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ABSTRACT BOOK

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Conclusions: These findings suggest that proliferating T cells are more abundant in acute diseases than in MS. The high percentage of CD8+ T cells proliferating in active lesions of MS suggests a major role of these cells in MS pathogenesis. The high number of CCR5+ cells in MS lesions may have therapeutic implications since CCR5 could be targeted as an anti-inflammatory treatment using Maraviroc.

P.B.34.19
Rai promotes astrocyte-dependent inflammation during experimental autoimmune encephalomyelitis

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Rai/ShcC negatively regulates Th17 cell differentiation and lupus autoimmunity. We have investigated the pathogenic outcome of the Th17 bias associated with Rai deficiency on MS development, using the EAE model. Unexpectedly, EAE was less severe in Rai-/- mice compared to their wild-type counterparts despite an enhanced generation of myelin-specific Th17 cells that infiltrated into the CNS. Nevertheless, when adoptively transferred into immunodeficient Rai+/+ mice, these cells promoted a more severe disease compared to wild-type encephalitogenic Th17 cells. This paradoxical phenotype was caused by a decreased inflammatory response of astrocytes, which were found to express Rai, to IL-17. Hence Rai plays an opposite role in Th17 cell differentiation and astrocyte activation, with the latter dominant over the former in EAE.

P.B.34.20
Mannan-conjugated myelin peptides induce dendritic cell (DC)-driven tolerogenic response

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Introduction: An increasing number of studies are focusing on the ability of tolerogenic DCs(tDCs) to induce antigen-specific non-responsiveness or tolerance in autoimmune diseases such as multiple sclerosis (MS). We explored the potential of tDCs loaded with mannan-conjugated myelin peptides for MS immunotherapy. Materials and Methods: Peripheral blood monocytes and T-cells were isolated from 2 patients with remitting-relapsing MS and 2 age/sex-matched controls. tDCs were generated from monocytes cultured with IL-4/GM-CSF/vitD3 for 6d. The resulted tDCs were loaded with myelin peptides conjugated with mannan (or peptide alone) and co-cultured with T-cells±IL-2 for 3 rounds of peptide stimulation (total of 25d). Cells were analyzed by flow cytometry to determine the phenotype of tDCs and the resulting T-cell populations. The DC cytokines IL-1β/IL-6/IL-8/IL-10/TNF-α/IL-12p70 and the T-cell cytokines IL-2/IL-4/IL-6/IL-10/IL-17A/TNF-α/IFN-γ, were measured by CBA. Results: tDCs showed a semi-mature phenotype and secreted low to zero levels of proinflammatory cytokines. After d_3 of co-culture the lymphocytes were >90% CD_3+CD_4+, and after the 1st antigen presentation all were differentiated into memory (CD_3+CD_4+CD45RO+) cells. At the end of the culture period with the mannan-myelin-peptide-loaded-tDCs, (i) the median % of nTregs (CD_4+CD25+FoxP3+) was 10.8 (x3fold higher than in cultures with tDCs+peptide alone) and (ii) the levels of IL-10 had increased significantly (>6fold) whereas the levels of all other cytokines were low to zero. The results were similar between patient and control cultures. Concusions: Our results indicate that mannan-myelin peptide-loaded tDCs can be eventually used for immunotherapy in MS patients.
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P.B.35 Immune Regulation at Barrier Sites - Part 1

P.B.35.01
Function of the Aryl hydrocarbon Receptor Repressor during polymicrobial and parasitic infections

