Peripheral blood mononuclear cell transcriptome allows discrimination between metabolically obese normal weight individuals, individuals with healthy overweight-obesity, and normal weight controls, in a sex-dependent manner

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Introduction: Peripheral blood mononuclear cells (PBMC) are a readily accessible biological material that in recent years has been demonstrated to be very useful in nutrition and obesity research as they reflect diet-related pathologies by changes in their gene expression pattern.

Objectives: We aimed to analyse PBMC transcriptome in volunteers with metabolically obese normal weight (MONW) phenotype and in healthy normoglycemic volunteers with overweight-obesity (OW-OB) in comparison to normal weight (NW) controls to identify altered metabolic pathways, as well as predictive risk biomarkers of metabolic impairment related to increased adiposity.

Methods: Standard PBMC global microarray hybridisation and analysis was performed in samples from 12 NW, 12 OW-OB, and 6 MONW subjects including men and women (50%/50%). We focussed on differential expressed genes (DEGs) in MONW and OW-OB groups *vs* NW. Significant biological pathways were functionally clustered using the Core Function of Ingenuity System Pathway Analysis (IPA).

Results: We identified 1,335 and 1,531 annotated DEGs in OW-OB and MONW *vs* NW, respectively ($p<0.05$). When men and women were analysed separately in each of the groups, overlapping genes between sexes only accounted for 4% of the DEGs, besides, most of them were inversely regulated. Pathway analysis supported these differences found between sexes. In men, antigen presentation (in OW-OB) and interferon signalling (in MONW) appeared as top regulated pathways. However, in women, the top regulated pathways were phospholipase C signalling (in OW-OB) and inhibition of ARE-Mediated mRNA degradation pathway (in MONW).

Hierarchical clustering based on the top 100 DEGs among the three phenotypes enabled to distinguish them clearly. Interestingly, shared DEGs between MONW and OW-OB were regulated in the same direction, although both phenotypes differed in anthropometric and biochemical parameters. Therefore, these common DEGs might be used as markers for predicting increased metabolic risk.

Conclusions: PBMC gene expression profiling allows discrimination of subjects with MONW and healthy OW-OB features. This provides evidence of the usefulness of PBMC as a tool to characterize further both phenotypes, and as a source of metabolic risk markers. Moreover, results show the importance of considering sex differences in obesity-related research.

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