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Research Article

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Identification of putative kidney-derived proteins in plasma using nanoparticle enrichment

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Abstract

Many diseases, including diabetes and hypertension, can lead to kidney damage, often resulting in long-term health complications and organ failure. Both animal and human studies have documented a causal relationship between high dietary sodium intake and elevated blood pressure. We explored a proteomics analysis of plasma samples to detect early kidney damage in response to a high-sodium (HS) diet through the quantification of putative kidney-derived proteins in plasma for early disease detection. Plasma samples from seven female baboons fed an HS diet for 6 weeks were collected before and after the HS diet challenge. Plasma samples were analysed using a novel nanoparticle enrichment protocol. Using Seer's Proteograph XT workflow, we identified 2294 plasma proteins across all the samples. Of these, 2139 proteins were annotated with gene IDs, including 453 proteins previously identified in kidney lysate. In the Human Protein Atlas, 1969 of these proteins were annotated as expressed in the kidney, and 37 were classified as elevated. Ninety-seven proteins were only detected in plasma samples collected after the 6-week HS diet. We also identified 35 nominally significant differentially abundant proteins ($P < .05$), with 84% of these detected at higher abundance after HS exposure. Additional proteins were identified in two animals that demonstrated an increase in blood pressure in response to the HS diet. Our analysis reports an increase in putative kidney-derived proteins in plasma after HS diet exposure, and demonstrates the suitability of the Seer's Proteograph technology to identify potential biomarkers for kidney tissue damage.

Introduction

Sodium intake plays a critical physiological role in regulating the fluid balance controlling blood pressure (BP) and nerve and muscle function. According to the National Institutes of Health (newsinhealthNIH.gov/special-issues) and the Center for Disease Control and Prevention, the daily recommended intake of sodium for adults is 2300 mg, and it is 1500 mg for those who are 51 or older, African American, or have high BP, diabetes, or chronic kidney disease. Excessive sodium intake can lead to high BP or hypertension (HT), increased water retention, and an increased risk of kidney disease. Sex differences have been noted in BP regulation; women who have entered menopause are the most susceptible to developing HT that is often resistant to treatment, yet current therapeutic recommendations for treating HT do not take sex into account [1, 2].

Proteomic analysis of plasma samples can be used to identify biomarker signatures correlated with the development and progression of chronic diseases, and may reveal new targets for treatment and prevention. However, a comprehensive analysis of plasma proteins and the characterization of the putative tissue(s) of origin of plasma proteins remain challenging. The leakage of proteins from a tissue into the bloodstream is a hallmark of various diseases with tissue and cell damage, and detection of early tissue damage may be a powerful diagnostic. As an example, two commonly measured proteins that are correlated with liver injury are aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Elevated plasma levels of AST and ALT indicate liver cell damage and are commonly used as biomarkers of liver injury [3].

With the recent advances in mass spectrometry–based plasma proteomics, including data-independent acquisition (DIA) protocols and

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the newly developed nanoparticle enrichment strategy that allows the effective enrichment of plasma proteins for mass spectrometry analysis [4, 5], this exploratory study was designed to assess our ability to detect early tissue damage in the kidney. The overarching goal of this pilot project was to establish and evaluate the Seer Proteograph™ platform for the analysis of plasma samples from baboons, and to investigate whether this advanced technology allows the detection of kidney damage by analysing plasma samples collected after exposure to a high-sodium (HS) diet. We used samples collected from female sodium-naïve baboons (*Papio hamadryas*) before and after a 6-week HS diet. Previous work has focused on the analysis of underlying kidney gene expression changes in response to salt exposure, and how these changes may mediate the BP response of these animals [6]. In contrast, our study explored whether this short-term high salt exposure is sufficient to induce kidney cell and tissue damage, either directly by salt exposure or by the resulting change in BP. All the baboon plasma samples were analysed using the SEER Proteograph XT workflow [7–10] and DIA mass spectrometry for a first-time analysis of nonhuman primate plasma samples using this approach.

Materials and methods

Study design, approval, and oversight

The baboons used in this study (*P. hamadryas*; Taxonomy ID 9557) were part of a pedigreed baboon colony housed at Southwest National Primate Research Center (SNPRC) (RRID:SCR_008292), at Texas Biomedical Research Institute (TBRI), in San Antonio, Texas. The SNRPC facilities at the TBRI, and the animal-use programmes, are accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC) under all National Institutes of Health (NIH) and US Department of Agriculture (USDA) guidelines. Veterinarians were responsible for care decisions as well as daily enrichment, with assessments from behavioural staff in accordance with AALAC, NIH, and USDA guidelines. All the processes and procedures followed Institutional Animal Care and Use Committee (IACUC) regulations (protocol 1512PC). For this study, female baboons were selected based on family history of HT, and the KINSHIP program (with the Stevens–Boyce algorithm) was used to ensure similar degrees of relatedness among females.

