and colorectal cancers. HLA-DQA1 mutation is involved cervical cancer, and it is involved in increased immune sensitivity and liver damage in breast cancer patients. The RAB7Ab and RAB7-interacting lysosomal protein (RILP) are regulators of endo-lysosomal trafficking and suppresses breast cancer cell invasion. To conclude, this study identifies several genes and their regulatory pathways in VAT which may contribute to the increased risk of cancer pathogenesis in obese individuals.

Adipose Tissue, Appetite, and Obesity
NOVEL MECHANISMS CONTROLLING ADIPOSE TISSUE PHYSIOLOGY AND ENERGY BALANCE

Interrupted IGF-1 Feedback in GHRH Neurons and Somatotrophs Results in Impaired Weight Gain and Increased Energy Expenditure

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Growth hormone (GH) expression and release are thought to be primarily regulated by the counter-regulatory effects of growth hormone-releasing hormone (GHRH) and somatostatin (SST). Several reports generated in our lab and others suggest that there are other factors that regulate GH production, such as insulin-like growth factor 1 (IGF-I). Using GH-Cre recombinase targeting of the somatotroph-specific IGF-1R knockout (SIGFRKO) mouse model, we have previously demonstrated the role of IGF-1 signaling in negative feedback regulation of GH production. This model, however, presented with an incomplete phenotype, suggesting additional regulatory pathways in the hypothalamus. To provide insight into this mechanism, we have developed new transgenic mouse models that maintain the integrity of the hypothalamic-pituitary GH axis, with the single exception of IGF-IR deficiency in both hypothalamic GHRH neurons and somatotroph cells, termed GHRH-somatotroph IGF-1R knockout (G-SIFGRKO). Axiological assessments showed normal linear growth until week 14 of age, both male and female G-SIFGRKO mice presented with a significant reduction in growth velocity compared to control animals. Indirect calorimetry assessment performed at 12–14 weeks of age demonstrated that G-SIFGRKO mice had higher volume O2 consumption and lower volume CO2 production associated with increased energy expenditure than controls. The calculated respiratory exchange ratio was significantly reduced in G-SIFGRKO mice with no changes observed in either ambulatory or total activity. Furthermore, glucose and insulin tolerance tests showed no differences in glucose metabolism between G-SIFGRKO and controls. Collectively, these data provide further confirmation of the combinatorial role of IGF-1 signaling in regulating GH production and, for the first time, highlight a new GHRH-IGF-1R mediated pathway to regulate body growth and energy balance. Targeting this pathway has the potential to lead to a better understanding of the intersection between growth and metabolism and therapeutic approaches for obesity.

Adipose Tissue, Appetite, and Obesity
NOVEL MECHANISMS CONTROLLING ADIPOSE TISSUE PHYSIOLOGY AND ENERGY BALANCE

Laminin-α4 Is Uniquely Upregulated in Subcutaneous White Adipose Tissue in Murine and Human Models of Obesity

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As research into the adipocyte microenvironment has advanced, it is becoming more widely accepted that the extracellular matrix (ECM) contributes to adipocyte dysfunction. The majority of current published work focuses on the role of collagens in metabolic disease while less emphasis has been placed on the contribution of laminins, an important component of the adipocyte basement membrane. Laminins are trimeric ECM proteins composed of α, β, and γ chains. The α chains contain sites which can interact with cell surface receptors and is considered the driver of tissue-specific expression and specialized signaling. Our group has shown that the laminin-α4 (LAMA4) chain, which is highly expressed in mature adipocytes, plays a role in adipocyte function and thermogenesis in mice (1). In this study we investigate the relationship between laminin α chain expression and obesity by assessing gene expression of LAMA1-5 in subcutaneous white adipose tissue (sWAT) from mice fed chow (RCD) and 45% high fat diet (HFD) for 8 weeks. Expression of LAMA2 and LAMA4 was significantly increased in the HFD sWAT compared to chow (6.1 fold, p=0.01 and 4.9 fold, p=0.001 respectively), however LAMA4 displayed a much stronger positive correlation with weight (R^2=0.697) than did LAMA2 (R^2=0.382). In order to validate the relevance of these findings in human models of obesity, we evaluated gene expression of LAMA2, LAMA4, and LAMA5 in sWAT biopsies from non-diabetic adult females with obesity (class II or higher). sWAT samples from obese subjects exhibited 4.5 fold higher LAMA4 expression (p=0.0089) than samples from non-obese control subjects, suggesting that the LAMA4 chain may play an important role in human obesity. Lastly we examined changes in sWAT LAMA4 expression following a period of weight loss in obese mice and in human subjects after bariatric surgery, and found that LAMA4 expression levels remain largely unchanged in both cases. In this study we demonstrate the relationship between LAMA4 expression and obesity and present findings that can be extended to human models of obesity.

Reference: (1) Vaicik et al., Endocrinology. 2018 Jan;159(1):356–67.

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NOVEL MECHANISMS CONTROLLING ADIPOSE TISSUE PHYSIOLOGY AND ENERGY BALANCE

Mice Deficient for an Intestinal G Protein-Coupled Receptor Expression Have Increased Satiety During