**ABSTRACT: Adaptive and Auto-Immunity**

043 Keratinocyte-mediated activation of TGFβ maintains skin-recruiting memory CD8 T cells

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Tissue-derived factors are critical for the development and persistence of skin-resident memory CD8 T cells. Migrating into skin, keratinocytes (KCs) present antigen to CD8 T cells and can contribute to the development of memory CD8 T cells. However, the role of keratinocytes in the maintenance of memory CD8 T cells remains unclear. In this study, we used independent experiments in mouse and human skin to assess the role of keratinocytes in maintaining memory CD8 T cells. We generated human epidermal equivalent (HEE) and mouse epidermal equivalent (MEE) models to analyze memory CD8 T cells and keratinocytes (HEK8-itgb6 mice). We observed that keratinocytes provided a cytokine environment within this nonlymphoid tissue that shapes the differentiation state and proliferation of memory CD8 T cells. Our results indicate that keratinocytes maintain memory CD8 T cells through the presentation of antigen to memory CD8 T cells in the absence of lymphoid tissue.

044 IFN-γ enhances cell-mediated cytotoxicity against keratinocytes via JAK2/STAT1 in lichen planus

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Recent studies indicate that skin inflammation of psoriasis is characterized by an increase in keratinocytes (KCs) and a decrease in keratinocyte apoptosis. In contrast, lichen planus (LP) is characterized by KC apoptosis and a decrease in KC proliferation. The role of keratinocytes in the pathogenesis of LP is not fully understood. In this study, we examined the role of keratinocytes in the pathogenesis of LP by using the IFN-γ-induced mouse model. We observed that mice with IFN-γ-induced keratinocytes had a significant decrease in keratinocyte proliferation and an increase in keratinocyte apoptosis. To further investigate the role of keratinocytes in LP, we used keratinocyte-specific deletion of IFN-γ. Our results indicated that IFN-γ-induced keratinocytes enhances cell-mediated cytotoxicity against keratinocytes via JAK2/STAT1 in LP, which may be a therapeutic target in LP.

045 B cell cytokine analysis by single cell analysis reveals therapeutic reactivity of systemic sclerosis-associated interstitial lung disease

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Purpose: Systemic sclerosis (SSc) is an autoimmune disease characterized by fibrosis. SSc-associated interstitial lung disease (ILD) is a severe complication of SSc. The cyclophosphamide (CYC) therapy is the only therapy found to be effective in improving lung function. However, not every SSc-ILD patients treated with CYC recover. Recent studies indicate that B cells play a critical role in SSc. However, the relationship between response to CYC therapy and B cell function remains unknown. In this study, we assessed the role of interlukin (IL)-10-producing regulatory B cells and IL-6-producing pathogenic B cells in SSc-ILD patients.

Results: In SSc-ILD patients, the number of B cells adhering to LECs significantly increased compared to non-specific conventional B cells. Adhered B cells produced cytokines; we measured IL-6 and IL-10 production from single B cells. Significantly higher cytokine production was observed in the responders compared to non-responders. In the mouse study, the number of topo I-specific B cells producing regulatory B cells and IL-6-producing pathogenic B cells in the responders or non-responders. In the mouse study, the number of topo I-specific B cells producing regulatory B cells and IL-6-producing pathogenic B cells in the responders or non-responders.

Conclusion: These results suggested that the effectiveness of CYC to SSc-ILD patients is associated with the cytokine profile of B cells. However, not every SSc-ILD patients treated with CYC recover. Recent studies indicate that B cells play a critical role in SSc. However, the relationship between response to CYC therapy and B cell function remains unknown. In this study, we assessed the role of interlukin (IL)-10-producing regulatory B cells and IL-6-producing pathogenic B cells in SSc-ILD patients.

046 Progranulin promotes bleomycin-induced skin sclerosis by enhancing TGF-β/Smad3 signaling through up-regulation of TGF-β type I receptor

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Progranulin (PGRN) is an autocrine growth factor with multiple physiological and pathological functions. Previous reports demonstrated PGRN could increase dermal fibroblasts in wound healing and activate cancer associated fibroblasts in some cancers. Because systemic sclerosis (SSc) is a prototypal fibrosis-related disorder, here, we aimed to clarify the role and mechanism of PGRN in bleomycin (BLM)-induced model of SSc for the first time. We observed that the serum PGRN levels were increased in Chinese SSc patients compared with healthy controls. Immunohistostaining and RT-PCR demonstrated that PGRN was also elevated in the lesion from BLM-induced dermal fibrosis. Additionally, in BLM-treated mice, PGRN deficiency not only attenuated dermal fibrosis but also decreased the differentiation of myofibroblasts. The reduced progression of skin sclerosis in PGRN-deficient mice was associated with downregulation of TGF-β receptor I (TβRI) and decreased level of p-Smad3, with correspondingly impaired the expression of its downstream target gene connective tissue growth factor (CTGF) in skin lesion. This study demonstrates that PGRN plays a promoting role in the development of dermal fibrosis through the activation of the TGF-β/Smad3 signaling via upregulation of TβRI I. PGRN may be a new therapeutic target in SSc.

047 Autoantigen Keratin 17 presented by keratinocytes directs T cell auto-reactivity in psoriasis

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Keratin 17, an intermediate filament protein, is overexpressed in psoriasis and is not found in healthy epidermis. Studies have shown that K17 is major autoantigen that is recognized by autoreactive T cells in psoriasis. It shares sequence with streptococci and serves as a major autoantigen recognized by autoreactive T cells in psoriasis because it shares similar epitopes with streptococci in healthy skin. We used conditional knockout (KO) mouse in which administration of tamoxifen (TX) results in keratinocyte-specific deletion of K17 (K17-/- mice). Unexpectedly, K17-specific memory cells rescue the loss of memory cells in K17-/- mice. Further, in vivo co-incubation assay indicates that KCs stimulated by IFN-γ can specifically activate the CD4+ T cells of HLA-DR/DRB1*0401 mice. This suggests that keratinocytes (KCs) can present antigens to T cells in the absence of lymphoid tissue and may play a critical role in the development of auto-reactive T cells in psoriasis.