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VGLL3, an orchestrator of female-biased autoimmunity, 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 a key factor in the Hippo signaling pathway to modulate both immune genes and established Hippo pathway targets. These targets include the pro-fibrotic factor CTGF and members of the TGF-β pathway, both of which are involved in SSc pathogenesis. Our current studies, performed in Vgl13 null mice with epidermal VGLL3 overexpression show gross and microscopic features of skin fibrosis. These findings elucidate the molecular mechanisms by which VGLL3 promotes autoimmunity and lead to the hallmark fibrosis of many autoimmune diseases such as SSc. Furthermore, this reveals a potential connection between a common autoimmune disease and the Hippo signaling pathway, which has recently been linked to organ fibrosis.

034  
Autoimmune blistering diseases accompanied with vitiligo

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Autoimmune blistering diseases (ABDs), mainly include 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 mucosa membrane. Circulating autoantibodies play a critical role in the pathogenesis, antibody-specific B cells and CD4+ T cells involved in various ABDs. For example, PV is associated with IgG autoantibodies reacting with BP180 and BP230, which are type I transmembrane proteins. The absence of BP180 is the cause of epidermolysis bullosa simplex (EBS), an inherited condition characterized by epidermal blistering, whereas the loss of BP230 causes EBA. We test this hypothesis and function in a first step on T cell repertoire profiling in blood and lesional skin of ABDs patients.

Biogeography is known to shape the human skin metagenome, which in turn, helps to shape the adaptive immune systems. The current study aimed to investigate specific gut bacteria and their regulation in the occurrence of AIBDs and vitiligo. Our results showed a significant increase of E. coli and Citrobacter in the patients of ABDs and vitiligo. Moreover, the transcriptional regulator of TRIM32 in the ABDs patients is also regulated by another gene, TRIM22. These results suggest that the pathogenesis of autoimmune blistering diseases could be modulated by gut bacteria, and they also provide a new direction for the treatment of autoimmune blistering diseases.

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 systems. Unfortunately, the role of gut microbiome (GBM) in autoimmune blistering diseases (AIBDs) and vitiligo (VIT) has been largely unexamined. Here we tested whether the GBM population and function differ by anatomic location and correlation between GBM and skin AIBDs or VIT. Our findings demonstrated significant differences in GBM population across different skin sites and between ABDs and VIT patients. This study provides new insights into the role of gut microbiome in the pathogenesis of autoimmune blistering diseases and vitiligo, which may help to develop new therapeutic strategies.