cells. Flow cytometry analysis showed that surface CD47 expression was increased in PC9GR and HCC827GR, whereas PD-L1 was significantly upregulated only in PC9GR compared to parental cells. Biotin pull-down identified HuR association with 3'-UTR of CD47 and PD-L1 mRNAs in PC9 cell line. In summary, HuR may regulate key factors involved in immune escape following TKI-induced resistance in NSCLC.

P43 Propagation competence of a lymphocytic choriomeningitis virus-based cancer vaccine determines antitumor efficacy in mouse melanoma

Sandra S. Ring[1], Mette-Triin Purde[1], Fabienne Hartmann[1], Sarah Schmidt[2], Felix Stemeseder[2], Klaus K. Orlinger[2], Burkhard Ludewig[1], Tobias Bald[3], Lukas Flatz[1,4,5]

[1]Institute of Immunobiology, Kantonsspital St. Gallen, St. Gallen, Switzerland

[2]Hookipa Pharma, Vienna, Austria

[3]QIMR Medical Research Institute, Brisbane, Queensland, Australia

[4]Department of Dermatology, Kantonsspital St. Gallen, St. Gallen, Switzerland

[5]Department of Dermatology, University Hospital of Tübingen, Tübingen, Germany

Despite the success of checkpoint inhibitors, the development of novel approaches is needed to further improve cancer immunotherapy. Recently, recombinant lymphocytic choriomeningitis virus (rLCMV)-based vectors have emerged as a new class of cancer vaccines. Here we investigated two molecularly similar LCMV-based vectors expressing the melanocyte differentiation antigen tyrosinase-related protein 2 (TRP2). In contrast to propagation-deficient rLCMV, a single application of the propagation-competent artLCMV vector resulted in the induction of a detectable TRP2-specific T-cell response. Strikingly, solely vaccination with artLCMV-TRP2 resulted in a TRP2-dependent tumor regression in different mouse melanoma models. Administration of artLCMV-TRP2 resulted in prolonged antigen availability, strong activation of dendritic cells, and high levels of type I interferons necessary for the generation of potent TRP2-specific T-cell responses. Treatment with artLCMV-TRP2 resulted in a type I interferon-dependent decrease in regulatory T cells, thereby increasing the ratio of CD8+ effector to suppressive T cells. Our observations show that propagation competence is a crucial hallmark of a successful virus-based cancer vaccine aiming to induce self-antigen-specific T-cell responses.

P44 Dual inhibition of APN/CD13 and DPP4/CD26 modulates microglia inflammatory responses via the Wnt signaling pathway promoting M2 differentiation in vitro and in vivo

Elmer Antileo[1,2], Carmen Wolke[2], Siegfried Ansorge[3], Michael Täger[4], Matthias Sendler[5], Linda H Shapiro[6], Uwe Lendeckel[2]

[1]Institute of Immunology and Transfusion Medicine, University Medicine Greifswald, Greifswald, Germany; [2]Institute of Medical Biochemistry and Molecular Biology, University Medicine Greifswald, Greifswald, Germany; [3]Otto-von Guericke University, Magdeburg, Germany; [4]BMD Life Sciences, Halle (Saale), Germany; [5]Department of Medicine A, University Medicine Greifswald, Greifswald, Germany; [6]Center for Vascular Biology, Department of Cell Biology, University of Connecticut School of Medicine, Farmington, CT, USA.

Inhibition of enzymatic activity of the membrane alanyl-aminopeptidase (APN/CD13) and/or dipeptidyl peptidase 4 (DPP4/CD26) exert strong immunomodulatory effects, among others by inducing expression of immunosuppressive cytokines, such as TGF-β1 and IL-10. APN Inhibition has been linked to Wnt pathway dysregulation. Dual inhibitors of APN/DPP4 have been shown to improve neuronal survival after cerebral ischemia and disease score of experimental autoimmune encephalitis (EAE) in mice. In macrophages, APN/CD13 governs the internalization of TLR4 upon LPS treatment. To what extent APN/DPP4 inhibition modulate microglia activation through Wnt signaling cascade is not known. The aim of this work was (I) to provide a comprehensive description of Wnt pathway components expression, (II) to elucidate the effect of dual inhibition of APN/DPP4 on LPS-mediated microglia activation, and (III) M1 / M2 microglia differentiation. Microglia, under basic conditions, express a broad panel of Wnt signaling pathway components that includes ligands, receptors and co-receptors, intracellular signal transducers, transcription factors, and target genes. This Wnt expression panel is predominantly downregulated in response to LPS stimulation. Here, we demonstrated that dual inhibition of APN/DPP4 increased the expression of Wnt8a, Fzd3, LRP6, SFRP1, TCFL1, TCFL2A, and TCFL2B that were downregulated by LPS, and attenuated the LPS-dependent upregulation of Wnt10b and FZD1 expression. Remarkable, expression of M2 markers such as CD206 and ARG1 was up-regulated and that of M1 markers, IL6 and IL8, was down-regulated by inhibitor IP10.C9 in microglia as is the number of CD206-positive cells in brain slices of APN/CD13 knockout mice. These findings suggest that inhibition of APN/DPP4 modulate microglial inflammatory responses, inducing microglia differentiation towards M2 phenotype which might contribute to neuroinflammation regulation, likely by modulating the Wnt signaling pathway. Such inhibitors could represent a novel tool for the treatment of neuroinflammatory diseases.

