These results suggested that both T and B cells can be programmed in their homing potential in a dynamic and reciprocal fashion by peripheral and gut-associated DCs or RA.

**Dr. O. Igarashi** from the Div. of Mucosal Immunology, Inst. of Med. Sci., Univ. of Tokyo, Minato-ku, Japan, described a critical role of mesenteric LNs in directing preferential migration of orally induced, antigen-specific CD4+ T cells to small intestinal LP (siLP). It had previously been shown by MHC class II tetramer staining that CTB-specific CD4+ T cells accumulate preferentially in siLP of CT-fed mice. Different lymphotoxin and TNF-receptor fusion proteins were used to create PP-null and PP/mesenteric LN (MLN)-null mice. Absence of PPs alone had no influence on the migration of CTB-specific T cells to siLP following oral immunization with CT. By contrast, absence of MLNs in addition to PPs resulted in no migration of CTB-specific T cells to siLP and no detectable CTB-specific fecal or serum IgA but normal levels of CTB-specific serum IgG. Similar results were obtained with CT-fed Id2 KO mice that lack isolated lymphoid follicles (ILFs) in addition to PPs and MLNs. It was concluded that MLNs are responsible for instructing preferential migration of CTB-specific CD4+ T cells to siLP, which appeared to be a prerequisite for subsequent induction of antigen-specific intestinal IgA responses. The siLP thus appears to be an inductive site for helper T cells.

Epithelial – T Cell Interactions: Summary

Co-Chairs: Kenneth Croitoru and Dominique Kaiserlian

The theme of this symposium was focused on T cell induced mucosal inflammation and epithelial cell damage.

Tang et al presented a study using an epithelial-specific IkBα mutant (NF-κB super-repressor) transgenic model (FABP-rtTA x TetO-IkBam, TG) which can be turned on with doxycycline. Presence of mutated IkBα prevents NFκB translocation into the nucleus. In the absence of NFκB activation, in vivo anti-CD3 induced T cell activation failed to induce the expected increase in intestinal permeability by preventing changes in occludins and ZO-1 proteins responsible for the integrity of the tight junctions. These findings suggested that NFκB activation is a critical step in the T cell induced changes in permeability.

Bharhani et al presented data showing that IL-10 prevented apoptosis in two murine intestinal epithelial cell lines, MODKE-K and EC4.1 induced by anti-Fas and inflammatory cytokines IFNγ and TNFα. The effect of IL10 in attenuating epithelial cell apoptosis was associated with a decrease in epithelial cell expression of Fas. In addition IL-10 treatment was associated with a decrease in pro-caspase 8 and an increase in FLIP, which could prevent Fas mediated apoptotic signalling.

Turner et al presented work using a transgenic mouse model in which a truncated OVA peptide was driven by a fatty acid binding protein promoter for selective expression in the intestinal epithelium. Tg mice were immunized with a VSV vector carrying OVA peptide to break tolerance and induce OVA peptide specific CD8 T cells. In spite of breaking tolerance the crossreactive CD8 T cells were not lytic. Systemic challenge of these mice with *Listeria monocytogenes* carrying ovalbumin induced crossreactive memory CD8 T cells with lytic activity, yet failed to induce mucosal inflammation. It was suggested that this model would allow for the examination of the mechanisms involved in the induction of autoreactive T cells.

Kawashima et al presented work showing that IL-13Rα1 expression was required for epithelial cell regeneration in a model of irradiation recovery. IL-4 receptor deficient mice were shown to have an altered response in terms of BrdU incorporation and ssDNA expression at day 1 and day 3 of irradiation. This was associated with an increase in IL-13 and an IL-4 dependent increase in IL-13Rα1. Using IL-13Rα1-Fc conjugate as a neutralizer of IL-13, they could reverse the effect and suggested a pathogenic role for IL-13. The discussion raised the possibility that IL-13Rα1 may have signalling activity.

McGee et al presented work showing that α3β1 integrin activation on epithelial cell Caco-2 with monoclonal anti-α3β1 Ab decreased IL-1 induced signalling to AP-1 via suppression of JNK1 kinase activity and JNK phosphorylation. This was reproduced by epithelial cell culture on Laminin-5 the ligand for α3β1.
SMI News

MEETINGS

- **SMI Presents Symposium at AAI, May 13, 2006**
  
  SMI members planning to attend *Immunology 2006* are invited to participate in the SMI-sponsored symposium, *Mucosal Immunity and Vaccine*, 12:30pm-2:30pm, Saturday, May 13, 2006, in Room 306, of the Hynes Convention Center, Boston, MA. SMI will host a hospitality suite after the symposium for current and prospective members. SMI Members can register for *Immunology 2006* at the special Guest Society Member rate. Visit [http://www.aai.org/Imm2006/Program.htm](http://www.aai.org/Imm2006/Program.htm) for more information about the meeting.

- **SMI Annual Meeting, June 1, 2006**

  *Innate Immunity for the Mucosal Immune System*, the SMI Annual Meeting, will be held June 1, 2006 at the San Francisco Marriott Hotel, San Francisco, California, in conjunction with FOCIS 2006.

  Registration fee for this 1-day symposium is $125 US SMI Members, $175 US Non members, $25 US SMI Student members & $50 US Non student members. Fee includes refreshment break, but not lunch. Register online at [www.socmucimm.org](http://www.socmucimm.org).

  For more information about the FOCIS 2006, visit [http://www.focisnet.org/meetings/am06/](http://www.focisnet.org/meetings/am06/)

- **ICMI 2007**

  Under the leadership of Professor Toshifumi Hibi, Chair, ICMI 2007 Steering Committee, planning has commenced for the ICMI 2007, which will be held June 8-12, 2007, at the Shinagawa Prince Hotel, Tokyo, Japan.

MEMBERSHIP

- **2006 Membership Renewal – Deadline May 31, 2006**

  If you have not renewed your membership for 2006, please do so now; 2006 dues must be must paid by **May 31, 2006**. Renew online at [www.socmucimm.org](http://www.socmucimm.org), then click on the Membership button.

- **Membership Recruitment**

  Colleague-to-colleague contact is the most effective way to encourage someone to become an SMI member. The Membership Committee asks all SMI members to promote the benefits of Society membership among your colleagues. Please contact the SMI Office (smi@paimgmt.com), if you need a copies of the membership brochure.