001 Maintenance of CD4⁺ T cell-mediated chronic inflammatory skin diseases by pT cell entry of CD4⁺ T cell memory T cells in skin perivascular clusters with CD301b⁺ dermal dendritic cells in a mouse model of allergic dermatitis

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Tissue-resident memory T cells (Trm) play a crucial role in local immunity by inducing rapid immune responses upon exposure to the antigen. However, how CD4⁺ T 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 expressed CD4⁺CD8⁻CD103⁺ Trm cell phenotype. Their resident cutaneous migration, fibrosis, and proliferation were impaired 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 (CD103⁺) infiltrates the dermis with CD103⁺ Trm cell infiltration. These CD301b⁺ DCs in Mgll2–diphtheria toxin receptor (DT) mice, which express the DTR under the regulation of the gene encoding CD301b, and found that the number of CD4⁺ T cells and their clusters were reduced after the depletion of CD301b⁺ cells. Taken together, these results suggest that CD301b⁺ DCs 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.

003 Anti-fractalkine monoclonal antibody therapy ameliorates murine scleroderma-like chronic graft versus-host disease


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 vascular endothelial cells and functions as an adhesion molecule for CX3CR1-positive leucocytes. Additionally, soluble fractalkine is involved in the migration of CX3CR1-expressing leucocytes into the lesional tissue. We previously reported that expression of fractalkine and its receptor CX3CR1 was both augmented in SSc patients, and anti-mouse fractalkine monoclonal antibody (mAb) suppressed inflammation, fibrosis, and vascular injury of the skin in a murine skin fibrosis model. However, the SSc-mediated fractalkine mAb treatment did not show any apparent adverse events. These data together further highlight the potential of PPAR-γ as a therapeutic target in type 2 immunopathology.

004 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. We previously showed that a genetic variant in the ST18 gene is associated with increased risk of disease expression and that the ST18 variant promotes the development of pathogenic antibodies in PV. Deletion of the ST18 promoter was sufficient to induce the development of pathogenic antibodies in a transgenic mouse model. To investigate the role of the ST18 promoter in the development of pathogenic antibodies, we investigated the utility of a mouse model of pemphigus in which PV is induced by treatment with the genotoxic agent methyl ethyl ketone (MEK). In this model, we found that deletion of the ST18 promoter abolished the induction of pathogenic antibodies. Furthermore, we found that deletion of the ST18 promoter was sufficient to induce the development of pathogenic antibodies in a transgenic mouse model. These findings suggest that ST18 is a key regulator of the development of pathogenic antibodies in PV. However, it is important to note that the role of ST18 in the development of pathogenic antibodies in PV remains unclear.

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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Pathogenic autoantibodies with reactivity to structural proteins in the skin. Furthermore, the development of a pathogenic autoantibody that targets BP230 and induces a bullous pemphigoid-like phenotype indicates the progression of autoimmune blistering diseases (AIID) in the absence of functional Tregs. Given the crucial role of autoimmune disease in scurfy mice, by mimicking spontaneously activated B cells were screened for antibodies against other poten- tial pathogenic target antigens. We found a murine IgG, autoantibody (H510) which is pathogenic in vivo as it induces subepidermal blisters in neonatal mice and binds to the blister floor on murine salt-split skin in indirect immunofluorescence (IF). After we excluded that H510 binds to laminin-332, we identified type VII collagen (Col7) as a potential auto- antigen. Western blot analysis and IF staining using skin from Col7−/− mice revealed that Col7-specific autoimmune antibody activity. We further mapped the antigenic epitope to the murine von Willebrand factor-A-domain 2 of Col7. In summary, we here present a recently identified, pathogenic autoantibody spontaneously developed in the absence of functional Tregs with reactivity against Col7 as a useful model for the induction of Epidermolysis bullosa acquisita in mice.

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