**007**

IL-6-producing effector B cell promotes fibrosis in scleroderma, while IL-10-producing regulatory B cells suppresses it; BAFF inhibition modulating effector and regulatory B cells in scleroderma

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**008**

An exploration of the histological features of dermatomyositis

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**009**

Proportion of CD4+CD49b+LAG-3+ type 1 regulatory T cells in the blood of psoriasis patients inversely correlates with psoriasis area and severity index


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Type 1 regulatory T (Tr1) cells are Foxp3+ IL-10-secreting regulatory T cells implicated as key regulators of peripheral immune tolerance. Recently it was identified that surface expression of CD4+CD49b+LAG-3+ is sufficient to identify this specific cell lineages. As IL-10 and LAG-3 expression in psoriasis lesions are extremely low, we hypothesized that impaired immune tolerance in psoriatic could be associated with reduced Tr1 cells. To test the hypothesis, we analyzed 12 psoriasis patients’ blood & skin tissues, and B control blood samples to compare Tr1(CD3+CD4+CD49b+LAG-3+) cells, Tregs(CD3+CD4+CD8-CD25+CD127+), and activated T(CD3+CD4+CD8+CD25-CD127+) cells. First, the proportion of activated T cells was higher in psoriasis patients (mean 0.42 vs control 0.19, p<0.015). In contrast, the proportion of Tr1 cells was lower in psoriasis patients (mean 0.18% vs control patients 0.51%, p<0.001). The proportion of conventional Treg tended to be lower in psoriasis patients mean 3.01% compared to normal subjects (mean 4.09%, but the difference was not significant (p=0.132). Second, the proportion of activated T cells was positively correlated with PASI (r=0.65, p=0.002). In contrast, the proportion of Tr1 cells was inversely correlated with PASI (r=-0.61, p=0.002). The proportion of Treg tended to be inversely correlated with PASI, but the correlation was not significant (r=-0.35, p=0.127). Lastly, 4-color immunofluorescence identified Tr1(CD3+CD4+CD8-CD25+LAG-3+DAPI+) cells in psoriasis non-lesional skin, but not in lesional skin. We propose that a decreased number of Tr1 cells in the blood of psoriasis patients could allow for excess expansion of psoriasis disease-related T cells in either lymph node compartments and thus lead to psoriasis disease progression.

**010**

Role of epithelial cell adhesion molecule (EpCAM) in iniquimod-induced psoriasis like dermatitis

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Psoriasis is a chronic skin disorder that is characterized by excessive skin inflammation with severe erythema and epidermal thickness. Epithelial cell adhesion molecule (EpCAM) is a cell surface protein that is expressed by Langerhans cells (LCs), a population of epidermal dendritic cells, and normal epidermal cells. LCs control initial immune response to antigens or pathogens and therefore we hypothesized that EpCAM expression was important for the development of epidermal homoeostasis. In the knockout mice lacking EpCAM in LC using huLanger promotor, contact hypersensitivity responses were enhanced. In those mice, LC migration from the epidermis was impaired. The role of EpCAM in psoriasis, however, is still unclear. Here, we evaluated the function of EpCAM in iniquimod (IMQ)-induced psoriasis-like dermatitis using the conditional knockout mice that lacked EpCAM expression in the dermal compartment of the skin. IMQ treatment in the ear skin after tamoxifen treatment for consecutive 6 days. Skin inflammation and epidermal thickness were attenuated in Ecam KO mice 6 days after IMQ treatment compared with control mice. The results suggest that EpCAM may have a crucial role for the development of psoriasis-like dermatitis. We are in the process of determining which cytokines or chemokines regulate skin inflammation influenced by Ecam and elucidating the role of EpCAM in psoriasis.

**011**

Intravenous immunoglobulin reduces pathogenic antibodies, serum IL-6 levels and disease severity in experimental bullous pemphigoid

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Bullous pemphigoid (BP) is an autoimmune blistering disease characterized by autoantibodies to type XVII collagen (COL17). Currently, systemic corticosteroids are used as first-line treatments for BP. Intravenous immunoglobulins (IVIG), which consists of high-dose IgG and the modulation of IL-6 production.

**012**

Treg dysfunction induces autoantibodies to type XVII collagen and BP230 in mice and humans

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Regulatory T cells (Tregs) are crucial for peripheral immune tolerance. However, it remains to be clarified whether the failure of peripheral immune tolerance influences the production of autoantibodies to epidermal components. We examined scurfy mice, which lack functional Tregs due to mutation in Foxp3. Scurfy sera reacted to the dermal-epidermal junction of the skin and to the epidermal side of artificial blisters induced by MN. Therefore, we focused on bullous pemphigoid (BP) autoantigens, type XVII collagen (COL17) and BP230 as antigens targeted by scurfy sera. Scurfy sera was found to react to the recombinant proteins of COL17 and BP230. The adoptive transfer of scurfy CD4+ T cells induced the production of autoantibodies to BP antigens in T cell-deficient mice. Interestingly, the knockout of the gene in scurfy mouse was found to decrease follicular helper T (Tfh) cells, which help B cells to produce antibodies, in the spleen and in the skin-draining lymph nodes and to diminish the production of autoantibodies. These findings suggest that Treg dysfunction triggers the activation of autoreactive CD4+ T cells, especially Tfh cells, resulting in the production of autoantibodies to BP antigens in a STAT6-dependent manner. Of note, sera from patients with PEP syndrome, a severe autoimmune disease caused by mutation in FOXP3, also was found to react to COL17 and BP230. Thus, Tregs contribute to the maintenance of immune tolerance to BP antigens at a steady state in mice and humans.