Transforming growth factor-β produced by keratinocytes undergoing apoptosis promotes skin fibrosis in chronic graft-versus-host disease-like reaction


Sclerosis nodosa cutis is one of the main clinical features of chronic graft-versus-host disease (cGVHD), in which donor immune cells react against host tissues after allogeneic hematopoietic stem cell transplant. It has been reported that interferon (IFN)-γ released by donor T cells promotes infiltration of donor T cells themselves into the skin, and mediates production of transforming growth factor-β (TGF-β) from keratinocytes in the pathogenesis of sclerosis nodosa cGVHD. To investigate the roles of host keratinocytes, which are the targets for donor T cells, in skin cGVHD, we established a new murine model of sclerodermatous cGVHD by using an autoimmune organ-specific model, collagen-induced arthritis (CIA) in human CD4+CD25+Foxp3+ regulatory T cells (Treg). In CIA, we observed the infiltration of donor T cells into the skin, and the production of TGF-β by keratinocytes undergoing apoptosis (0 pg/ml). Collectively, TGF-β production by keratinocytes themselves and infiltrating donor T cells promotes infiltration of donor T cells themselves into the skin, and mediates production of TGF-β from keratinocytes in the pathogenesis of sclerosis nodosa cGVHD.

Collectively, TGF-β production by keratinocytes themselves and infiltrating donor T cells promotes infiltration of donor T cells themselves into the skin, and mediates production of TGF-β from keratinocytes in the pathogenesis of sclerosis nodosa cGVHD.

**Abstracts**

**379 Increased frequency of CD4+ tissue resident memory T cells in skin lesion of lupus erythematosus and the underlying mechanism**

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Lupus erythematosus (LE) is a spectrum disease, from skin manifestation (discoid LE, DLE), subcutaneous LE (SLE) to systemic involvement (SLE). The pathogenesis of LE has been extensively studied. However, the current knowledge of aberrant effector T cells cannot explain the release of LE, resulting in difficulties in treatment. Tissue resident memory T (TRM) cells are a type of T cells resident in tissue, differentiated from effector T cells and cannot return to the circulation. Increasing evidence has shown a critical role of TRM cells in the relapse of psoriasis and vitiligo. In our study, in the skin lesion from DLE, SLE and LE patients, we found a dramatically increased frequency of TRM cells in dermis, compared with healthy controls and psoriasis patients. DLE patients show the highest frequency of TRM cells (p < 0.01). When TRM cells were cultured, either in CD4+ TCMs or from dermis from SLE skin lesion, we found that compared with healthy controls, statistically increased CD4+ TRM cells were found in SLE patients (p < 0.05), rather than DTR+ TRM cells. When we sequenced the CD4+ TRM cells by single cell sequencing, we found that 46 genes were up-regulated and 60 genes were down-regulated in SLE CD4+ TRM cells. Among these genes, absent in melanoma 2 (AIM2) was obviously expressed high by SLE CD4+ TRM cells. This phenomenon is also confirmed in SLE skin lesion (p < 0.01) by multi-color IHC with PerkinElmer Vectra. In addition, AIM2 was found to be regulated by IL-21 induced TET2 enrichment on the promoter region of AIM2, and TET2 and IL-21 was also observed to be expressed widely in lupus skin lesion. Our findings indicate that increased CD4+ TRM cells might contribute to the relapse of LE, providing potential biomarkers and therapeutic targets.

**041 Anti-thyroid peroxidase antibodies target a cytoplasmic protein in keratinocytes and may contribute to blister formation in pemphigus vulgaris**

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In addition to having reactivity to the classical targets, desmoglein (Dsg) and -1, there is accumulating evidence that Pemphigus vulgaris (PV) patients harbor non-Dsg autoantibodies. The disease relevance of non-Dsg targets in PV is under investigation. We have shown that PV patients carry anti-thyroid peroxidase (TPO) antibodies at significantly higher levels than healthy controls and that anti-TPO reactivity is driven by HLA status and the absence of Dsg-anti-Dsg antibodies. We have also shown functional effects of anti-TPO on cell adhesion and cellular reactivity. We have also shown that patients carry anti-thyroid peroxidase (TPO) antibodies at significantly higher levels than healthy controls and that anti-TPO reactivity is driven by HLA status and the absence of Dsg-anti-Dsg antibodies. We have also shown functional effects of anti-TPO on cell adhesion and cellular reactivity.

**042 The sand fly Lutzomyia longipalpis LJM17 protein induces cross-reactive antibodies against desmoglein-1 in Fogo Selvagem**

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Fogo Selvagem (FS) is a lethal skin disease mediated by pathogenic IgG4 autoantibodies to desmoglein-1 (Dsg1). FS is prevalent in certain regions of Brazil, where Leishmaniasis and Chagas disease are endemic. Normal individuals and leishmaniasis patients from these regions possess non-pathogenic anti-Dsg1 antibodies. They are chronically exposed to bites of the sand fly Lutzomyia longipalpis (LL), which elicits an IgG response in PS and early treatment of primary disease is most important for prevention it. Here, we investigated which anti cytokine antibody is effect for prevention of gastrointestinal amyloidosis.