was assessed using the degree method to define hub genes. Functional and pathway enrichment analyses were performed based on Gene Ontology (GO) terms and KEGG Pathways. **Results:** The search on the DisGeNET database retrieved 191 childhood obesity-related genes. The PPI network of these genes showed 19 hub genes (*STAT3*, *SIRT1*, *BCL2*, *IRS1*, *PPARG*, *SOCS3*, *TGFB1*, *HDAC4*, *DNMT1*, *ADCY3*, *PPARA*, *NEDD4L*, *ACACB*, *NR0B2*, *VEGFA*, *APOA1*, *GHR*, *CALR*, and *MKKS*). These hub genes were involved in biological processes of lipid storage / kinase activity, regulation of fatty-acid metabolic processes, regulation of pri-miRNA transcription by RNA polymerase II, and negative regulation of small molecules and carbohydrate metabolic processes. In terms of molecular functions, repressing of transcription factors biding was found enriched. Regarding KEGG Pathways, the hub genes are involved with adipocytokine signaling, insulin resistance, longevity regulation, and cytokine signaling pathways. **Conclusion:** Our approach identified 19 hub genes, which are highly connected and probably have a key role in childhood obesity. Moreover, functional enrichment analyses demonstrated they are enriched in several biological processes and pathways related to the underlying molecular mechanisms of obesity. These findings provide a more comprehensive information regarding genetic and molecular factors behind childhood obesity pathogenesis. Further experimental investigation of our findings may shed light on the pathophysiology of this disease and contribute to the identification of new therapeutic targets.

Adipose Tissue, Appetite, and Obesity

NOVEL MECHANISMS CONTROLLING ADIPOSE TISSUE PHYSIOLOGY AND ENERGY BALANCE

Identifying a New Mechanism of Sarcopenia by Autophagy

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Sarcopenia is one of the critical factors in reducing Activity of Daily Life and associated with morbidity and mortality. Sarcopenia has also been linked to metabolic syndrome. In recent years, it has been reported that autophagy is one of the mechanisms as a cause of sarcopenia. Therefore, we focused on autophagy as a system that can regulate both sarcopenia and metabolic syndrome in skeletal muscle and revealed that non-receptor tyrosine kinase Fyn not only participates in metabolic syndrome but also regulates autophagy regulating sarcopenia through STAT3 regulation, mainly using transgenic mice (Cell metabolism 2010, Cell Rep. 2012). However, since these were non-physiological studies, we proceeded with further studies and demonstrating that Fyn dependent STAT3 phosphorylation by IL6, which is involved in chronic inflammation and metabolic syndrome, was observed in mouse C2C12 myotube cells. Autophagy was decreased in those cells by both IL6 dependent and Fyn dependent mechanisms. Furthermore, in the denervated mouse model, not only both Fyn and IL6 gene expressions as well as the key muscle specific E3 ubiquitin ligases, Atrogin1 and MuRf1 were increased but the expression and phosphorylation levels of STAT3 were also augmented, while the autophagy activity was decreased. We believe that a denervated mouse model alone is not enough as a model for sarcopenia, thus we next introduced a hind limb suspension mouse model that promotes disuse atrophy by suspending the hind limb. Using this model, we found that muscle atrophy was observed mainly in the soleus muscle, tibialis anterior muscle, and the gastrocnemius muscle with Atrogin1 and MuRf1 increased. Increase of both IL6 and STAT3 expression/phosphorylation were also observed in the muscles of hind limb suspension mice. Autophagy activity, examined by intraperitoneal administration of colchicine, was decreased. These results strongly suggest that Fyn is involved not only in the metabolic syndrome but also in the pathogenesis of sarcopenia, and may lead to a better understanding of the pathology of sarcopenia obesity and the development of therapeutic methods.

Adipose Tissue, Appetite, and Obesity

NOVEL MECHANISMS CONTROLLING ADIPOSE TISSUE PHYSIOLOGY AND ENERGY BALANCE

Inhibition of Angiopoietin-Like 3 (ANGPTL3) Reduces Adipose Tissue Insulin Resistance in Patients With Familial Partial Lipodystrophy

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Familial partial lipodystrophy (FPLD) is a rare disease characterized by selective loss of peripheral subcutaneous fat, usually affecting the trunk and limbs, but preservation in other areas, such as the face and neck. It is usually associated with dyslipidemia and diabetes mellitus, and currently, there are no approved specific therapies for this disease in the US. Reductions in circulating levels of ANGPTL3 either by homologous loss-of-function mutations in humans or by pharmacological inhibition in rodents are associated with reductions in triglyceride (and other atherogenic lipid) levels and protect from atherosclerosis, making it an attractive target for patients with FPLD and metabolic dyslipidemia. We performed a proof-of-concept study to assess the early efficacy and safety of targeting ANGPTL3 via antisense oligonucleotide ISIS-703802 (vupanorsen) in a small number of patients with FPLD. Four patients with FPLD (3F/1M; age range: 39–48; 1 with *LMNA* R482Q, 1 with *LMNA* R584H, and 2 with no causative genetic variant), diabetes (HbA1c>6.5%) and hypertriglyceridemia (>250 mg/dL at screening) were included. Patients received the study drug at a subcutaneous dose of 20 mg weekly for 26 weeks. The primary endpoint was the change in triglycerides at week 27. Other end-points of interest measured at the same time points included insulin secretion, sensitivity, lipid and hormonal changes in response to a 5 hour long mixed meal test and body composition measured by dual energy absorptiometry (DEXA). Treatment resulted in a 59.9±26.3 (mean±SD)

