001 Maintenance of CD4+ tissue-resident memory T cells via perivascular clusters with CD301b+ dermal dendritic cells in a mouse model of allergic dermatitis

R Nakamura, G Egawa, S Nakazato and K Kabashima Dermatology, Kyoto University, Kyoto, Japan

Tissue-resident memory T (T RAM) cells play a crucial role in local immunity by inducing rapid immune responses upon exposure of the antigen. However, how CD4+ T RAM cells retained in the skin after allergic inflammation remains largely unknown. To clarify the mechanism, we used a delayed-type hypersensitivity model, which is mediated by CD4+ T cells. T cell receptor (TCR)-β deficient mice were transferred with CD4+ T cells from GFP-expressing, ovalbumin (OVA)-specific TCR-transgenic (OT-II) mice and sensitized with OVA emulsion, followed by initial challenge with OVA in ear skin (day 0). On day 35, in spite of the resolution of ear swelling, CD4+ T cells remained in the dermis and exhibited CD4+CD69+ expression. Their residence was mediated by CD301b via parabiosis and photo-convertible protein (KikGR)-expressing OT-II T cells. In addition, two-photon microscopy revealed that CD4+ T cells were retained in perivascular clusters on day 35. Immunohistochemical analysis revealed that CD301b+ conventional dendritic cell (DC) subset 2 (cDC2) cells critical for T cell circulation. In conclusion, we demonstrated that CD301b+ cDC2 cells in Mg2-dipherthia toxin receptor (DTR) mice, which express the DTR under the regulation of the gene encoding CD301b, and found that the number of CD4+ T RAM cells and their clusters were reduced after the depletion of CD301b+ cells. Taken together, these results suggest that CD301b+ cDC2 cells are critical in the tissue residency of CD4+ T RAM cells after the resolution of allergic inflammation. This mechanism provides a potential new strategy, for preventing the recurrence of CD4+ T cell-mediated chronic inflammatory skin diseases.

002 Anti-fractalkine monoclonal antibody therapy ameliorates murine sclerodermatous chronic graft-versus-host disease

Atsukuniya1, V Huy Luong2, T Chino3, N Oyama1, T Matushita1, N Iishi1, H Ogasawara2, T Mochizuki2, H Bode3, N Tanaka4, K Hirose2 and M Takamiya1

1 Dermatology, Kobe University, Kobe, Japan; 2 Department of Human Molecular Genetics and Biochemistry, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Sclerodermatous chronic graft-versus-host disease (sSc) is a severe and irreversible complication, characterized by thickening and fibrosis of the skin and other tissues. It is caused by alloimmune T cell responses in the graft-versus-host (GvHD) setting. SSc can be mimicked in severe SCID mice by adoptive transfer of allogenic bone marrow and sublethally irradiated BALB/c mice reproduced organ fibrosis and autoimmune phenotypes resembling human sSc-CGVHD or SSc. An intraperitoneal administration of anti-fractalkine mAb increased survival rate in a dose dependent manner. The mAb therapy significantly suppressed fibrosis of the skin and lungs. Moreover, the mAb dose-dependently attenuated the local infiltration of T lymphocytes in the skin and lungs and macrophages in the lungs. Furthermore, the mAb inhibited the expression of proinflammatory cytokines such as IL-6, TNF-α, and proangiogenic cytokine IL-8 in the skin and the TNF-α expression in the lungs. Anti-fractalkine mAb treatment did not show any apparent adverse events. These data together with our previous findings in other mouse models indicate that the systemic administration of anti-fractalkine mAb can be an attractive therapeutic approach for human sSc-CGVHD and SSc.

003 Up-regulation of ST18 drives pemphigus vulgaris pathogenesis: a perpetuum mobile model

A Tsurumi1,2, J Mohamad1, L Mallk2, K Malovitch1,2, O Sargi3, D Vodo1 and I Sprecher1

1 Dermatology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan; 2 Department of Dermatology, Tel Aviv University, Tel Aviv, Israel

Pemphigus vulgaris (PV) is a life-threatening autoimmune mucocutaneous blistering disease. We previously showed that a genetic variant within the ST18 promoter promotes ST18 up-regulation in a p35/p63-dependent manner and is associated with a 6-fold increased risk to develop PV. ST18 was also found to be overexpressed in the skin of patients. In addition, it has been shown that desmoglein 3 (DSG3) down-regulation is associated with increased p35 expression and activity. Based on these data, using a combination of reporter assays, Western blotting, confocal immunofluorescence-microscopy, we investigated the possibility that ST18, DSG3 and p35 may be jointly involved on the pathogenesis of PV. First, we demonstrated that antibody-mediated DSG3 down-regulation results in enhanced expression of p35. Second, we showed that DSG3 down-regulation activates the ST18 promoting activity. Third, p35 silencing abolished the DSG3-mediated activation of the ST18 promoting activity. Finally, we demonstrated that ST18 overexpression in keratinocytes significantly augments antibody-mediated DSG3 down-regulation in keratinocytes. Taken collectively, these data indicate that ST18 up-regulation triggers a pathophysiological self-amplifying cycle involving DSG3 and p35 dysregulation, which may underlie the genetic association of ST18 variants with PV. Supporting the clinical relevance of these findings, a genetic variant causing increased ST18 promoter activity was found to be associated (p = 0.003) with more severe phenotype in a cohort of 100 PV patients.

