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

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Sclerodermia is one of the main clinical features of chronic graft-versus-host disease-like reaction (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 (TGF)-β from keratinocytes in the pathogenesis of sclerodermia cGVHD. To investigate the roles of host keratinocytes, which are the targets for donor T cells, in skin fibrosis of cGVHD, we established a new murine model of sclerodermia cGVHD by using transgenic mice expressing transgenic mouse CD4+ T cells expressing T-cell receptor (TCR) specific for normal-mouse 12.15 pg/ml, measured by an enzyme-linked immunosorbant assay, P<0.01) as well as when treated with an apoptosis-inducer agent (AT1O1, 107.8±12.18 pg/ml, P<0.01), compared to untreated keratinocytes (17.8±5.5 pg/ml) and biorate-treated keratinocytes undergoing necrosis (0 pg/ml). Collectively, TGF-β produced by keratinocytes undergoing IFN-γ-induced apoptosis is implicated in the pathogenesis of sclerodermoid cGVHD.

038 Gastrointestinal amyloidosis by long-lasting inflammatory skin disease

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We recently demonstrated that persistent release of IL-1α from inflammatory skin causes weight loss, vascular sclerotic changes, and severe systemic amyloidosis in multiple organs. In this study, we investigated the pathogenesis of gastrointestinal amyloidosis by IL-1α. We produced caspase-1 transgenic mice (KCASP1Tg). In inflammatory diseases such as rheumatoid arthritis, secondary intestinal amyloidosis occurs which causes malabsorption and bowel movement obstruction. Also in KCASP1Tg mice, long-lasting expression of IL-1α causes intestinal amyloidosis. Usually, gastrointestinal amyloidosis is irreversible in many cases and early treatment of primary disease is most important for prevention. Here, we investigated which anti cytokine antibody is effective for prevention of gastrointestinal amyloidosis.

039 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 intensively 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). While TCR-αβ+ or CD69+ TRM cells 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 CD8+ 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 high expressed 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 of AIM2 gene. This finding indicates 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)3 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-3 and Dsg-1.

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

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In endemic areas, the sandfly Lutzomyia longipalpis LJM17 (LJM17) is prevalent in certain regions of Brazil, where Leishmaniasis and Chagas disease are endemic. The sandfly is of medical importance because bite of the sand fly Lutzomyia longipalpis (LJM17), which elicits an IgG response to LE salmonin proteins LJM17 and LJM17 and could contribute to the development of FS. We tested the antibody response to (Dsg1) and LJM17 IgG4 in normal settlers (n=108). FS patients (n=68) from Linhas Verde (LY), an endemic focus of FS, and distinct non-endemic control populations (Brazil (n=33), USA (n=111) and Japan (n=70)). We also studied the antibody response in mice to these antigens and assessed the protein sequence homology between LJM17 and Dsg1. We demonstrate that healthy individuals and FS from LV had higher values of IgG4 anti-LJM17 antibodies than control groups from non-endemic areas (p<0.001). Levels of IgG anti-Dsg1 and IgG4 anti-LJM17 antibodies were positively correlated in normal settlers (r=0.56) and FS (r=0.38). Mice immunized with rLJM17 produced IgG1 antibodies against LJM17, which cross-react with Dsg1. These cross-reactive antibodies were purified by ion-exchange chromatography and were inhibited by Dsg1. These cross-reactive IgG antibodies that lead to FS in a subset of genetically predisposed individuals.

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