030 VGLL3, an orchestrator of female-biased autoimmune, interfaces with the Hippo pathway to modulate genes involved in immunity and fibrosis
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Autoimmune disease is the leading cause of morbidity among women. For largely unknown reasons, many autoimmune diseases show a striking female bias. Fibrosis is a common feature of female-biased autoimmune diseases. This is exemplified by systemic sclerosis (SSc), a debilitating disease marked by progressive skin hardening and organ damage that affects women at ninefold the rate of men. We previously identified the transcriptional cofactor VGLL3 as an immune regulator enriched in female skin whose targets overlap significantly with genes dysregulated in SSc. We further showed that excess epidermal VGLL3 causes a T-cell-mediated, with multiple melanocyte-derived autoantibodies also detectable in part of the patients, although its pathogenicity remains undetermined. AIBDs concomitant with vitiligo have rarely been reported. We report 3 cases in our institution, highlighting to date the second case of EBA with vitiligo and the first case of vitiligo underlying PV. While in the literature the onset of AIBDs was mostly preceded by vitiligo. It is not clear whether the combination of AIBD and vitiligo may have some immunological or pathophysiological pathways perhaps develop just as a mere chance occurrence. Some interesting correlation has been noticed in the onset, severity, and location of the two entities, which might indicate the interaction in their pathogenesis. We hypothesis that a probable undiscovered antigen-antibody crossover reaction or activation of auto-reactor after some component exposure caused by the cell destruction in the underlying diseases may explain the situation of the comorbidity. Genetic susceptibility may contribute to the occurrence of multiple autoimmune diseases in an individual while infection, trauma, and anxiety can act as a trigger. In a word, the clinicians should be aware of the possible coexistence of vitiligo and AIBDs, the inner immunopathological interaction leaves more to explore.

034 Autoimmune blistering diseases accompanied with vitiligo
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Autoimmune blistering diseases (AIBDs), mainly bullous pemphigoid, epidermolysis bullosa acquisita (EBA), pemphigus vulgaris (PV) and bullous pemphigoid (BP), are a large class of autoimmune diseases presenting the blistering eruptions on the skin and mucous membrane. Circulating autoantibodies play a critical role in the pathogenesis, antibody-specific B cells and CD4+ T cells involved as well. While vitiligo, a common pigmentation disorder, is mostly considered as CD8+T cell-mediated, with multiple melanocyte-derived autoantibodies also detectable in part of the patients, although its pathogenicity remains undetermined. AIBDs concomitant with vitiligo have rarely been reported. We report 3 cases in our institution, highlighting to date the second case of EBA with vitiligo and the first case of vitiligo underlying PV. While in the literature the onset of AIBDs was mostly preceded by vitiligo. It is not clear whether the combination of AIBD and vitiligo may have some immunological or pathophysiological pathways perhaps develop just as a mere chance occurrence. Some interesting correlation has been noticed in the onset, severity, and location of the two entities, which might indicate the interaction in their pathogenesis. We hypothesis that a probable undiscovered antigen-antibody crossover reaction or activation of auto-reactor after some component exposure caused by the cell destruction in the underlying diseases may explain the situation of the comorbidity. Genetic susceptibility may contribute to the occurrence of multiple autoimmune diseases in an individual while infection, trauma, and anxiety can act as a trigger. In a word, the clinicians should be aware of the possible coexistence of vitiligo and AIBDs, the inner immunopathological interaction leaves more to explore.

035 Biogeographical differences in gene segment usage
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Biogeography is known to shape the human skin metagenome, which in turn, helps to shape the adaptive immune system. Clearly, immune-mediated diseases (e.g. hidradenitis, lichen planus, atopic dermatitis, psoriasis, palmoplantar psoriasis/pustulosis) have predilections for specific anatomical sites (axillae, groin, and inguinal folds; dorsal hands, volar wrists, anterior lower legs and oral mucosa; antecubital fossa and popliteal fossa; elbows and knees; and palms and soles, respectively). A better understanding of how immune composition and function differs by anatomic location remains a major gap in our understanding of skin composition and function; to date, no consistent antigen-antibody crossover reaction or activation of auto-reactor after some component exposure caused by the cell destruction in the underlying diseases may explain the situation of the comorbidity. Genetic susceptibility may contribute to the occurrence of multiple autoimmune diseases in an individual while infection, trauma, and anxiety can act as a trigger. In a word, the clinicians should be aware of the possible coexistence of vitiligo and AIBDs, the inner immunopathological interaction leaves more to explore.

