LBC1.04

In silico gut microbiome metabolic modeling identifies metabolites associated with metabolic health status that are modifiable by dietary interventions

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Introduction: Obesity and diabetes are associated with major alterations in the human gut microbiome composition and function. Both host phenotype and lifestyle factors, such as diet, are recognized to play a vital role in shaping the gut microbiome. Likewise, the interaction between diet and gut microbiome metabolism influences host metabolic phenotypes. Recent advances in in silico gut microbiome metabolic modeling have increased the capacity to understand diet-microbiome community functional and mechanistic relationships underlying the generation of metabolites that can influence both gut barrier and host health. These models may hold the key to generate in silico biomarkers and guide future precision nutrition interventions in clinical populations.
Objectives: Using the MetaCardis cross-sectional European Cohort (n = 2000 participants) and the GutInside weight loss French cohort (n= 1855 participants), we evaluated (1) the ability of in silico gut microbiome community metabolic modeling to delineate host metabolic health, 2) the validity of in silico signatures using metabolomics, and 3) the effect of dietary interventions to drive predicted metabolites toward signatures reflective of improved metabolic health.
Methods: Using shot-gun metagenomics and dietary records data from participants, we conducted compartmentalized constraint-based in silico microbiome community metabolic modeling and determine predicted metabolites related to obesity and metabolic health. Cardiometabolic disease and heterogeneous obesity phenotypes were studied using clinically driven classifications, and metabolic health was assessed with a data-driven metabolic health index. In silico predicted metabolites were evaluated for their association with serum metabolomics. Finally, we generated dietary pattern interventions to determine if diet significantly modifies predicted metabolites, denoting potential metabolic health effects in the host.
Results: Our results identified 62 total predicted metabolites associated with obesity-related phenotypes independently of usual dietary habits. A total of 19 of these identified metabolites were common across Class I to Class III obesity. A further 14 predicted metabolites were associated with a metabolic health index comprising diagnostic variable defining the metabolic syndrome. Predicted metabolites were significantly correlated with serum metabolomics for a sub-population of predicted metabolites, including metabolites commonly related to host metabolic health. Finally, using distinct dietary pattern interventions and nutrient compositions, we found diet shifted predicted metabolites in both diet- and individual-dependent manners.
Conclusions: Our findings demonstrate in silico gut microbiome metabolic models provide predicted metabolite signatures stratifying host obesity- and metabolic health with potential clinical relevance. These models also identify pathways through which diet-gut microbiome functional interactions can influence or reflect host health. Collectively, this work paves the way for using in silico models to develop stratified precision or personalized nutrition interventions to improve metabolic health.

LBC1.05

Regulated on Activation, Normal-T cell expressed and Secreted (RANTES/CCL5) levels: an association with epicardial adipose tissue thickness in women affected by abdominal obesity

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Introduction: Epicardial adipose tissue (EAT) is a unique and multifunctional adipose compartment of the heart, located between the myocardium and the visceral layer of the epicardium. EAT thickness is considered an index of visceral adiposity and an indicator of high cardio-metabolic risk. Evidence shows that EAT is a metabolically active organ and a source of inflammatory adipo-chemocytokines that may predispose to a chronic inflammatory condition in this small cardiac fat depot. The potential links between cardiac adiposity and circulating levels of inflammatory adipo-chemokines, as markers of subclinical inflammation, are not completely understood. Our aim is to evaluate whether cardiac adiposity, measured as EAT thickness, is related to Regulated on Activation, Normal T Cell Expressed and Secreted (RANTES/CCL5) levels, in patients with obesity.
Methods: EAT thickness (measured by echocardiography, on the free wall of right ventricle), RANTES/CCL5 and other inflammatory markers (by ELISA kit) were measured in 36 women with abdominal and general obesity (BMI 41.6±5.6 kg/m^2) and in 15 controls with normal-weight. Abdominal visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) were assessed by computed tomography (CT).
Results: Patients affected by obesity had thicker EAT (6.8±0.9 vs. 1.3±0.3 mm, p<0.0001) (Fig.1) and higher RANTES/CCL5 levels (2468.9±745.5 vs. 1272.1±413.7 pg/ml, p<0.03) than controls (Fig. 2). EAT thickness positively correlated with RANTES/CCL5 concentrations (r2=0.65, p<0.001) (Fig.3). Moreover, EAT thickness and RANTES/CCL5 concentration were directly correlated with indices of fat distribution (VAT, VAT/SAT and waist, p<0.001 for all). Notably, when using multiple regression analysis, RANTES/CCL5 levels most closely correlated with EAT thickness (t=3.93) and VAT areas (t=3.77), while other indices of fat distribution did not enter the model.
Conclusions: EAT thickness, an indicator of cardiac adiposity, may be related to inflammatory adipo-chemokines in patients with abdominal obesity and might be used as an early marker of subclinical inflammation. Elevated RANTES/CCL5 levels, contributing to the pro-inflammatory state, may also lead to cardio-metabolic disorders.