P45 CHARACTERIZATION OF INNATE LYMPHOID CELLS IN THE GLIOBLASTOMA TUMOR MICROENVIRONMENT WITH or WITHOUT IDH1 MUTATIONS

Serife Erdem[1], Halil Ulutabanca[2], Ahmet Kucuk[2], Alperen Vural[3], Ahmet Eken[1,4]

[1]Erciyes University School of Medicine, Department of Medical Biology, Kayseri, Turkey

[2]Erciyes University School of Medicine, Department of Neurosurgery, Kayseri, Turkey

[3]Erciyes University School of Medicine, Department of Otorhinolaryngology, Kayseri, Turkey

[4]Betul Ziya Eren Genome and Stem Cell Center, Kayseri, Turkey

Background Gliomas are the most common primary tumors which arise from supporting cells of the central nervous system called glia. Isocitrate dehydrogenase 1 (IDH1) gene mutations, particularly IDH1R132H, is one of the most common mutations in glioma which affects prognosis. Innate lymphoid cell (ILCs) subsets have similar functions and phenotypes to helper T cells based on cytokine profiles and the transcription factors they express. Our aim was to characterize ILCs directly in the GBM biopsies taken from patients with/or without mutations in IDH1 or those cocultured with wild type and IDH1 mutant-U-87 isogenic cell lines. Methods ILCs were isolated by FACSAria III from the discarded human tonsils. ILCs were cocultured with WT or IDH1R132H mutant U-87MG cell lines in the presence and absence of cytokines (IL-7, IL-2, IL1B, IL-23). Subsequently, expression levels of CTLA-4, KLRG-1, PD-1 on ILCs and cell proliferation were analyzed. Similarly, ILC phenotype in the GBM patient brain tissues were characterized from 7 patients without IDH1 mutations and 3 with IDH1 mutation. Results ILCs significantly upregulated the expression of CTLA-4, KLRG-1 and PD-1 when co-cultured with U-87 cell lines regardless of the IDH1 mutations. Coculture of ILCs with WT U-87MG led to significantly higher expression of CTLA-4, KLRG-1 compared with that of IDH1 mutant-U-87 cells. In addition, the proliferation of ILCs in cocultures with WT U-87MG was significantly less compared to those with IDH1 mutation. ILC3 frequency was higher in the IDH1 mutant GBM primary tissue than that of IDH1 WT patients. Lastly, KLRG-1 and PD-1 was elevated on ILC3 and ILC2 subsets only, respectively, in the primary GBM tissue with WT IDH but comparable in other subsets. Conclusion We report that absence of IDH1 mutation in GBM is associated with elevated checkpoint molecule expression by and reduced proliferation of ILCs.

P46 Carvedilol down- regulates matrix metalloproteinase- 9 production in human leukemic MOLT-4 T cells

Fatemeh Hajighasemi*[1], Amirhossein Gaeini[1]

Department of Immunology, Faculty of Medicine, Shahed University, Tehran, Iran

Background: Matrix metalloproteinases (MMPs), a big cluster of enzymes destroy the extracellular matrix, are complicated in numerous inflammatory- based diseases. MMP-9 plays a fundamental role in inflammation. Carvedilol is a nonspecific β- blocker has been applied for controlling of hypertension and congestive heart failure. Moreover the anti-inflammatory properties of carvedilol have been revealed. In present study the effect of carvedilol on MMP-9 production in leukemic MOLT-4 cells has been studied in vitro. Materials and methods: Human leukemic MOLT-4 cells were cultured in RPMI complete medium. Subsequently the cells at logarithmic growth stage were inspired with optimal dose of PMA and treated with different concentrations of carvedilol (0.001-0.1 mg/ml) for 24 hours. Levels of MMP-9 in culture supernates were defined by an enzyme-linked immunosorbent assay kit (R&D system). Results: Carvedilol significantly declined MMP-9 creation by leukemic MOLT-4 cells dose dependently in comparison with untreated control cells. Conclusion: Our results showed that carvedilol down- regulates production of MMP-9 in human leukemic MOLT-4 cells. As MMP-9 has an important role in inflammation, the anti-inflammatory properties of carvedilol may be partly owing to its inhibitory effects on MMP-9 production. Thus it appears that carvedilol might be valuable for treatment of inflammatory diseases such as asthma in which MMP-9 is highly expressed. Key words: Carvedilol; MOLT-4; MMP-9