004 PPAR-gamma promotes proliferation of pathogenic Th2 cells through regulation of IL-2 signaling

F Luther1, NL Bertichi2, O Steck1, C Bazzini1, K Keller1 and C Schlaphack1

1 Dermatology, Innsbruck, Bern University Hospital, Bern, Switzerland; 2 Interfaculty Bioinformatics Unit and Swiss Institute of Bioinformatics, University of Bern, Bern, Switzerland

Recent studies have identified Th2 (pTh2) cells, based on their crucial role in mediating type-2-related immunopathology. pTh2 cells exhibit high levels of the ligand-activated transcription factor peroxisome proliferator-activated receptor gamma (PPAR-g). The functional role of PPAR-g for pTh2 cells, however, remains incompletely understood. Here, we analyzed the effect of PPAR-g inhibition on basic T cell functions such as IL-2 or T cell receptor (TCR)-induced proliferation in pTh2 cells isolated from peripheral blood. Strikingly, PPAR-g inhibition strongly reduced IL-2-induced proliferation, but not TCR-induced proliferation, suggesting specific control of pTh2 cell functions. Furthermore, we showed that ST18 overexpression in keratinocytes significantly augments antibody-mediated ST18 promoter activity. Third, p35 silencing abolished the DSG3-mediated activation of the ST18 promoting activity. Finally, we demonstrated that ST18 overexpression in keratinocytes significantly augments antibody-mediated DSG3 down-regulation in keratinocytes. Taken collectively, these data indicate that ST18 up-regulation triggers a pathophysiological self-amplifying cycle involving DSG3 and p35 dysregulation, which may underlie the genetic association of ST18 variants with PV. Supporting the clinical relevance of these findings, a genetic variant causing increased ST18 promoter activity was found to be associated (p = 0.003) with more severe phenotype in a cohort of 100 PV patients.

005 Pathogenic autoantibody derived from Treg-deficient scurfy mice targets Type VII Collagen and induces Epidermolysis bullosa acquista-like blistering disease

E Vicari1, S Haebeler1, V Boldska1, T Ramcke1, A Vorobyev2,3, S Goletz3, H Iwata4, R Pandey1, T Krausgruber3, D Atzmuller1, P Wohlfarth4, C Rock5 and W Rabitsch1,2

1 Department of Dermatology, Medical University of Vienna, Vienna, Austria; 2 Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases, Medical University of Vienna, Vienna, Austria; 3 Centre for Molecular Medicine, Medical University of Vienna, Vienna, Austria; 4 Department of Internal Medicine I, Bone Marrow Transplantation Unit, Medical University of Vienna, Vienna, Austria; 5 Department of Laboratory Medicine, Medical University of Vienna, Vienna, Austria

Skin-resident memory T cells are thought to be non-circulating cells providing rapid recall responses against outside pathogens. Recent observations in humanized mouse models indicate that a subset of tissue-resident memory T cells (Trm) may exit the skin and form a discrete circulating T cell population in the blood. To explore the existence of a skin-derived circulating Trm population in humans, we characterized circulating T cells with a skin Trm phenotype in the blood of patients after allogeneic hematopoietic stem cell transplantation (HSC). We found a small and stable population of CD4+CD103+CLA+ T cells in the blood of all patients analyzed and verified their tissue origin in gene-edited mice in sex-mismatched HSTC recipients. Transcriptional analysis on single-cell level revealed their striking resemblance to skin Trm. Blood from patients with GvHD contained elevated numbers of host-derived CD4+CD103+CLA+ T cells producing pro-inflammatory Th2/Th17 cytokines, which highlights the potential of skin Trm to contribute to inflammation on a systemic level. Importantly, gastrointestinal GvHD lesions contained CD4+CD103+ T cells expressing the cutaneous leukocyte antigen CLA, indicating potential regulatory function of skin Trm in the gut. Collectively, our data offers first proof of a distinct Trm-like circulating T cell type, which mirrors cutaneous inflammation and may disseminate disease via the blood circulation.

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