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

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Tissue-resident memory T (TRM) cells play a crucial role in local immunity by inducing rapid immune responses upon exposure of the antigen. However, how CD4+ TRM cells are 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 CD44+CD69+ TRM cell phenotype. Their residency in the dermis was confirmed using a CD301b+ conventional dendritic cell (DC) reporter mouse model. Next, we found that CD301b+ DC cells formed perivascular clusters around blood vessels in the ear dermis of mice. These clusters are CD301b+DC cells and their clusters were reduced after the depletion of CD301b+ cells. Taken together, these results suggest that CD301b+DC2 cells are critical in the tissue residency of CD4+ T 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 systemic sclerosis chronic graft-versus-host disease

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Systemic sclerosis (SSc) is an autoimmune disease characterized by fibrosis and vascular injury of skin and internal organs. Fractalkine (CX3CL1) is a chemokine that is expressed on various endothelial cells and functions as an adhesion molecule for CX3CR1-positive leukocytes. Additionally, soluble fractalkine is involved in the migration of CX3CR1-expressing leukocytes into the lesional tissue. We previously reported that the expression of fractalkine and its receptor CX3CR1 were both augmented in SSCs patients, and anti-mouse fractalkine monoclonal antibody (mAb) suppressed inflammation, fibrosis, and vascular injury of the skin in a mouse model of graft-versus-host disease (GvHD) induced by sublethally irradiated BALB/c mice. In the current study, we investigated the utility of anti-mouse fractalkine therapy in a murine sclerodermatous chronic graft-versus-host disease (Scl-cGVHD) model. Allogeneic bone marrow transplantation into lethally irradiated BALB/c mice produced organ fibrosis and autoimmune phenomena resembling human Scl-cGVHD or SSC. An intraperitoneal administration of anti-fractalkine mAb increased survival rate in a dose-dependent manner. The mAb therapy significantly suppressed the fibrosis of the skin and lungs. Moreover, the mAb dose-dependently attenuated the localization 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 proinflammatory cytokine IL-14 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 Scl-cGVHD and SSC.

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

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Pemphigus vulgaris (PV) is a life-threatening autoimmune mucocutaneous blistering disease. Recently, we showed that desmoglein-3 (DSG3) down-regulation is associated with increased p53 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 p53 may be jointly involved on the pathogenesis of PV. First, we found that antibody-mediated DSG3 down-regulation results in increased expression of p53. Second, we showed that DSG3 down-regulation activates the ST18 promoter activity. Third, p53 silencing abolished the DSG3-mediated activation of the ST18 promoter 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 pathophysiologic self-amplifying cycle involving DSG3 and p53 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 a more severe phenotype in a cohort of 100 PV patients.

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

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Skin-resident memory T cells are poised for systemic Th2/Th17-driven inflammation and may re-seed at distant sites during graft-versus-host disease

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