031 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 immunomodulated (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 thickening, 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 thickening, CD4+ cell infiltration, the mRNA levels of inflammatory cytokine IL-1β, IL-6, IL-17F and IL-23 in IMQ-induced psoriasis lesions, and TNF-α in 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.

033 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 (TNF-α) superfamily. TIPE1 expression was 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 cellular 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.

034 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 underlying 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. Immunohistochemistry 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 ≥PD-1, ≥CTLA-4/PD-1 combination or ≥LAG-3/PD-1 combination. Immunohistochemical pre-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 (CD1c+ p=0.03) in the dermis vs controls. More moderate enrichment of macrophages (CD68+) was observed in rash vs control samples and dermal Langerhans cells (CD1a+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 CD1a (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.

035 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, cytotoxic DNA by the cGAS-STING-type 1 interferon IFN signaling pathway in tumor-infiltrating dendritic cells (DCs). However, cytotoxic DNA can also be recognized by AIM2, a cytotoxic DNA sensor that generates IFN-β and IL-18, and also induces pyroptosis, whose function in the melanoma microenvironment remains unclear. Here we report that an intravenously injected pmel1 melanoma cell vaccine (PMEL) peptide-pulsed A2a-depleted dendritic cell vaccine (A2a-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 vaccine. Furthermore, the addition of an intratumoral injection of DNA 1 to ACT with Aim2-/- DC-PMEL abrogated the phenomenon, 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-/- Il18r1-/- or Il18-/- DC-PMEL revealed that the Aim2-/- DC-PMEL enhances activation of STING-type IFN signaling, which promotes tumor antigen-specific CD8+ T-cell infiltration into the tumor via CXCL10. In addition, we observed a similar immunomodulatory effect via inhibiting IL-17 and IL-23 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.

036 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 versus T cells was evaluated in the imiquimod mouse model of psoriasiform dermatitis whereas STAT3 is also thought to promote IL-17A/F production by T cells. Therefore, in this study we compared 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 but not T cell-intrinsic STAT3 signaling. Rash samples were obtained from 7 patients receiving ≥PD-1, ≥CTLA-4/PD-1 combination or ≥LAG-3/PD-1 combination. Immunohistochemical pre-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 (CD1c+ p=0.03) in the dermis vs controls. More moderate enrichment of macrophages (CD68+) was observed in rash vs control samples and dermal Langerhans cells (CD1a+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 CD1a (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.