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, autoimmunone 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

Adipine 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 dehydrogenase (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
Adipose inflammation and metabolic dysfunctions. In vitro experiments showed that the lactate promoted M1 polarization through direct interation and inhibition of the PHD2, which subsequently stabilizes HIF-1alpha. In addition, a positive correlation between adipose lactate level and adipose tissue inflammation was found in obese patients. Conclusion: In obese condition, increased production of lactate from adipocytes enhances adipose tissue inflammation by promoting the proinflammatory polarization of adipose macrophages.

Adipose Tissue, Appetite, and Obesity

NOVEL INSIGHTS INTO THE REGULATION OF ADIPOSE TISSUE REMODELING

Breast Cancer Endocrine Therapy Exhausts Adipocyte Progenitors Promoting Weight Gain and Glucose Intolerance

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Breast cancer survivors treated with anti-estrogen therapies report weight gain and have an elevated risk of type 2 diabetes. Here, we show that current tamoxifen use did not influence body mass index but associated with larger breast adipocyte diameter only in women with obesity, suggesting adipose tissue may be targeted by breast cancer therapies. To understand the mechanisms behind these clinical findings, we investigated the impact of estrogen deprivation and tamoxifen in a relevant pre-clinical murine model of obesity. Specifically, mature female mice were housed at thermoneutrality and fed either a low-fat/low-sucrose (LFLS) or a high-fat/high-sucrose (HFHS) diet. Consistent with the high expression of Esr1 observed in single-cell RNA sequencing of mesenchymal stem cells from mouse adipose tissue, endocrine therapies associated with adipose accumulation and preadipocyte expansion, but resulted in adipocyte progenitor depletion only in the context of HFHS. Consequently, 7-week endocrine therapy supported adipocyte hypertrophy and was associated with hepatic steatosis, hyperinsulinemia, insulin resistance, and glucose intolerance, particularly in HFHS fed females. We administered HFHS fed females either metformin or pioglitazone, glucose lowering drugs used to treat diabetes, or treadmill interval exercise during endocrine therapy with the goal of improving whole body metabolism. All interventions prevented the effects of tamoxifen but not estrogen deprivation on adipocyte size and insulin resistance in HFHS-fed mice. This translational study suggests that endocrine therapies may act via ER-alpha to directly disrupt adipocyte progenitors and support adipocyte hypertrophy, leading to ectopic lipid deposition that may promote hyperinsulinemia, insulin resistance and type 2 diabetes. Interventions that target insulin action should be considered for some women receiving life-saving endocrine therapies for breast cancer.

Adipose Tissue, Appetite, and Obesity

NOVEL INSIGHTS INTO THE REGULATION OF ADIPOSE TISSUE REMODELING

Endothelin-1 Receptor A Blockade Attenuates Metabolic and Proinflammatory Profile in Mice Fed a High Fat Diet

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Endothelin-1 (ET-1) is elevated in patients with obesity; however, its contribution to the pathophysiology related to obesity is not fully understood. Obesity is associated with dyslipidemia and insulin resistance, which may in part be mediated by inflammation and alterations to immune cell subsets within the adipose tissue. ET-1 promotes inflammation via the ET-1 type A (ET_A) receptor, and blockade of ET_A receptors improves dyslipidemia in patients with chronic kidney disease. We hypothesized that ET-1 causes dyslipidemia and inflammation within the adipose tissue of obese mice. To test this hypothesis, C57BL/6J mice were fed either normal diet (NMD) or high fat diet (HFD) for 8 weeks followed by 2 weeks of treatment with either vehicle or atrasentan (ET_A receptor antagonist, 10mg/kg/day). HFD mice had significantly higher fat mass than NMD mice, with no significant effect of treatment with atrasentan. HFD mice had significantly higher circulating non-esterified free fatty acids, an effect that was ameliorated in mice treated with atrasentan (1.0±0.07 vs 0.5±0.02 mEq/L, p<0.05). Atrasentan-treated mice had significantly attenuated increase in liver triglycerides compared to non-treated HFD mice (3.8±0.7 vs 7.5±1.3 mg/dL respectively, p<0.05). Mice treated with atrasentan had significantly improved glucose tolerance (10150±1031 vs 6563±975 AUC, p<0.05) and insulin tolerance (-27962±386 vs -9825±319 AUC, p<0.05) compared to non-treated insulin-resistant HFD mice. Plasma adiponectin, an insulin sensitizing adipokine that is inversely associated with adiposity and insulin resistance, was significantly increased in atrasentan-treated mice compared to non-treated HFD (4.8±0.1326 vs 6.5±0.3 µg/ml, p<0.05), with no differences in plasma insulin levels. Gene expression analysis of visceral fat showed improved expression of genes negatively associated with insulin resistance that were downregulated in non-treated HFD mice vs. NMD (IRS-1, PPAR-gamma, GLUT4, and adiponectin). Flow cytometric analyses of visceral adipose tissue indicated that HFD mice had a significantly higher number of both CD4+ and CD8+ T cells compared to NMD mice, which was attenuated by treatment with atrasentan. Further, eosinophils, which are important in maintaining adipose tissue health and reducing inflammation, were significantly decreased in HFD mice compared to NMD. Atrasentan treatment abolished the decrease in eosinophils. Taken together, these data indicate that ET_A receptor blockade improves peripheral glucose homeostasis, dyslipidemia, and liver triglyceride levels, and also attenuates the proinflammatory immune profile in visceral adipose tissue. These data suggest a potential use for ET_A receptor blockers in the treatment of obesity-associated dyslipidemia and insulin resistance.