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Title: Multi-omics phenotyping highlights organ-specific metabolic and inflammatory shifts associated with differential plant and animal protein intake in high fat fed rats

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Introduction: The dietary transition from less animal protein (AP) to more plant protein (PV) sources has been advocated mostly for sustainability reasons but has also been associated to beneficial health effects such as decreased cardiometabolic risk. AP and PP differential amino acid (AA) compositions could contribute to explain those health effects. With this study, we aimed at characterizing metabolic and inflammatory adaptations associated to AP and PP intake in the context of plethoric diets, which currently remains mostly unknown.

Methods: 44 Wistar male rats were fed with 4 iso-protein diets, where protein was provided by either a milk protein isolate (AP) or a blend of 50% pea protein isolate-50% wheat protein (PP), in a regular normal fat (NF) or a high-fat (HF) context. Plasma, liver, intestine, skeletal muscle and adipose tissue samples were collected after 4 months. Tissue targeted transcriptomics (TLDA) and fluxomics (D₂O tracer) and plasma untargeted metabolomics (LC-MS) were used for a multi-omic phenotyping. Clinical biomarkers and natural ¹⁵N enrichment (EA-IRMS) were also measured. Both multivariate (AMO-PLS) and univariate (ANOVA) statistical analyses were conducted.

Results: Distinct plasma metabolomics signatures were related to the energy level (HF vs NF), the protein type (AP vs PP) and their interactions, explaining respectively 12.7%, 11.5% and 4.7% of total variability. Natural ¹⁵N enrichment analysis revealed a higher AA reshuffle associated to PP in muscle, intestine and liver, which was further confirmed by increased mRNA levels related to AA and protein metabolism (BCAA oxidation, AA transport, myogenesis and muscle atrophy) in liver and muscle. At the hepatic level, AP diets were associated to a higher fat content and increased lipogenesis, assessed by fluxomics and enzyme activities. mRNA results were more heterogeneous, in particular in the adipose tissue, where a trend for increased lipogenesis and cholesterol synthesis-related targets was observed. Regarding glucose homeostasis, the PP diets resulted in an improved whole-body insulin sensitivity (HOMA-IR), only in a HF context, and an up-regulation of insulin-related genes in the muscle at both energy levels (HF and NF). Several inflammation-related transcripts were also modified by the protein source, especially in the muscle and the liver, but the direction of the association remained unclear.

Discussion and conclusion: While the alterations observed at the adipose tissue level and some inflammatory markers (hepatic Tnfa) would deserve further attention, overall, our multi-omics approach highlighted several beneficial effects of PP intake: a reduced hepatic lipid accumulation through down-regulated lipogenesis, better whole-body insulin sensitivity associated with more

responsive insulin pathway at the muscle level, and changes related to some inflammatory markers (muscle Tnfa).

Keywords: Metabolomics, transcriptomics, fluxomics, animal protein, plant protein, cardiometabolic risk