Integrated systems biology to study non-alcoholic fatty liver disease in obese women

Lesley Hoyles1†, José-Manuel Fernández-Real2, Massimo Federici3, Matteo Serino5, Vincent Azalbert4, Vincent Blasco3, James Abbott1, Richard H. Barton1, Josep Puig1, Gemma Xifra1, Wilfredo Ricart1, Mark Woodbridge1, Christopher Tomlinson1, Marina Cardellini4, Francesca Davato1, Iris Cardolini8, Ottavia Porzio1, Paolo Gentilesci5, Frédéric Lopez1,†, Fabienne Foufelle1, Catherine Postic1, Sarah A. Butcher1, Elaine Holmes1, Jeremy K. Nicholson1, Rémy Burcelin4,5, Marco-Emmanuel Dumas4,†

1Surgery and Cancer, MRC-HEC Centre for Environment and Health, Imperial College London; 2Department of Endocrinology, Diabetes and Nutrition, University of Granada, Spain; 3Department of Systems Medicine, University of Rome Tor Vergata, Italy; 4Institut National de la Santé et de la Recherche Médicale (INSERM), Toulouse, France; 5Università Paul Sabatier (LPS), Institut des Maladies Métaboliques et Cardiovasculaires (IDMC), France; 6Department of Experimental Medicine and Surgery, University of Rome Tor Vergata, Rome; 7Sorbonne Universités, UPMC Univ Paris 06, UARS 1138, Centre de Recherche des Cordeliers, Paris, France.

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*These authors made equal contributions to the work.

Faecal, liver biopsy, blood and urine samples and data for 28 clinical variables were collected for 56 obese (BMI >35 kg/m²) women from Italy (n = 31) and Spain (n = 25) who elected for bariatric surgery. Confounder analyses of clinical data were done using linear modeling. Histological examination of liver biopsies was used to grade NAFLD (NAFLD activity score: 0, 1, 2, 3). Faecal metagenomes were generated and analysed using the Scalable Automated Metagenomics Pipeline (ScAMP)1. Differentially expressed genes were identified in hepatic transcriptomes using limma2, and analysed using Enrichr3. network analyses and Signaling Pathway Impact Analysis (SPIA)4. 1H-NMR data were generated for plasma and urinary metabonomes5. Clinical, metagenomic, transcriptomic and metabolomic data were integrated using partial Spearman’s correlation, taking confounders (age, BMI and cohort) into account. Interactions between the faecal microbiome and the clinical/molecular phenotype were quantified, with the resulting Receiver Operating Characteristic (ROC) curve confirming the diagnostic power of molecular phenomic and metagenomic indices in NAFLD.

NAFLD activity score was (a) anti-correlated with microbial gene richness, and (b) correlated with abundance of Proteobacteria. (c) Microbial gene richness was correlated with clinical markers of NAFLD.

(a) Plasma and (b) urine metabolomic profiles highlighted imbalances in branched-chain amino acid metabolism, gut-derived microbial metabolites resulting from metabolism of amino acids and choline metabolism. There was no significant correlation of TMAO and TMA with NAFLD. Instead our data suggest choline is excreted rather than used by the gut microbiota.

NAFLD-associated hepatic transcriptomes were associated with branched-chain amino acid metabolism, endoplasmic reticulum/phagosome. Hepatic genes significantly correlated with NAFLD activity score AND microbial gene richness were significantly associated with immune responses linked to non-specific microbial infections and insulin resistance, and the most connected gene was INSR (insulin receptor).

KEGG analyses of metagenomic data suggested increased microbial processing of dietary lipids and amino acids, as well as endotoxin-related (LPS) processes related to Proteobacteria.

There is a close association between the gut microbiome, host metabolome, hepatic steatosis, and clinical and molecular insulin resistance in morbid obesity; and interplay between the microbiome and host gene expression in inflammation and host metabolism.

References


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Contact
Lesley.Hoyles@imperial.ac.uk

*These authors made equal contributions to the work.