% of reduction in triglycerides, 54.7±9.8% of reduction in serum ANGPTL3 levels and 50.8±27.4% of reduction in ApoCIII. Treatment with vupanorsen led to a reduction of 209.3±120.4 in adipose tissue insulin resistance (ADIPO-IR) from a baseline of 470.3±114.3 and the area under the curve (AUC) for circulating free fatty acid levels were decreased by 32.1±21.4 mmol/L/min from a baseline of 215.8±55.2 mmol/L/min. Glucose AUC and triglyceride AUC also decreased after treatment (-14.0±5.2 and -60.1±26.5 mg/dL/min, respectively). Analyzing body fat distribution using DEXA, we observed that the fat mass index (FMI) and trunk mass index (TMI) did not change from baseline, but the ratio of total fat mass/ fat mass from limbs decreased by 10.7±12.2. These data show a tendency for redistribution of central body fat to limbs. There were numerous adverse events observed that were related to common serious complications associated with diabetes and FPLD. Although limited, these results suggest that targeting ANGPTL3 with vupanorsen in patients with FPLD may have a therapeutic role by addressing multiple problems.

Adipose Tissue, Appetite, and Obesity

NOVEL MECHANISMS CONTROLLING ADIPOSE TISSUE PHYSIOLOGY AND ENERGY BALANCE

Inhibition of CXCR2 by Glucocorticoids in Adipose Tissue

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Obesity-induced chronic adipose tissue inflammation is a significant risk factor for metabolic and cardiovascular disease (CVD), which affects 30.3 million adults in the United States. Interaction of adipocytes with hormonal, metabolic and immune systems play an integral role in the underlying pathophysiological mechanisms that leads to development of obesity-related complications. Despite this association, the mechanisms that coordinate the inflammatory mediators in causing adipose tissue inflammation are not well understood. Glucocorticoids (GC) are well known for their potent anti-inflammatory actions; however, the mechanism by which GC coordinate the inflammatory response of adipocytes are unknown. From our genome-wide microarray data derived from adipocyte-specific glucocorticoid receptor (GR) knockout (AdipoGRKO) mice, we found that GR inactivation leads to a significant increase in pro-inflammatory gene in white adipose tissue (WAT). Additionally, WAT isolated from AdipoGRKO mice showed significant increase in immune cell infiltration, which correlates with our gene expression data. Among the top up-regulated genes, we found the C-X-C Motif Chemokine Receptor 2 (Cxcr2), which is a powerful mediator of chemotaxis to the sites of inflammation. Although studies have shown the presence of Cxcr2 in adipocytes and suggested the contribution of Cxcr2 signaling in adipocyte development, its role in integrating adipose tissue inflammatory response is unknown. This led us to hypothesize that GR is critical to repress Cxcr2 gene expression and its pro inflammatory effects in adipocytes. Our in vitro studies using 3T3-L1 cells derived adipocytes showed that treatment with the synthetic glucocorticoid, Dexamethasone (Dex) led to a significant repression of Cxcr2 mRNA and protein levels. Furthermore, these effects are mediated by GR acting directly to repress Cxcr2 gene expression. Systemic administration of corticosterone significantly altered Cxcr2 expression in adipose tissue compared to untreated mice further supporting our results. Together our findings suggest that administration of glucocorticoids could inhibit adipose tissue inflammation and alleviate the comorbidities that arise from inflamed adipose tissue.

Adipose Tissue, Appetite, and Obesity

NOVEL MECHANISMS CONTROLLING ADIPOSE TISSUE PHYSIOLOGY AND ENERGY BALANCE

Interactome Profile of Visceral Adipose Tissue in Obesity Links Key Genes to Cancer Pathogenesis

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Obesity increases the risk of the development of several malignancies. The visceral adipose tissue (VAT) depot is one of the pivotal contributors behind the obesity-related pathogenetic mechanisms. In this study, we analyzed the differential gene expression profile in the VAT of obese children using two Gene Expression Omnibus datasets. GSE29718 and GSE9624 were sorted and 68 common differentially expressed genes (DEG) with fold change 1.5 upregulation or downregulation (cutoff $|\log FC| \geq 0.58496$) were obtained. Gene ontology and functional enrichment and protein-protein interaction (PPI) network for the DEG were analyzed in Search Tool for the Retrieval of Interacting Genes (STRING), which revealed 37 biological processes, 3 cellular components, and 1 molecular function to be significantly associated. Reactome pathway analysis showed the DEG to be involved in- one carbon pool by folate, glycine degradation, transcriptional regulation by TP53, ERK inactivation, G1/S-specific transcription, Fanconi anemia pathway, beta-catenin phosphorylation cascade, RAF activation, and negative regulation of the MAPK pathway. The PPI network was set with a minimum interaction score of 0.400 and a maximum of 10 interactions, and it was significantly enriched (p-value 0.047) with 66 nodes and 46 edges. Target prediction was performed using miRNet. Several miRNA, including hsa-miR-1-3p, hsa-let-7b-5p, hsa-miR-16-5p, hsa-miR-27a-3p and hsa-miR-34a-5p were part of the mRNA-miRNA interaction network. Using the CytoHubba plugin in Cytoscape, the top 10 hub genes from the PPI network were discovered. Thymidine phosphorylase (TYMP) and dihydrofolate reductase (DHFR), essential components of nucleic acid metabolism, have been shown to be involved in angiogenesis and endothelial cell growth, and correlated to p53 mutations, respectively. Protein phosphatase 2, regulatory subunit A & regulatory subunit B (PPP2R1A and PPP2R1B) mutations are involved in ovarian, endometrial, lung