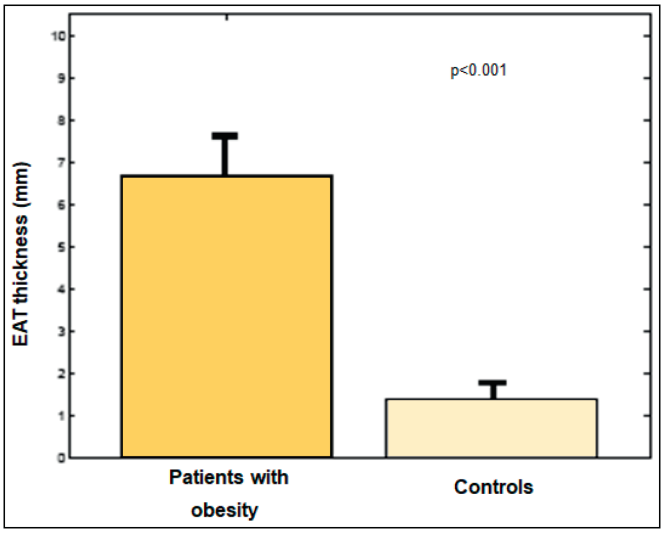

Fig.1. EAT thickness in patients with obesity vs control group.

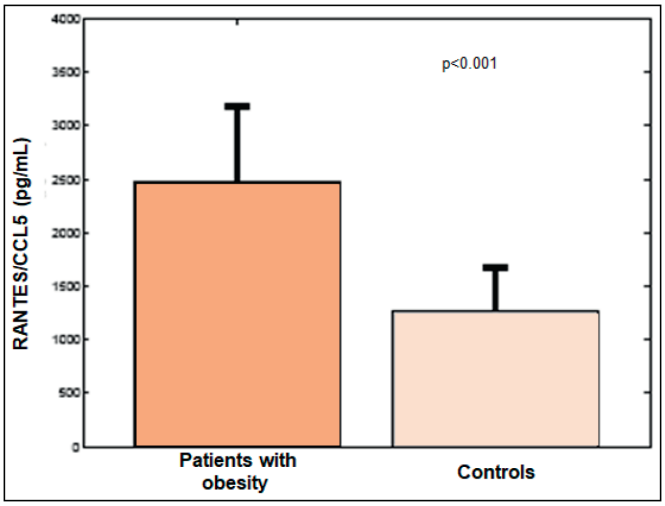

Fig. 2. Circulating values of RANTES/CCL5 in patients with obesity vs control group.

