had periportal lymphocytic and eosinophilic infiltration on liver biopsies when undertaken during transaminitis and developed portal hypertension, splenomegaly and biliary obstruction while preserving synthetic liver function over time, suggesting that their clinical course may be consistent with nodular regenerative hyperplasia (NRH). Patients also developed a wide range of immune-dysregulatory features including IgA deficiency, common variable immunodeficiency, autoimmune hives, angioedema, eczematous dermatitis, autoimmune hypothyroidism, Graves' disease, atrophic gastritis, juvenile dermatomyositis, rheumatoid arthritis, polyarthritis, immune thrombocytopenia, cutaneous morphea, lentigo, peripheral T cell lymphoma, graft versus host disease, hemophagocytic syndrome, interstitial lung disease, autoimmune hemolytic anemia, autoimmune colitis, Crohn disease, and periodic fevers. Low complement 4 levels were detected in 5 patients, and 3 had low complement 3 levels. Genetic workup revealed *CTLA-4* haploinsufficiency in one case and variants of uncertain significance in *P4HA3, TTN, TNFRSF13B, and NLRP3* genes in several others. One distinctive patient was heterozygous for a pathogenic *LRBA* variant. The exact etiology of AGL is unknown and heterogeneity creates a diagnostic challenge. While panniculitis is a distinct initial presentation in some cases, immune dysregulation affecting multiple organs with accompanying NRH may constitute a new subgroup of AGL. Immune check-point perturbation via gremlin mutation may also lead to AGL. Collective review of cases with predetermined clinical and laboratory evaluation criteria may be helpful to describe subgroups of AGL.

Adipose Tissue, Appetite, and Obesity

NOVEL INSIGHTS INTO THE REGULATION OF ADIPOSE TISSUE REMODELING

Activin A Plays a Critical Role in Adipose Tissue Wasting in the Progression of Cancer Cachexia

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Background: Nearly 50% of cancer patients suffer from cancer cachexia, a wasting syndrome with atrophy of white adipose tissue (WAT) and skeletal muscle. Cachexia leads to negative energy balance, limits cancer therapies, and reduces survival rate. It is characterized by body weight loss due to negative nutrients and energy balance from involuntary reduced food intake and abnormal metabolic conditions such as insulin resistance and hypertriglyceridemia. Cancer-driven factors such as activin A and IL-6 (interlukein-6) contribute to the occurrence of cachexia symptoms during cancer progression. While the importance of muscle atrophy has been emphasized in cachexia research, the underlying mechanism of adipose tissue wasting remains unclear. One proposed theory is that WAT switches to brown adipose tissue (BAT), characterized by the high expression level of UCP1 (uncoupling protein 1). **Hypothesis**: We hypothesize that activin A plays a critical role in adipose tissue wasting during cancer cachexia progression. **Experiment**: *GDF9-iCre+; PIK3CA** female mice which shows cachexia symptoms in cancer progression were sacrificed before and after cachexia development. In addition, we injected FST288, an antagonist to activin A, for two weeks during cancer cachexia development. We harvested and analyzed multi-sites adipose tissues (gonadal, subcutaneous, interscapular and perirenal), muscle and liver. Serum activin A and IL-6 were measured using ELISA kits. DEXA and calorimetry analyses were performed, as well as immunohistochemistry, qPCR and western blotting assay. **Results:** *GDF9-iCre+; PIK3CA** female mice started to display bilateral ovarian tumors around postnatal day (PD) 60, lose body weight around PD70 and became cachexia condition around PD80 with an increased level of serum activin A. Along with that, other body organs including liver, pancreas, muscle, and adipose tissues became dramatically small in mass. Our data proved that cachexia progression is correlated with the level of activin A rather than IL-6 in serum of *GDF9-iCre+; PIK3CA** female mice. As serum activin A increased, adipocytes lost lipids and had distinct browning phenotypes in some adipocytes within WAT. Interestingly, calorimetry analysis did not display an increase in energy expenditure in cachectic mice although browning was evident in WAT. However, treatment with FST288 during cancer progression kept body weight and WAT in *GDF9-iCre+; PIK3CA** female mice. Most of all, FST288 protected the size and lipid droplets of adipose tissues against WAT wasting during cachexia development. **Conclusion**: The progression of cancer cachexia impacts adipose tissues. Injection of FST288 supports the key role of activin A in the progress of cachexia. FST288 prevented adipose tissue wasting and cachexia development, revealing another evidence of the efficacy of activin A antagonist in preventing cancer cachexia development.

Adipose Tissue, Appetite, and Obesity

NOVEL INSIGHTS INTO THE REGULATION OF ADIPOSE TISSUE REMODELING

Adipocyte-Derived Lactate Potentiates Obesity-Evoked Adipose Macrophage Inflammation

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Introduction: Obesity is characterized by mobilization of macrophage inflammation, which represents the major events of obesity-associated adipose tissue inflammation. . On the other hand, lactate accumulation in adipose tissue long been observed. However, whether elevation of lactate plays an essential role in adipose inflammation is not known. In this study, we sought to examine the intermediary role of lactate in macrophage polarization and adipose inflammation upon obesity. **Method**: Lactate level and activity of lactate dehydrogense (LDH), the key enzyme of lactate production, were measured by biochemical assays. Adipocyte- and macrophage- specific *Ldha* knock out mice were constructed by cre-LoxP system to study the physiological role of lactate in diet induced obesity. Macrophage polarization and inflammation were examined by western blotting and Q-PCR. **Results:** Lactate and LDH activity were selectively upregulated in adipose tissues of obese mice. Adipocyte-, but not macrophage-selective deletion of LDHA, led to a significant improvement of