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Abnormal elevation of galactose aggravates inflammation and epidermal proliferation in psoriasis

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Psoriasis is an immune-mediated inflammatory skin disease which is associated with clinical features of metabolic syndrome. Galactose is a key source of energy and crucial structure element in complex molecules. Whether galactose is involved in psoriasis pathogenesis remains unclear. The aim of this study is to explore the association between galactose metabolism and psoriasis in human and the role that galactose plays in immiquimod (IMQ)-induced psoriasis mouse model. The levels of galactose, glucose and lipid metabolism index in fasting blood were compared between 30 healthy controls and 60 psoriasis vulgaris patients without diabetes or metabolic syndrome. The correlation between galactose and other metabolism index was analyzed. Galactose was gavage administrated into IMQ-induced psoriasis mice to test its influence on epidermal thickning, inflammatory cell infiltration and cytokines production. The effect of galactose on HaCaT cell proliferation was measured by the CCK-8 assay. We found that fasting blood galactose, insulin resistance and triglyceride were higher, while high density lipoprotein was lower significantly in psoriasis ($p<0.05$). Serum galactose level positively correlated with insulin resistance, triglyceride, while negatively correlated with apolipoprotein A in psoriasis ($p<0.05$). Excess galactose promoted psoriasis skin severity, ear swelling, epidermal thickning, CD45+ cell infiltration, the mRNA levels of inflammatory cytokine IL-1β, IL-6, IL-17F and IL-23 in IMQ-induced psoriasis lesions, and proliferation of HaCaT cells. In conclusion, Abnormal elevation of galactose in psoriasis vulgaris patients is associated with insulin resistance and lipid disorder. Excess galactose induced inflammation and epidermal proliferation in psoriasis model, indicating that galactose might promote the development of psoriasis.

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Il-1b is essential for anti-galectin3 antibody induced cutaneous vasculitis in systemic lupus erythematosus

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Cutaneous vasculitis is one of the most common skin findings in systematic lupus erythematosus (SLE). However, the molecular mechanisms underlying this pathological process remain elusive. Our previous research suggested that anti-galectin-3 antibody was strongly related to the occurrence of cutaneous vasculitis in SLE patients. We here reported that anti-galectin3 antibody isolated from SLE patients induced cutaneous vasculitis in a dose-dependent manner by intradermal injection into mice. This antibody dysregulated the function of endothelial cells by inhibiting cell migration, capillary tubule formation and promoting inflammatory mediators production such as E-selectin, ICAM-1, IL-4 and IL-1b as well. Cutaneous vasculitis induced by anti-galectin-3 antibody was greatly reduced by anti-IL-1b antibody intradermal injected into mice. We further generated a lupus-like mouse model by footpad injection of recombinant human galectin-3 protein plus adjuvant. These mice were not only characterized by skin damages but also featured by internal organ (lung and kidney) and serological disorders (elevated ANA, anti-dsDNA antibody) as well. IL-1b was copiously accumulated around and within the cutaneous vasculitis area in this lupus-like model. Overall, these findings suggest that IL-1b is critical for the pathogenesis of cutaneous vasculitis induced by anti-galectin3 antibody in the context of SLE and provide a novel systemic lupus-like model.

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TIPE1 is induced in psoriasis lesions and promotes keratinocyte proliferation

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Psoriasis is a chronic inflammatory skin disease characterized by abnormal proliferation of epidermal keratinocytes and infiltration of inflammatory cells. TIPE1 (TNFAIP8L1, Tumor necrosis factor-α-induced protein 8-like 1) is a member of tumor necrosis factor-α-induced protein 8 family. Here, we showed that TIPE1 expression increased in the lesioned epidermis from the patients with psoriasis vulgaris and skin lesions from the imiquimod (IMQ)-treated mice. Expression of TIPE1 in cultured keratinocytes (HaCaT and HEKa) was also induced by M5, a mixture of 5 pro-inflammatory cytokines including IL-17A, IL-22, IL-1α, Oncostatin M and TNF-α. Lentiviral induced over expression of TIPE1 increased cell proliferation and cell apoptosis. Conversely, knockdown of TIPE1 by siRNA suppressed G1/S transition. In addition, TIPE1 overexpression increased the phosphorylation and activation of ERK. Taken together, these results suggest that induced expression of TIPE1 may contribute to the pathogenesis of psoriasis.

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Skin rash secondary to checkpoint inhibitor immunotherapy is associated with a dense T cell and dendritic cell infiltrate and greater cellular proliferation in the dermis

