Combination of breathing exercises, cold exposure, and meditation mitigates psoriasis — open label, randomized, controlled trial

C. Gaughran1,2, H. Roth2, A. MacGregor1, S. Grand1, S. Barbosa1, P. Knopf1, K. Dittmann4, M. Ocken3, B. Bennett2, R. Lotti1,2, A. Marconi1,2, J. E. Hundt3, C. Mols2, H. Hammers3, F. Zagari2, M. Camboni2, R. J. Bennett2, R. J. Pichler1

1 Werner Siemens Imaging Center, Eberhard Karls Universität Tübingen, Tübingen, Germany, 2 Medical Oncology and Pneumology, Eberhard Karls Universität Tübingen, Tübingen, Germany, 3 Dermatology, Eberhard Karls Universität Tübingen, Tübingen, Germany, and 4 Radiation Oncology, Eberhard Karls Universität Tübingen, Tübingen, Germany.

CD4 T cell helper cells are capable of mediating long-term autoimmune immune responses. We developed a combined immunotherapy (COMBO) using tumor antigen-specific T helper 1 cells (Tag-Th1), dual PD-L1/LAG-3 immune checkpoint blockade, and a low-dose total body irradiation (TBI) of 2 Gy, that was highly effective in controlling the tumor burden of non-malignant Rag2−/−CD45.2−/− mice in a model of murine Pemphigus Vulgaris (PV). We aimed to explore the impact of 2 Gy TBI on the treatment efficacy and the underlying mechanisms to boost CD4 T cell-based immunotherapies by position emission tomography, optical imaging and flow cytometric analyses. First, we determined a significant longer survival of RIP1-Tag–mice and an increased CD4 T cell tumor infiltrate in 2 Gy TBI was applied in addition to Tag-Th1 cell and PD-L1/LAG-3 treatment. In non-tumor-bearing CH1 mice, TBI induced a moderate host lymphodepletion and a tumor antigen-independent accumulation of Tag-Th1 cells in lymphoid and non-lymphoid organs. In RIP1-Tag– mice, we found increased numbers of effector memory-like Tag-Th1 and endogenous CD4 T cells in the pancreatic tumor tissue after TBI, accompanied by a tumor-specific Th1-driven immune response. Further, the spleen negatively regulated T cell effector function by upregulation of PD-L1/LAG-3 and Th1 immune checkpoints, providing a further rationale for this combined treatment approach. Thus, low-dose TBI represents a powerful tool to foster CD4 T cell-based cancer immunotherapies by favoring Th1-driven autoimmune immunity. Being a clinically approved and well-established technique, TBI could be easily implemented in the clinical setting.

PC111, a monoclonal anti-Fas Ligand antibody, blocks blister formation in human pemphigus

R. Lotti1,2, A. Mancini3, J. E. Hundt2, C. Mols2, H. Hammers3, M. Camboni2, B. Bennett2, R. J. Pichler1

1 Werner Siemens Imaging Center, Eberhard Karls Universität Tübingen, Tübingen, Germany, 2 Medical Oncology and Pneumology, Eberhard Karls Universität Tübingen, Tübingen, Germany, 3 Dermatology, Eberhard Karls Universität Tübingen, Tübingen, Germany.

Pemphigus is a rare and debilitating autoimmune blistering disease due to keratinocyte cell-cell detachment (acantholysis). Treatments focus on immune suppression but are often associated with severe side effects, gradual onset of action and clinical relapse; therefore, new and more targeted and non-immunosuppressive therapies are needed to provide rapid, safer and longer-lasting responses. Patients’ autoantibodies (PvGg) are fundamental for initiating the pathomechanisms of pemphigus. Yet, we have recently demonstrated that soluble Fas Ligand (sFasL) is constitutively produced by keratinocytes upon FasL binding, is essential for blister formation. FasL activates caspases, which degrade desmogleins (Dsgs), resulting in cytolysis of keratinocytes and autoantibody formation. We have previously shown that the anti-Fas monoclonal antibody PC111, which is a high-affinity Fab fragment of a recombinant human IgG4 monoclonal antibody with high affinity to FasL (Kd = 150 pM), potently inhibits autoantibody formation in mouse models of pemphigus. Here, we report the results of a phase I clinical trial evaluating the safety, tolerability, and antipemphigus efficacy of PC111 in blocking blister formation up to 272 hrs. These initial results indicate that PC111 is a promising clinical candidate for the treatment of pemphigus; in continuation training and IND enabling studies are planned.

