A METABOLOMICS APPROACH TO ADIPOSE TISSUE AND BETA CELL CROSS-TALK

Maria Vinaixa[1,2], Rita Malpique[2,3], Sandra Rebufat[2,3], Miguel A. Rodríguez[1,2], Toni Beltran[1,2], Sara Samino[1,2], Oscar Yanes[1,2], Ramon Gomis[2,3], Xavier Correig[1,2]

1-Metabolomics Platform, IISPV-CIBERDEM-Universitat Rovira i Virgili; 2-CIBER de Diabetes y Enfermedades Metabólicas(CIBERDEM); 3-Diabetes and Obesity Laboratory,IDIBAPS,Hospital Clínic, Universitat de Barcelona

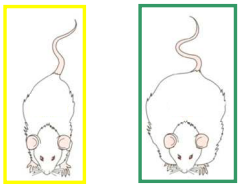
[@] maria.vinaixa@urv.cat

1. INTRODUCTION & GOALS

Beta cell mass dynamically changes in response to altered metabolic demands such obesity. The mechanism that regulates the plasticity of beta cell to adapt to such demands is not yet fully understood. Changes in the adipokine secretion profile of visceral-pancreatic adipose tissue due to diet-induced obesity have demonstrated to increase the rate of beta cell replication *(Balañá NP, Plasticitat de la cèl·lula beta en l'obesitat. Universitat de Barcelona,2010)*. To study whether such changes are also accompanied by changes in the metabolic secretion profile, a metabolomics study on the secretomes of different white adipose tissue (WAT) explants in a diet-induced obese model is attempted.

2. EXPERIMENTAL DESIGN

Control (STD) | Diet-induced obesity model (CAF) | SECRETOMES



N=6 | N=8

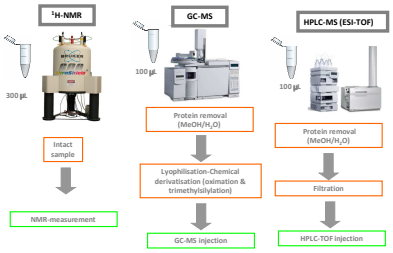
Epididymal (WAT)

Mesenteric (MES)

1. White Adipose Tissue collected from two different depots surrounding the pancreas: epididymal (WAT) and mesenteric (MES).
2. The secretomes (conditioned media) from the two collected white adipose tissue depots were obtained by culturing the isolated tissues in serum-free medium for 24 hours.

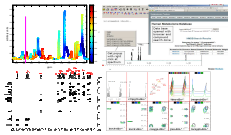
3. METHODS

Comparative secretomes analysis was assayed using a multiplatform untargeted metabolomics approach [^{1}H-NMR, GC/MS and HPLC/MS]



NMR DATA ANALYSIS

1. Identification of spectral regions (2D, S-TOCSY, HMDB)



2. Integration of spectral regions identified

NMR regions or buckets

SAMPLES

3. Univariate or Multivariate analysis

MS DATA ANALYSIS

1. XCMS automatic GC-MS and HPLC-TOF peak detection & alignment

mzRT features

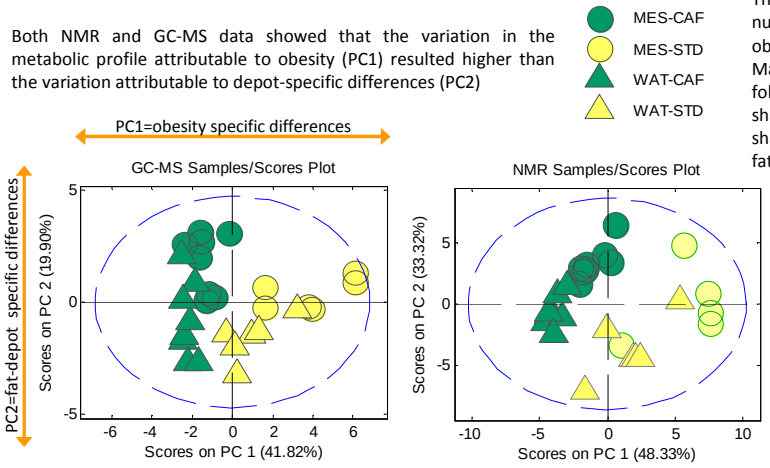
SAMPLES

2. Univariate statistical analysis and tentative identification of those mzRT relevant features using AMDIS/Fiehn or NIST libraries for GC-MS analysis.

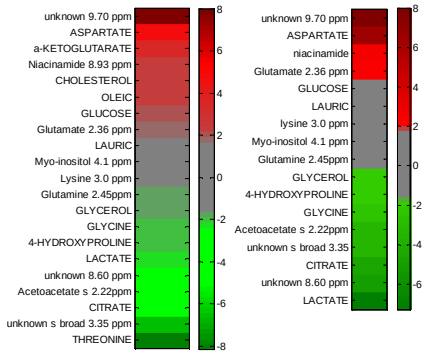
3. MS/MS (HPLC-QqQ) of the most relevant features and metabolite identification through MS/MS fragmentation spectra using METLIN database.

4. RESULTS

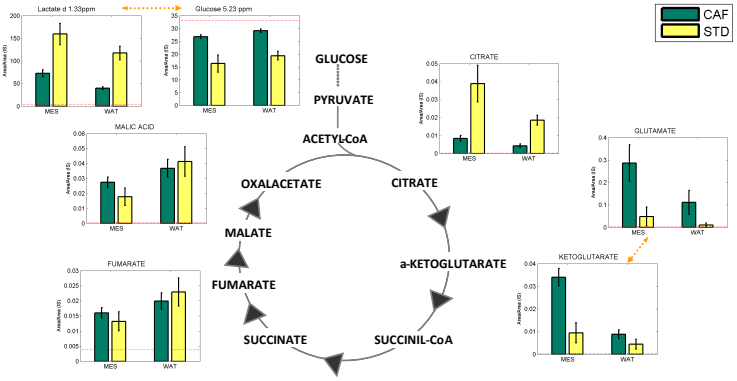
Both NMR and GC-MS data showed that the variation in the metabolic profile attributable to obesity (PC1) resulted higher than the variation attributable to depot-specific differences (PC2)



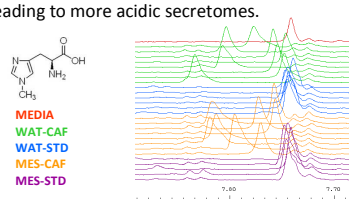
The mesenteric fat depot accounted for a higher number of significantly varied metabolites due to obesity as compared to epidymial fat depot ($p<0.05$, Mann-Witney U-test). These heatmaps represent the fold change of upregulated metabolites (red shadows) and downregulated metabolites (green shadows) for CAF animals as compared to STD in each fat depot



Obese animals showed lowered glucose uptake and enhanced TCA anaplerosis



A downfield shift of the 1-methylhystidine aromatic proton resonances was observed for obese animals exclusively. Since these protons are especially sensitive to changes in the acidity of the medium they provide a useful probe of aqueous pH. Hence, even buffered conditions, obesity induced a decrease of the pH leading to more acidic secretomes.



4. CONCLUSIONS

- Even obesity induced higher metabolic variation than fat-depot regional differences; mesenteric fat depot resulted in higher metabolic changes than obese epididymal fat depot due to obesity.
- Overall secretomes from obese animals showed a lowered glucose uptake, blunted uptake of nicotinamide enhanced TCA anaplerosis and more acidic secretomes.
- Further work is in progress to characterize the effect of these metabolic changes on beta cell mass and function in relevant in-vivo models.

ACKNOWLEDGEMENTS

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