036 Enhancing Th2 cell differentiation by TRIM12 deficiency is negatively associated with PKCα
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Atopic dermatitis (AD) is a chronic skin inflammatory disease characterized by skin barrier defects and the sustained activation of Th2-related inflammation. Despite the importance of Th2 cell activation in AD pathogenesis, the mechanism of Th2 activation in AD remains largely unidentified. Here, we show that the motif-containing protein (MCP) 12 (TRIM12) is an E3 ubiquitin ligase with innate antiviral activity. In our previous studies, we showed that Trim12 null mice developed Th2-biased skin inflammation in response to iniquimod and associated low level of TRIM12 with high IL-4/IL-13 production. We further show that the TRIM12 deficiency leads to enhanced Th2 cell differentiation in vitro. Analysis of TRIM12-associated proteins from public databases identified PKCα as a TRIM12-associated protein that contributes to the regulation of Th2 signaling. We demonstrated that PKCα was specifically ubiquitinated by TRIM12, and further, that the half-life of PKCα was decreased in the Th cells from Trim12-mutant animals. Furthermore, Pkcbz null mice showed compromised AD-like phenotypes in the MC903 AD model. Consistently, the high PKCζ and low TRIM12 ratio were associated with CD4+ cells in AD human skin and in Th2 cells differentiated in vitro from AD patients compared to healthy controls. Taken together, these findings suggest that TRIM12 functions as a regulator of PKC that controls the differentiation of Th2 cells important for AD pathogenesis. Because TRIM12 is an E3 ubiquitin ligase with innate antiviral activity, Th2 regulation by TRIM12 provides a potential connection between defective innate immunity and Th2 activation in AD pathogenesis.

037 mI-146a regulates the interleukin-17 inflammatory response to Cutibacterium acnes in human peripheral blood mononuclear cells
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Inflammation from the immune response targeting Cutibacterium acnes plays a significant role in the pathogenesis of acne vulgaris. Previous studies have shown that C. acnes is a potent inducer of T helper 17 (Th17) cells, a unique class of CD4+ T cells characterized by production of the highly inflammatory cytokine interleukin-17 (IL-17). Emerging evidence has indicated that microRNAs (miRNAs) play an important role in modulating the body’s inflammatory response, including regulation of IL-17 differentiation and IL-17 production. However, the role of miRNAs in acne pathogenesis has not been extensively looked at in prior studies. Here we investigated the role of mi-146a in the response of human peripheral blood mononuclear cells (PBMCs) to C. acnes. miR-146a has been shown to negatively regulate differentiation of Th17 cells in various autoimmune diseases, dampening production of IL-17. Increased expression of miR-146a was detected in C. acnes-stimulated PBMCs, with a significant increase in mononuclear cells (PBMCs) compared to C. acnes-stimulated monocytes. In the presence of miR-146a overexpression, production of IL-17 by C. acnes-stimulated PBMCs was reduced nearly 2-fold, as well as a 2-fold reduction in gene expression of Th17 promoting cytokines. A corresponding increase in IL-17 production was seen in the presence of a miR-146a inhibitor. Furthermore, we found that miR-146a expression was decreased 6-fold in human-derived monocytes (THP-1) with toll-like receptor 2 (TLR2) knocked out, suggesting the role of TLR2 in miR-146a induction. Finally, cells isolated from acne lesions showed decreased expression of IL-17 and pro-inflammatory precursors that lead to the production of miR-146a. The role of miRNAs in Th17 development in acne lesions has not been previously studied and further provides insight into the regulation of the body’s inflammatory response. miRNAs represent a new angle in acne pathogenesis and highlight the potential for future miRNA-based therapies.