Detection of rare autoreactive T cell subsets in patients with pemphigus vulgaris by the CD154 activation assay

A. Böhm1, K. Brandmüller1,2, A. J. Reineke1,2, M. T. D. Schmid1,2, D. Schmid1,2, J. Czarnecki

1 Werner Siemens Imaging Center, Eberhard Karls Universität Tübingen, Tübingen, Germany, 2 Medical Oncology and Pneumology, Eberhard Karls Universität Tübingen, Tübingen, Germany.

Our study shows for the first time that high numbers of Dsg3-specific Tfh17 and Th17 cells in comparison to remittent PV patients and HC suggesting a predominant involvement of IL-17-secreting T cells in acute stages of PV. In addition, intracellular cytokine staining revealed a significant increase of IL-21 (+) and interferon-γ (+) cells, in activated CD154+ T cells. In summary, here we show that analyzing CD154 expression allows the detection of rare antigen-specific T cell subsets and the discrimination of different Dsg3-specific Th1 and Th17 cell populations in PV patients according to their clinical disease stage.

Detecting the function of T regulatory subsets in pemphigus

A. M. Fernández1,2, F. Hilke1, M. Soliman1 and K. Ghoreishi2

1 Department of Dermatology, Venerology and Allergology, Charité-Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany.

Pemphigus is a severe blistering disorder of skin and mucosa characterized by autoantibodies against desmoplakin proteins of the skin. The interaction between T (follicular) helper cells and autoantigen-producing B cells is important in disease pathogenesis. We focused in the role of T regulatory cells (Treg) as critical cellular checkpoints leading to tolerance or autoimmunity. Peripheral blood mononuclear cells were collected from pemphigus patients and healthy controls for flow cytometry analysis. The cells were gated based on Th/Tfh cell surface markers and specific markers for regulatory T cells including CD25+CD127−FoxP3+. Further subsets were determined by their chemokine receptor profile. In addition, we sorted Treg/Tc and analyzed their cytokine transcriptions. The results for our pemphigus patients characterized four Treg/Tfr subsets based on their chemokine receptor expression profile. We analyzed the percentage of type 1 (CXCR3+CCR6−), type 2 (CXCR3−CCR6+), type 17 (CXCR3+CCR6−) or type 17.1 (CXCR3+CCR6+) regulatory subsets in pemphigus patients (n=63) and healthy individuals (n=19). We found significant higher percentages of type 17.1 Tfr and Tc cells in pemphigus patients compared to controls. We further explored the expression of cytokines and transcription factors that confirm the regulatory characteristics of the aforementioned subsets by positive expression of FOXP3 and TGFβ. We observed some common but also different expression levels of cytokines between specific cell subsets. Our flow cytometry panel allowed us to characterize Treg and Tfr cell subsets in an auto-antibody-mediated blistering skin disease, where we specifically found a dominance of Th17 and Th1 and Tfr cells. We are currently studying the functional role of these regulatory T cell subsets in cellular assays and longitudinal studies.

Non-infectious Complications of Rituximab during Treatment for Autoimmune Blistering Diseases

A. Mohammed1,2, D. Hekman1, W. Li1, C. Miquish1,2 and S. Rahnama-Moghaddam1

1 Department of Dermatology, Indiana University School of Medicine, Schererville, IN and 2 Brown University Library, Brown University, Providence, RI.

Rituximab is considered the first-line treatment in new-onset moderate-to-severe pemphigus and/or patients who do not achieve clinical remission with systemic corticosteroids and/or immunosuppressive agents. Studies have demonstrated that rituximab has few side reactions, infections, and laboratory abnormalities to generally be well tolerated by patients with pemphigus. The adverse events of rituximab treatment that providers may not be to focus on non-infectious complications of rituximab treatment that providers may not be aware of. Our search was performed between 22 February 2019 and 10 July 2019 and consisted of all studies published in English. A total of 1,438 references were included and 193 patients (46.7%) had minor adverse events and 210 patients (47.8%) had major adverse events. The most frequent major adverse events include infection, infection and autoimmunity, blistering skin diseases, where we specifically found a dominance of Th17 and Th1 and Tfr cells. We are currently studying the functional role of these regulatory T cell subsets in cellular assays and longitudinal studies.

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