

Differential Regulation of PI3K Related Transcripts in Visceral Adipose Tissue from Obese Adolescent African-American Females

Matthew D. Barberio, Margaret Morrison, Samantha Sevilla, Evan P. Nadler, Monica J. Hubal FACSM.
Children's National Medical Center, Washington, DC, Duke University, Durham, NC

Accumulation of excess visceral adipose tissue (VAT) in obesity is associated with increased risk of cardiometabolic diseases. However, cardiometabolic diseases and other obesity-related comorbidities show ethnic disparities across populations. Insulin resistance (IR), a hallmark of type 2 diabetes mellitus, is more prevalent in African-Americans (AA; 13%) as compared to Caucasians (C; 7%). The underlying molecular mechanisms driving these differences are poorly understood. **PURPOSE:** We sought to identify transcriptional signatures in VAT unique to young obese AA females (as compared to age and gender-matched C) that could explain the increased rate of IR in AA. **METHODS:** VAT samples were collected during abdominal surgery from lean (n= 10, Age = 16 ± 2 , BMI = 21.8 ± 2.9) and obese (n=10, Age = 16 ± 2 , BMI = 47.3 ± 10.2) African American (Lean = 5, Obese = 5) and Caucasian (5;5) females. Total RNA was extracted from 150-250 mg tissue (Qiagen Qiazol kits) and global gene expression profiles were generated (Affymetrix Hu133 Plus 2.0 arrays). mRNA profiles were analyzed with ANCOVA (ethnicity*group with age covariate; Partek Genomics Suite) and *post-hoc* specific group comparisons within each ethnicity. The resultant mRNA lists were filtered at $P < 0.05$ and fold change $> |1.2|$, then uploaded into biological pathway analysis software (Ingenuity Pathway Analysis) for interpretation. **RESULTS:** ANCOVA detected 3239 differentially regulated transcripts in VAT from obese as compared to lean subjects at $p < 0.05$ and $FC > |1.2|$. 1211 genes differentially regulated with obesity were unique to the AA population. The top ranked IPA pathway unique to Obese VAT in African Americans was identified as phosphoinositide 3-kinase (PI3K) signaling, including uncoupling protein 3 (UCP3; 17.18-fold), protein kinase AKT2 (AKT2; -5.92-fold), and ras homolog family member Q (RHOQ; 2.98-fold). **CONCLUSION:** Global gene expression profiling and pathway analysis suggests that dysregulation in insulin signaling and fat metabolism pathways involving PI3K signaling in adipose may contribute to the increased incidence of insulin resistance in African-Americans. Future studies should explore these transcripts and their regulation in relationship to the pathology of peripheral insulin resistance, in addition to how they change with intervention.