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Transcriptomic coordination in the human metabolic network reveals molecular links between fat intake and metabolic health

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Understanding the functional relationships between diet, gene expression and phenotype is a key challenge in nutritional science. The LIPGENE project was an international research effort assessing the impact of genotype and dietary fat intake on metabolic health[(1)]. In the final stage of this project, we generated adipose tissue microarray data in order to examine the effect of habitual dietary components on transcriptomic activity and, subsequently, markers of metabolic health.

A sub-cohort of participants in the LIPGENE human intervention study were included in this analysis of adipose tissue transcriptomic signatures[(2)]. Habitual dietary data included SFA, MUFA, ω–3 and ω–6 PUFA, carbohydrates, protein and alcohol. Blood samples were collected and assessed for 46 markers of metabolic and cardiovascular health including cholesterol, TAG, insulin sensitivity and glucose metabolism (assessed by IVGTT) and markers of inflammation and oxidative stress. Plasma fatty acid composition was also determined as a marker of dietary fat intake, and urinary 8-iso-PGF2a as a marker of oxidative stress.

As an alternative to pathway analysis, we have taken a network-based approach to the analysis of dietary, transcriptomic and comprehensive plasma marker profile. Sparse partial least squares and regularised canonical correlation analyses were used to identify strongly correlated diet-gene and plasma marker-gene pairs, which were then mapped to a high-quality reconstruction of the human metabolic network. Diet-sensitive and transcriptionally co-expressed sub-paths were subsequently extracted from the network using an algorithm designed to trace paths of enzymatic metabolite conversion.

With this approach we identified a prominent sub-path in the network that was transcriptionally correlated with dietary ω-3 PUFA intake and strongly co-expressed within the sub-path. This sub-path interlinked the related processes of glycerophospholipid, arachidonic acid and linoleic acid metabolism – and was shown to correlate with plasma markers of metabolic health including plasma DHA and urinary 8–9-iso-PGF2a. Promoter analysis further revealed a number of significantly over-represented adipogenic transcription factors (such as *pparg* and *klf4*) in the promoter regions of genes that were positively correlated with ω-3 PUFA intake. This integrated bioinformatics approach highlighted novel regulatory and metabolic mechanisms relating dietary ω-3 PUFA intake to metabolic health via adipogenic transcription factors and interconnected lipid metabolism pathways.

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