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Checkpoint inhibitor immunotherapy is associated with a wide range of immune related adverse events (irAEs). Of these, skin rash is often the first to appear and severity may determine if therapy is interrupted or even withdrawn. In contrast, rash development has also been associated with improved survival. However, the mechanism underpinning rash development during immunotherapy remains unknown. Thus, we examined the makeup of immunotherapy-associated skin rash infiltrates with the goal of uncovering mechanistic insights behind rash development. Immunohistochemisty was used to describe the immune infiltrate in skin biopsies from healthy subjects and from a lesional site of patients with rash. Rash samples were obtained from 7 patients receiving α-PD1, α-CTLA4/α-PD1 combination or α-PDL1/α-NKG2A combination. Acetone-fixed sections from frozen biopsies were stained for CD3, CD8, CD68, CD11c, CD1a, CD207, or Ki67. Cell abundance in the dermis was compared among groups. Rash samples showed significant enrichment of T cells (CD3 $p=0.01$), CD8 T cells ($p=0.03$) and dendritic cells (CD11c $p=0.03$) in the dermis vs controls. More moderate enrichment of macrophages (CD68) was observed in rash versus control samples and dermal Langerhans cells (CD1a or CD207) showed equal abundance among groups. Finally, we observed a higher cellular proliferation in the dermis of rash vs control samples (Ki67 $p=0.024$), associated with areas of dense immune infiltration. Ki67 expression was highly correlated with both CD68 ($r=0.89$; $p=0.012$) and CD11c ($r=0.786$; $p=0.048$), suggesting myeloid cell proliferation. In conclusion, immunotherapy-associated skin rash contains an immune infiltrate dominated by T cells, CD8 T cells and dendritic cells, with increased cellular proliferation at sites of immune infiltration. These data strongly suggest skin rash may involve mechanisms beyond T cell activation.

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AIM2 regulates anti-tumor immunity from dendritic cell vaccination within the melanoma microenvironment

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Successful immunotherapy strategies for melanoma must elicit the infiltration of $CD8^+$ T cells into the tumor, which is mediated by the recognition of tumor-derived, cytosolic DNA by the cGAS–STING-type I interferon (IFN) signaling pathway in tumor-infiltrating dendritic cells. However, cytosolic DNA can also be recognized by AIM2, a cytosolic DNA sensor that generates IL-1β and IL-18, and also induces pyroptosis, whose function in the melanoma microenvironment remains unclear. Here we report that an intravenously injected premelanosome protein (PMEL) peptide-pulsed *Aim2*-deficient dendritic cell vaccine ($Aim2^{-/-}$ DC-PMEL) significantly improves the efficacy of adoptive T-cell therapy (ACT) and anti-PD-1 immunotherapy in WT mice with B16F10 melanoma compared to similar treatment with the wild-type (WT) DC-PMEL. In contrast, the addition of an intratumoral injection of DNase I to ACT with $Aim2^{-/-}$ DC-PMEL abrogated the phenotype, suggesting that the enhanced anti-melanoma immunity of the $Aim2^{-/-}$ DC-PMEL is dependent on the recognition of tumor-derived DNA within the melanoma microenvironment. Mechanistic studies using ACT in combination with WT, $Aim2^{-/-}$, $Aim2^{-/-}Sting^{-/-}$, $Aim2^{-/-}Ifnar^{-/-}$, $Aim2^{-/-}Cxcl10^{-/-}$, $Il\text{-}1\beta^{-/-}$, or $Il\text{-}18^{-/-}$ DC-PMEL revealed that the $Aim2^{-/-}$ DC-PMEL enhances activation of STING-type I IFN signaling, which promotes tumor antigen-specific $CD8^+$ T-cell infiltration into the tumor via CXCL10. In addition, the activation of STING-type I IFN signaling and suppression of IL-1β and IL-18 production in response to tumor-derived DNA by $Aim2^{-/-}$ DC-PMEL prevent regulatory T-cell tumor infiltration. Finally, the administration of AIM2 siRNA-transfected WT DC-PMEL also improved the efficacy of ACT. Collectively, these data indicate that AIM2 is a regulator of multiple immunosuppressive signaling pathways in tumor-infiltrating DC vaccine and may be targeted to improve the efficacy of immunotherapy for melanoma.

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CXCL10 expression is regulated by keratinocyte STAT3 signaling and inhibits skin inflammation

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The role of STAT3 signaling in psoriasis is not entirely clear as transgenic mice that overexpress STAT3 in keratinocytes (K14-stat3c) spontaneously develop psoriasiform dermatitis whereas STAT3 is also thought to promote IL-17A/F production by T cells. Therefore, in this study, the relative contribution of STAT3 in keratinocytes versus T cells was evaluated in the imiquimod mouse model of psoriasiform dermatitis by evaluating cre/lox mice with either keratinocyte inducible deletion of STAT3 ($K5\text{-}cre^{ERT2}\times STAT3^{fl/fl}$ [K5-STAT3]) or specific deletion of STAT3 in T-cells ($Lck\text{-}cre\times STAT3^{fl/fl}$ [Lck-STAT3]). Unexpectedly, psoriasiform skin inflammation was diminished in K5-STAT3 mice whereas Lck-STAT3 mice developed similar skin inflammation as WT mice. In addition, K5-STAT3 mice had increased IFN-γ+ T cells but less IL-17+ T cells compared to wt mice, indicating that loss of STAT3 signaling in keratinocytes dampened inflammation by inhibiting IL-17 responses while promoting IFN-γ responses. Interestingly, mRNA and histologic expression of the interferon response gene, CXCL10, inversely correlated with the skin inflammation in deletion or overexpression of STAT3 in the K5-STAT3 or K14-stat3c mice, respectively. Additionally, we discovered that neutralizing CXCL10 signaling enhanced imiquimod-induced skin inflammation, suggesting that CXCL10 acts to inhibit skin inflammation in this model. Taken together, these findings define a novel mechanism by which keratinocyte but not T cell-intrinsic STAT3 signaling induces psoriasiform-like skin inflammation via regulation of CXCL10 expression, proinflammatory IL-17 and anti-inflammatory IFN-γ T cell responses.