042 Tumor neoantigens and a novel hapten vaccine promote immune targeting of wild type tumor antigens and improve response to immune checkpoint blockade

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In metastatic melanoma, both tumor neoantigen load and development of vitiligo have been associated with favorable response to immunotherapy. We hypothesize that in the context of immune checkpoint blockade (ICB), neoantigens facilitate epitope spreading and immune targeting of tumor lineage self-antigens. We also aim to harness this process with a hapten-based vaccine to improve ICB response. Previously, our lab demonstrated in a murine model of melanoma that tumors with high neoantigen load respond significantly better to ICB than syngeneic tumors with low neoantigen load. We show that this response is associated with increased immune recognition of a melanocyte self-antigen (gp100) and that long-term survivors develop a durable immune response. Here, we demonstrate that co-administration of a novel hapten vaccine may further promote epitope spreading into novel vaccine targets and improve ICB response.

043 The role of inflammatory cytokines in regulating adipose tissue function

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Adipose tissue (AT) is the largest endocrine organ producing bioactive products called adipocytokines, which regulate several metabolic pathways, especially in the inflammatory condition. On the other hand, evidences were accumulated that chronic inflammatory skin disease is closely associated with AT abnormal remodeling, however, the mechanism is still unclear. We addressed this problem using keratin 14-specifically overexpressing caspase-1 transgenic mouse (KACS1P1Tg) that shows severe erosive dermatitis from 6 weeks, followed by reepithelialization and parakeratotic scale-crust formation with elevated circulating plasma IL-1β level derived from severe skin inflammation, causing vascular sclerotic change and severe systemic amyloidosis. In this study, we investigated the influence of the long-lasting dermatitis to AT pathological and functional change. Firstly we examined the influence of skin inflammation to the whole body and perigonadal white adipose tissue (GWAT) weight, and both of them were decreased in KACS1P1Tg showing small “burn-out" adipocytes histopathologically with increased stromal cell and TLR (Toll-like receptor) 4/CD11b positive monocyte infiltrates. Adipocytes isolated from KACS1P1Tg had elevated levels of TNF-α and MCP1-1 and adiponectin. After 4°C cold challenge, the expression of thermogenic proteins, uncoupling protein 1 (UCP1) mRNA in adipocyte was elevated, but the body temperature decreased rapidly in KACS1P1Tg, revealing the impaired thermogenesis ability of AT due to the AT atrophy. These AT disability was reproduced by cytokine intra-peritoneal administration, suggesting the influence of circulating skin-derived inflammatory cytokines. Our study suggested that tight control of inflammatory skin disease leads to the prevention of AT complications.

044 Effect of the adipoctice tissue by inflammation from seven skin dermatitis

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Adipose tissue (AT) is the largest endocrine organ producing bioactive products called adipocytokines, which regulate several metabolic pathways, especially in the inflammatory condition. On the other hand, evidences were accumulated that chronic inflammatory skin disease is closely associated with AT abnormal remodeling, however, the mechanism is still unclear. We addressed this problem using keratin 14-specifically overexpressing caspase-1 transgenic mouse (KACS1P1Tg) that shows severe erosive dermatitis from 6 weeks, followed by reepithelialization and parakeratotic scale-crust formation with elevated circulating plasma IL-1β level derived from severe skin inflammation, causing vascular sclerotic change and severe systemic amyloidosis. In this study, we investigated the influence of the long-lasting dermatitis to AT pathological and functional change. Firstly we examined the influence of skin inflammation to the whole body and perigonadal white adipose tissue (GWAT) weight, and both of them were decreased in KACS1P1Tg showing small “burn-out" adipocytes histopathologically with increased stromal cell and TLR (Toll-like receptor) 4/CD11b positive monocyte infiltrates. Adipocytes isolated from KACS1P1Tg had elevated levels of TNF-α and MCP1-1 and adiponectin. After 4°C cold challenge, the expression of thermogenic proteins, uncoupling protein 1 (UCP1) mRNA in adipocyte was elevated, but the body temperature decreased rapidly in KACS1P1Tg, revealing the impaired thermogenesis ability of AT due to the AT atrophy. These AT disability was reproduced by cytokine intra-peritoneal administration, suggesting the influence of circulating skin-derived inflammatory cytokines. Our study suggested that tight control of inflammatory skin disease leads to the prevention of AT complications.

