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High fat diet induced association of anti-inflammatory phospholipid and CRP levels in human adipose tissue in the NUGAT study

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Background and aims: Lipid metabolism and signaling might be either controlled genetically or by environmental factors. The aim of the study was to correlate lipidomic and genomic data of human subjects to identify specific gene-modules responsible for the regulation or connected with the function of specific lipid metabolites.

Materials and methods: In the NUGAT-Study 46 healthy mono- and dizygotic twin-pairs first were standardized for their nutritional behavior by a carbohydrate-rich low-fat diet for 6 weeks (LF), immediately followed by a high-fat diet for 1 week (HF1) and additional 5 weeks (HF6). At each CID periumbilical fat biopsies were taken for determination of gene expression on Agilent 8×60K gene micro Arrays. Plasma was measured for lipid metabolites and cytokines (ELISA). Weighted gene Co-Expression Network Analysis (WGCNA) and regularized Canonical Covariance Analysis (rCCA) were used for identification of co-expressed gene-networks and their correlation with lipidome data.

Results: Analysis of the 5000 strongest regulated genes revealed a gene-module highly correlated with CRP ($r=0.31$; $p=6 \times 10^{-4}$) and highly associated ($r=-0.32$, $p<0.0004$) with an anti-inflammatory/anti-bacterial lysophosphatidylethanolamine specimen (LPE18:1). Application of rCCA showed an increasing association of a set of genes involved in lysophosphatidic acid (LPA) receptor signaling with the decreasing concentrations of LPE specimen. When stratifying the cohort for individuals with a $CRP<1$ or $CRP \geq 1$ at HF6, LPE18:1 levels decrease more pronounced in individuals with high CRP ($p=0.042$). Remarkably, in individuals with low CRP the detected inflammatory gene-module is not associated with LPE18:1 ($r=-0.04$; $p=0.7$) while highly associated in people with high CRP ($r=-0.6$; $p=0.008$).

Conclusion: Our data show for the first time in humans that high-fat diet induces a gene set with inflammatory character which might be involved in lysophosphatidic acid (LPA) receptor signaling. Specifically we identify down regulation of the anti-inflammatory phospholipid LPE and increasing synchronization of LPE concentration with gene expression patterns as a mediator of inflammatory processes in the adipose tissue in a CRP associated manner.

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Dysregulation of sirtuins and key metabolic genes in skeletal muscle of pigs with intrauterine growth restriction is associated to alterations of circulating IGF-1

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Background and aims: Prenatal and early postnatal lives are important determinants of future health, and intrauterine growth restriction (IUGR)-associated low birth weight predisposes to the development of metabolic and cardiovascular disease in adult life, but the mechanisms are largely unknown. We hypothesize here that IUGR might confer gene expression alterations, predisposing to metabolic disease.

Materials and methods: Using a porcine model of spontaneous IUGR, we determined in utero (71, 112 days post-conception) and early-postnatal (2 days post-birth) IGF-1, insulin and leptin levels, and in parallel we investigated skeletal muscle (Longissimus dorsi) gene expression of sirtuins and key metabolic genes (IRS1, GLUT4, HK2 and GAPDH). **Results:** In IUGR, we observed impaired IGF-1, insulin and leptin serum levels. Gene expression of sirtuin 1, 5, 6, 7, GLUT4 and HK2 exhibited significant correlations with gestational age or fetus/newborn body weight. SIRT1 and HK2 expression displayed an age- and weight-dependent downregulation in controls, which was lost in IUGR pigs. Conversely, SIRT2 and GLUT4 were upregulated in IUGR pigs. Within the set of genes studied, we found a significant correlation between IGF-1 levels and gene expression, indicating that IGF-1 is limiting in IUGR. IUGR-dependent gene alterations were partly linked to epigenetic changes on histone H3 acetylation and methylation.

Conclusion: Our observations indicate that several sirtuins and metabolic genes display specific gene expression trajectories during fetal and early postnatal life, which are altered in IUGR, and are related to hormonal dysregulations observed in IUGR. Given the importance of these genes in metabolic control, their perinatal alterations might contribute to the predisposition to metabolic disease and diabetes in adulthood.

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