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

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We recently demonstrated that persistent release of IL-1α from inflammatory skin cells causes weight loss, vascular sclerotic changes, and severe systemic amyloidosis in multiple organs. In this study, we investigated the inflammatory milieu in chronic graft-versus-host disease-like reaction (cGVHD) and the possible trigger of amyloidosis. We showed that keratinocytes undergoing apoptosis were induced in cGVHD lesions and that IL-1α induced the release of IL-1β by keratinocytes. This finding may imply that the inflammatory milieu established by keratinocytes undergoing apoptosis promotes skin fibrosis in chronic graft-versus-host-disease-like reaction.

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 effecter 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 we detected CD8+ or CD4+ TRM cells from dermis from LE 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 Perforin/Emerin Vecta. 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.

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 Dign-reactivity. We have also shown functional effects of anti-TPO on cell adhesion and cellular processes associated with blister formation in human keratinocytes. TPO is known as an enzyme primarily involved in iodination of thyroglobulin in the thyroid gland with no known function in the skin. The exact target of anti-TPO antibodies in skin remains unclear. To clarify, we assessed TPO mRNA and protein expression by RT-PCR, Western Blot (WB) and immunofluorescence (IF) in the human keratinocyte cell line HaCaT. We show that TPO is indeed expressed in HaCaT cells by PCR. At the protein level, we show definitive cytoplastic staining with anti-TPO Abs, with no overlap with anti-Dsg3 binding or cytokeratin components by IF. Interestingly, by Western Blot, we detect binding of anti-TPO antibodies to TPO in SDS-SDS PAGE size, which is not the case for the cytoplasmic TPO variant (103 kDa). Variants of TPO of sizes close to 75 kDa have been described. Additionally, a number of TPO orthologs such as lacto-, myelo- and eosinophil peroxidase exhibit a high degree of sequence similarity to TPO ectodomains. Our data conclusively indicate that anti-TPO antibodies target a cytoplasmic protein that may function in the context of PV.