Furthermore, infusion of Tregs, particularly those expressing CD62L, can prevent or ameliorate GVHD in mice. Therefore, we sought to determine if GVHD in humans is also associated with a dearth of Tregs. We identified 63 HSCT recipients with or without GVHD at the point of diagnosis, prior to any alteration of their immunosuppressive regimen, and obtained both peripheral blood for flow cytometric analysis and GI biopsy material for immunohistochemical analysis. However, we found the percent of T cells that were FOXP3+ to be no lower in the blood or GI mucosa with GI GVHD, and actually found more FOXP3+ cells to be present in the blood when GVHD was histologically evident in both the upper and lower GI tract. Furthermore, the fraction of FOXP3+ T cells that were CD62L+ in the blood was actually higher in patients with histological evidence of GI GVHD than in those without, contrary to murine data. Among patients with GVHD, Treg frequency did not correlate with GVHD severity. In conclusion, we found no evidence that GI GVHD is caused by a lack of Tregs, and suggest that proposed clinical trials of Treg infusions for GVHD may prove less beneficial for humans than they have for mice.

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F.110. Spontaneous Liver Allograft Survival is Associated with a Lack of Expression of NKG2D Ligands

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Transplantation of histoincompatable livers between strains of rodents often results in spontaneous acceptance of the graft. Lewis rats reject DA livers in 14 days while DA recipients of Lewis livers have long-term graft survival. The mechanism of this spontaneous graft survival is not known. NK cells and subsets of T cells express NKG2D. On NK cells, NKG2D functions as a stimulatory receptor that induces effector functions. We examined NKG2D receptor and ligand expression post-transplant. Groups of Lewis rats received livers from DA (rejection combination) or Lewis donors (syngeneic) and DA rats received livers from Lewis (non-rejection combination) or DA donors (syngeneic). NKG2D expression was low in syngeneic grafts but increased 7-fold in Lewis→DA grafts and 17-fold in DA→Lewis grafts by day 7 post-transplant. Ligands of NKG2D were not expressed in normal liver but were detected in all liver grafts by day 1 post-transplant, suggesting that ischemia/reperfusion injury and trauma induce expression of these ligands. RAE1L and RRLT were significantly up regulated specifically in DA→Lewis liver grafts by day 7 post-transplant. In marked contrast, the expression of RAE1L and RRLT in Lewis→ DA liver grafts was similar to the levels detected in syngeneic liver grafts suggesting that signals that lead to an increase in NKG2D ligand expression are absent in this strain combination. In conclusion, the absence of NKG2D ligand expression in the liver graft may play a role in preventing rejection, and decreasing the expression of these proteins may be a useful strategy to promote graft non-responsiveness.

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F.112. Human BAFF-R Deficiency is Associated with Primary Antibody Deficiency Syndrome

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B cell survival depends on signals induced by interactions between B cell activating factor (BAFF) and its receptor BAFF-R. Screening common variable immunodeficiency (CVID) patients we identified two siblings carrying a homozygous deletion in the TNFRSF13C gene encoding BAFF-R. Removing most of the BAFF-R transmembrane part, the deletion precludes BAFF-R expression and results in B-cell lymphopenia, reduced numbers of memory B cells and a relative increase of transitional B cells. Both siblings had reduced IgG and IgM, but unlike most CVID patients normal IgA serum concentrations. One BAFF-R deficient sibling developed recurrent infections. Immunological and genetic screening of CVID and IgA-deficient patients identified additional patients carrying either a homozygous P21R variant or patients homozygous for P21R combined with a heterozygous H159Y allele. P21R is adjacent to the extracellular BAFF binding site and H159Y to the intracellular TRAF3 binding domain. Both changes represent polymorphisms. Functional analysis of these BAFF-R variants and their impact on B cell development and survival will be presented. While human BAFF-R deficiency parallels the immunological phenotype discovered in mouse models it differs by the variable penetrance of the clinically relevant immunodeficiency.

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F.113. Local LIF Production in the CNS Limits Autoimmune Demyelination

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Multiple sclerosis (MS) is a demyelinating disease of the central nervous system (CNS) with an inflammatory and a neurodegenerative component. The neuropoietic cytokine leukemia inhibitory factor (LIF) is expressed in MS lesions, but its effect on lesion development is far from understood. LIF is suggested to be an interesting candidate for MS therapy, as it has neuroprotective properties and may also promote survival of myelinating oligodendrocytes. However, therapeutic administration of LIF is complicated by its limited abitility to cross the blood-brain barrier and its pleiotropic actions outside the CNS. To circumvent these problems, we used lentiviral vectors to achieve a stable expression and secretion of LIF in the CNS of adult mice. Gene therapeutic expression of LIF in the CNS significantly reduced immune-mediated demyelination and ameliorated

EAE symptoms with enhanced efficacy compared to systemic treatment. These findings demonstrate that local LIF production is a promising therapeutic option to limit lesion progression in neuroinflammatory disease.