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The Aryl hydrocarbon Receptor (AhR) is a ligand-activated transcription factor, which directs the metabolism of environmental and endogenous low molecular weight chemicals. More recently, the AhR has been identified as a potent immune regulator. AhR activity is regulated by feedback inhibition through the AhR Repressor (AhRR).
Using AhRR-EGFP reporter mice we could show, that the AhRR is mainly expressed in immune cells of the intestine and skin. AhRR-deficient mice are protected from LPS induced septic shock, suggesting a connection between the AhR/AhRR-system and the defense against pathogens. In this project, we are analysing the function of the AhRR in systemic and intestinal infections using the Colon Ascendens Stent Peritonitis (CASP) model, which leads to polymicrobial sepsis, and an ileitis model based on oral infection with the parasite *Toxoplasma gondii*. First results show a slightly higher survival rate of AhRR-deficient mice compared to wildtype controls after CASP surgery. In contrast, AhRR-deficient mice appear to be more susceptible to parasite induced ileitis compared to wildtype controls. Since the AhR is also known to regulate the T_h17 and T_{reg} cell development, the expression of the AhRR in *in vitro* generated T effector cell subsets was analysed. We found that the AhRR/EGFP-reporter is expressed in the majority of T_h17 and T_{reg} cells, to a lesser extent in T_h22, but not in T_h1 and T_h2 cells. No significant differences between AhRR-deficient and wildtype cells with regard to cytokine expression were detectable. Additionally, we were able to show, that AhRR-deficient mice establish normal endotoxin tolerance.

P.B.35.02
Regulation of AhRR expression through environmental AhR ligands in intestinal immune cell subsets

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The aryl hydrocarbon receptor (AhR) is a ligand activated transcription factor, which senses small environmental chemicals. The AhR is expressed in several types of immune cells like dendritic cells (DC), macrophages, T cells and innate lymphoid cells (ILC). AhR activity is regulated through the AhR repressor (AhRR) via a negative feedback loop.
We investigated AhRR expression in the gut of AhRR-reporter mice in dependence of the presence of AhR ligands in the diet or microbiota using microscopy and flow cytometry. IL17, IFNγ and IL-22 production was assessed in the steady state or after elicitation of dextran sodium sulfate (DSS) colitis.
We found the AhRR to be expressed in CD11c+ DC, macrophages, T cells, intraepithelial lymphocytes (IEL) and RORγt+ ILC of the small intestine and colon. These observations could be made in conventionally housed as well as germfree mice. In mice fed an AhR ligand deficient diet, AhRR was only expressed in DC. Further, we observed an inverse correlation of IL22 and AhRR expression in ILCs, despite similar frequencies of IL22 producing cells in WT and knockout animals. TCRγδ+ IEL were significantly reduced in the colon but not small intestine of AhRR-deficient mice.
Our findings indicate that AhRR expression in immune cells of the lamina propria mainly depends on dietary AhR ligands and not so much on the microbiota. We additionally revealed a connection between AhRR and IL22 expression and differential alterations in the composition of intestinal immune cell subsets.

P.B.35.03
Changes of the Wnt signalling in bronchial epithelial cells can affect the immune response in asthma

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Background: The Wnt signalling pathway is mainly linked to lung developmental processes, but there is recent evidence for contribution of the Wnt signalling to asthma. However the impact of IL-4, a key cytokine in asthma, on the Wnt signalling of bronchial epithelial cells is still unknown.
Aim: To investigate the Wnt signalling in the cross-talk of Th2 cells (IL-4) with bronchial epithelial cells.
Methods: Primary human bronchial epithelial cells (NHBEs) were stimulated with IL-4 up to 48h. The expression of Wnt and FZD genes was analysed using qPCR and confirmed by Western blot. Epithelial cells lines BEAS-2B and 16HBE 140- as well as NHBEs were stimulated with significant regulated Wnts for 24h and the cytokine and chemokine profile was measured.
Results: Significant gene expression changes of several Wnt ligands and FZD receptors were observed. Wnt5a was 1.3 fold (95% CI, 1.2-2.0) upregulated after 6h, while FZD10 was 6-7 fold upregulated over 48h of IL-4 treatment. Wnt4 was time-dependent upregulated with a maximal induction of 3 fold (95% CI, 1.4-10.7) compared to control at 48h. Upregulation of Wnt5a could be confirmed by Western blot. First results reveal an induction of CXCL8 secretion by Wnt4 in BEAS-2B and 16HBE 140- cells and by Wnt5a in NHBEs.
Conclusion: The results indicate that IL-4 influences the expression of several Wnt signalling proteins in the bronchial epithelium. These proteins seem to be able to act on the immune response via the bronchial epithelium, suggesting a contribution of the Wnt signalling to the inflammation in asthma.