045 Pigilatone, a PPAR γ Agonist, alleviates imiquimod-induced pustular-like skin lesions by regulating keratinocyte proliferation and differentiation through inhibition of STAT3 activity

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Psoriasis is a chronic autoimmune skin disease, characterized by abnormal keratinocyte proliferation and differentiation. Peroxisome proliferator activated receptor (PPAR) γ is a ligand-activated nuclear transcription factor, which is involved in the regulation of inflammatory cytokines synthesis in immune cells and regulates keratinocyte proliferation and differentiation. Pigilatone, a PPAR γ agonist, has been shown to have significant improvements when treated patients with psoriasis. However, the mechanism is still unclear. In this study, we investigated the underlying mechanism. In vivo, we applied pigilatone to imiquimod (IMQ)-induced mouse model of psoriasis and found that pigilatone ameliorated IMQ-induced pustular-like dermatitis, with reduced inflammation, less Ki67 positive cells, expression of pro-inflammatory cytokines and the IL-17A response. We confirmed that pigilatone inhibited STAT3 activity and differentiation of keratinocytes. Hacat cells were stimulated with IL-17A/TNF-α to model the skin inflammation in psoriasis. We found that pigilatone suppressed cell proliferation, promoted cell differentiation and inhibited the expression of inflammatory cytokines in Hacat cells. In addition, pigilatone significantly down-regulated the phosphorylation of signal transduction and activator of transcription 1 (p-Stat1). Therefore, pigilatone alleviates IMQ-induced pustular-like skin lesions possibly by regulating keratinocyte proliferation and differentiation via inhibiting Stat1 signaling pathway.

046 Generalized pustular psoriasis (GPP) and palmoplantar pustulosis (PPP) both show upregulation of the IL-36, neutrophil chemokine, and innate pathways that are modulated by solpalamib, an anti-IL-36 receptor antibody, treatment

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Generalized pustular psoriasis comprises a spectrum of inflammatory skin conditions, including GPP and PPP. GPP, characterized by neutrophil infiltration of the epidermis and development of visible sterile pustules. GPP is a rare, multisystemic, potentially life-threatening, flaring disease, whereas PPP is a localized, relapsing, debilitating, chronic disease. Here, gene and protein expression of lesional skin from 7 patients with a moderate GPP flare, 8 patients with moderate-to-severe PPP, and skin samples from the thigh (n=10) or palms (n=6) of healthy donors were compared. In lesional skin samples, 7,614 genes in GPP and 1,651 in PPP were found to be differentially expressed compared with healthy donors. In PPP and GPP, 1,207 transcripts were commonly up- or downregulated (adjusted p <0.01, absolute fold-change ≥2). Markedly upregulated genes in lesions vs non-lesional skin include IL16A, KRT6A, detoxins, IL6, CXCL1, CXCL8, IL17A, IL17A, and IL10; common molecular pathways included increased TH1 and TH17 signaling, keratinocyte-driven inflammation, and a strong upregulation of neutrophil attractants, inflammatory mediators, and the IL-36 pathway. Treatment of 7 PPP patients with a single 10 mg/kg IV dose of solpalamib (III 653130; NCT02978769) led to rapid clinical improvements and modulation of the transcriptomic profile and select proteins in the skin (NE and lipocalin 2) and blood (IL-6, CRP, CXCL1, IL1RN, CCL2) common to GPP and PPP.

050 Malignant melanoma cell growth is prevented in the systemic inflammatory environment

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A wide range of dermatis such as psoriasis is considered as a systemic inflammatory disease. Here, we examined the effects of inflammation on malignant melanoma development in the skin-derived systemic inflammatory mouse model. Melanoma cells were injected subcutaneously into the dorsal non-eczema skin region and the progress of the tumor growth was measured. Tumors grew more slowly with significance compared to wild-type mice. Serum from inflammation mice did not show a direct effect on melanoma cells compared to wild type mice. Tumor infiltrating lymphocytes (TILs) was also analyzed by flow cytometry. TILs from inflammation mice tended to release more inflammatory cytokines such as TNF-α and IFN-γ compared to wild-type mice, suggesting that systemic inflammation may inhibit tumor growth.

051 Non-steroidal anti-inflammatory drugs as adjuvant in allergic sensitization

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Allergic disease, including asthma, food allergies and atopic dermatitis, are on the rise. Concurrently, the use of non-steroidal anti-inflammatory drugs (NSAIDs) is also growing resulting in 30 billion American doses yearly. NSAIDs, which inhibit cyclooxygenase enzymes (COX) have been associated with worse allergic diseases and is thought to exacerbate allergic inflammation by shunting arachidonic acid metabolism towards leukotriene synthesis. We hypothesize that NSAIDs possess adjuvant properties and are sufficient to induce allergic sensitization, and thus may partially explain the exponential increase in the prevalence of allergic diseases. To test this hypothesis, mice were sensitized mice to the model antigen ovalbumin (OVA) with commonly utilized NSAIDs. We found that certain NSAIDs, irrespective of COX specificity, but not other commonly used analogics such as acetaminophen, were sufficient to induce the immune, inflammatory memory recall response, regardless of strain, produced high levels of OVA-specific IgE and IgG1 during sensitization, and anaphylactically to OVA, but not NSAID, challenge. This suggests that the widespread use of NSAIDs may be a major contributor to the development of allergic disease and has broad implications for their use as supportive therapy in a variety of conditions, including in children with asthma.