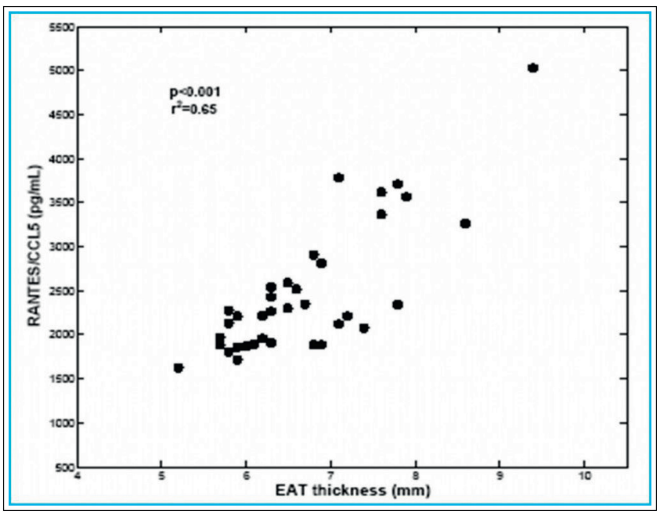

Fig. 3. Simple linear correlation among EAT thickness and RANTES/CCL5.

LBC1.06

The mechanosensor Piezo1 acts as an on-off switch in balancing the osteogenic and adipogenic potential of bone marrow mesenchymal stem cells

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Introduction: Bone marrow mesenchymal stem cells (MSCs) are non-hematopoietic multipotent stem cells which can be differentiated into osteoblasts and bone marrow adipocytes. The inverse relationship between MSC-derived adipogenesis and osteoblastogenesis forms a balance to maintain a homeostatic state. Disruption of this balance will lead to osteoporosis or marrow adiposity, whereas the underlying molecular machineries remain poorly understood. Piezo1 is a mechano-sensitive ion channel transducing mechanical stimuli into intracellular biochemical signals, which is highly expressed in bone marrow MSCs. In this study, we investigated the role of Piezo1 in controlling the cell fate of MSCs.
Methods: Piezo1flox/flox mice were crossed with platelet-derived growth factor receptor α (PDGFRα, a marker of MSCs)-Cre transgenic mice to generate PDGFRα-Piezo1 knockout (KO) mice. Eight-week-old Piezo1 KO mice and their littermate controls were subjected to treadmill exercise for 6 weeks (5 days per week, 30 min per day, at a speed of 15 m/min) or intraperitoneal injection of lipocalin-2 (Lcn2) neutralizing antibody (4 mg/kg, once a week) for 7 weeks. Tibias were isolated for micro-CT analysis and osmium tetroxide staining to visualize bone volume and bone marrow adipocytes, respectively. MSCs isolated from KO and control bone marrows were differentiated into osteoblasts and adipocytes in vitro.
Results: Invalidation of Piezo1 in MSCs results in lower body weight, osteoporosis and marrow adiposity. MSCs lacking Piezo1 preferentially differentiate into bone marrow adipocytes rather than osteoblasts. The beneficial effect of exercise-induced mechanical loading on bone health is compromised by Piezo1 ablation. MSCs treated with conditioned medium collected from Piezo1 KO MSCs display enhanced adipogenic potential but reduced osteogenic potential. ELISA analysis identifies a significant increase of the pro-inflammatory cytokine Lcn2 in the conditioned medium of Piezo1 KO MSCs. Olink proteomics analyses also identify elevated pro-inflammatory chemokines including Ccl2, Ccl3 and Ccl5 in the culture medium of Piezo1 KO MSCs, indicating that Piezo1 depletion initiates the pro-inflammatory status of MSCs. Mechanistically, Piezo1 ablation in MSCs leads to NFκB activation, which further enhances Lcn2 expression and secretion, and thus initiates the inflammatory response of MSCs to secrete pro-inflammatory chemokines. Genetic inhibition or antibody neutralization of Lcn2 in MSCs could reverse the enhanced adipogenesis of MSCs caused by Piezo1 invalidation both in vitro and in vivo, thereby restoring the osteogenic potential of MSCs.
Conclusion: The mechanosensitive cationic channel Piezo1 acts as an "on-off switch" in determining the lineage commitment of MSCs.

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LBC1.07

GLP-1: Investigating Its Role in Intestinal Barrier Integrity

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Introduction: Obesity, a metabolic disease now treatable with pharmacological interventions, benefits from the class of glucagon-like peptide 1 (GLP-1) agonists. GLP-1 is known for its anti-inflammatory effects and blood sugar regulation capabilities. Our recent findings suggest that