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F.114. Mucosal Injury and Activation of NFkB in the Initiation of Intestinal Inflammation

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Intestinal macrophages lack expression of pattern recognition receptors and costimulatory molecules. Given that these receptors are indispensable for induction of innate / adaptive immune responses, initiation of inflammation in the intestinal mucosa remains obscure. We applied an intestinal organ culture model to study early activation of the local lamina propria lymphocyte population in response to an inflammatory stimulus. Briefly, mucosal damage is induced by detachment of epithelial cells from normal non-inflamed mucosa pieces by EDTA treatment. Loss of epithelial cells causes emigration of LPMC ("walk-out" WO-LPMC) through pores onto the denuded basement membrane. Flowcytometric and gene expression analysis reveals that WO-LPMC are activated: WO-LPMO express surface antigens like CD14, CD16, CD54, CD86, HLA-DR and TLRs, while expression of CD25, CD69, CD98 is up-regulated on WO-LPT. Furthermore, cytokines and chemokines (e.g. IL-1beta, IL-6, MCP-1) known to be up-regulated during intestinal inflammation *in vivo* are detected in the organ culture supernatant by cytokine array analysis. Culturing mucosal samples in the presence of the NFkB-inhibitor APDC at least partially inhibits activation of WO-LPMC as well as inflammatory cytokine /chemokine production but not their emigration. In conclusion, mucosal injury induces a local immune response characterized by the up-regulation of pattern recognition receptors and costimulatory molecules on LPMC as well as release of pro-inflammatory cytokine/chemokines. Mucosal injury therefore represents one possible requirement for the initiation of an innate and antigen-specific intestinal immune response. Activation of NFkappaB seems to be an essential signalling event during the initiation of intestinal inflammation.

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F.115. Histamine Regulates Myelin-activated T Cell Function and Adhesiveness in Inflamed Brain Microcirculation

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Histamine has been shown to potently influence the immune response, and several data suggest a role for this mediator in the regulation of the autoimmune response in experimental autoimmune encephalomyelitis (EAE), animal model of human multiple sclerosis. However, the effects of histamine on encephalitogenic T cell function are largely unknown. Here we show that histamine *in vitro* through H1R and H2R inhibits proliferation and IFN-γ production by T cells activated against the self antigen myelin proteolipid protein (PLP)139-151. Moreover, on these cells histamine through H1R and H2R reduces extracellular signal regulated kinases 1/2 (ERK 1/2) activation, a known regulator of T cell proliferation and IFN-γ production, and increases the levels of the cyclin-dependent kinase inhibitor p27 (p27kip1), that controls cell cycle and induces T cell anergy. Activation of encephalitogenic T cells through H1R and H2R reduces both spontaneous and chemokine-induced adhesion to ICAM-1 *in vitro*, inhibits integrin activation, and blocks *in vivo* firm adhesion in inflamed brain microcirculation. These data suggest that histamine importantly regulates encephalitogenic T cell activation and trafficking through the CNS.

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F.116. The Pronounced Th17 Profile in Systemic Sclerosis (SSc) Together with Intracellular Expression of TGFβ and IFNγ Distinguishes Different SSc Clinical Phenotypes

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Systemic sclerosis (SSc) is an autoimmune disease were large controversy on the role of Th1/Th2 balance dominates. Here we investigated whether the recently discovered Th17 pattern was present and if SSc clinical phenotypes could be stratified using the combination of IL-17 with IFNγ or TGFβ. Methods: Patients were subdivided as having limited SSc (lSSc, n = 12) or diffuse SSc (dSSc, n = 24) and further subdivided upon the duration of the disease. As a comparator group 14 healthy controls were studied. CD3+ cells were isolated using FACS and subsequently studied for the expression of CD4, CD8, CD25, CD45Ro, CD45Ra, IL-23, GITR, CD69 and intracellular expression of IL-17, TGFβ and IFNγ using flow cytometry. Levels of IL-17, IL-6, IL-1α and IL-23 were performed using Bioplex assays. Results: SSc patients have more CD4+ cells, which display a more activated phenotype as reflected by their increased expression of CD69 and GITR. CD4, CD45Ro and CD45Ra cells from SSc patients highly express the IL23R. Interestingly, CD45Ro and CD45Ra cells from all SSc patients express high levels of IL-17 whereas IFNγ and TGFβ were selectively up regulated on T cells from patients with lSSc/early(e)dSSc and lSSc/late(l)dSSc, respectively, and T cells isolated from these SSc phenotypes spontaneously secrete higher levels of these cytokines. Furthermore circulating levels of IL-17 inducing cytokines IL-6, IL-23 and IL-1α were increased