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.

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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 atrasentran (1.03±0.07 vs 0.58±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±1.3mg/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 (-2796±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.