The study design strived to promote baboon well-being, including an indoor/outdoor environment and one vasectomized male (not in study) to promote full social and physical activity. The animals were raised and maintained on a standard monkey chow diet (high complex carbohydrates; low-fat 'Monkey Diet 15%/5LE O', LabDiet, PMI Nutrition International) before the start of the study. Prior to the high salt exposure, animals were brought together and acclimated in a group cage for at least 8 weeks. To monitor feeding *ad libitum*, females were run into individual cages for 4 h (passing over an electronic weighing scale) and fed 500 g food once a day. They were fed a low-sodium (LS) diet (17.3 mmol Na^+/500 g food consumed) for 6 weeks. This was followed by an HS diet (210 mmol Na^+/500 g food consumed) for 6 weeks. Food consumption was used to calculate the overall sodium intake. Additional health status information, such as body weight, menses cycle, and BP, were measured as described [6].

Blood sample collection

Whole blood was obtained from seven adult premenopausal female baboons ($n = 7$, age 17.86 + 1.35 years). Blood was drawn in EDTA tubes from each animal at the 6-week (LS) and 12-week (HS) time points. EDTA tubes containing fresh blood were spun at 1000 × *g* for 10 min and 200 μl aliquots of plasma were obtained. These were snap-frozen in dry ice with an isopropanol bath and kept on the bath, and then stored at −80°C until use.

Blood plasma preparation

Fourteen 125 μl aliquots of baboon plasma (seven samples per time point) were processed for untargeted proteomics analysis. The aliquots were diluted 1:1 to 250 μl by Seer (Redwood Shores, CA, USA) in preparation for analysis on the Proteograph™ platform [8, 11]. Tubes were loaded onto the SP100 automation instrument to process and extract purified peptides for liquid chromatography-mass spectrometry (LC–MS). Each plasma sample was incubated with five proprietary nanoparticles for protein corona formation. After incubation, a magnet was used to pull down the nanoparticles and their bound proteins. Samples were washed, reduced, alkylated, digested with trypsin/Lys-C, purified, and dried overnight with a vacuum concentrator. This protocol generates five distinct nanoparticle-enriched peptide fractions per plasma sample, corresponding to the five proprietary nanoparticles in the Proteograph™ assay. Dried peptides were returned to the Center for Precision Medicine (Wake Forest University School of Medicine, Winston-Salem, NC, USA) for mass spectrometry analysis.

Mass spectrometry analysis

Peptides were reconstituted in 0.1% formic acid and water. An amount of 1 μg per sample was loaded on a Thermo Fischer Scientific Easy-nLC 1200, with an Acclaim PepMap 100 C18 trap column (75 μm × 2 cm, 3 μm) and separated through a PepMap RSLC C18 easy-spray column (3 μm, 100 Å, 75 μm × 15 cm). Peptides were separated at flow rate of 300 nl/min using a 33-min gradient of mobile phase A (0.1% formic acid in 95:5 water and acetonitrile) and mobile phase B (0.1% formic acid in 80:20 acetonitrile and water). The following gradient programme was used for peptide elution: 1% B for 3 min, 1%–25% B in 19 min, 25%–40% B in 5 min, 40%–90% B in 30 s, 90%–1% B in 1 min, 1% B for 4.5 min. Peptides were analysed using a Q-Exactive HF mass spectrometer (Thermo Scientific). Data were acquired in MS1 with a scanning range of 380–1200 *m/z* at a resolution of 60 000. Automatic gain control (AGC) was set to 1×10^6, maximum injection time to 50 ms, and Spectrum Data Type to Profile. For MS/MS data acquisition, the scanning range (*m/z* = 380–1200) was divided into 82 continuous windows of 10 *m/z* and fragment ions were scanned with a 60 000 resolution with an AGC target of 1×10^6. The MS/MS collision mode was higher-energy C-trap dissociation (HCD) mode with a maximum injection time of 60 ms. All the data acquisition was done using Thermo Scientific Xcalibur software.

Data-independent acquisition analysis

Peptide precursors were quantified in the Proteograph Analysis Suite (PAS) using DIA-NN version 1.8.1. as the search engine [12, 13]. The data was searched against the closest high-quality reference proteome: *Papio anubis* (*P. anubis* Uniprot Reference Proteome ID UP000028761 with 43 406 protein entries) in library-free mode and filtered to 1% peptide and protein false discovery rate (FDR) for identification on peptide and protein group level. The parameters for the search were kept at default with three key exceptions: match

between runs (MBR) set to true and maximum of two missed cleavages allowed. The following variable modifications were included in the search: (i) oxidation (M) and (ii) acetylation (protein N-term). Carbamidomethyl (C) was included as a fixed modification. All 70 DIA LC–MS files (5 nanoparticle eluates × 14 samples) were processed independently in PAS. PAS first computes peptide and protein group abundance separately for each nanoparticle-derived fraction (NP level). For the panel-level output used in this study, PAS then summarizes the NP-specific abundances for each peptide and protein group into a single quantitative value per sample through a maximum representation algorithm [4], which selects the intensity value from the nanoparticle that most consistently measures that feature across the cohort.

Panel-level protein group intensities were exported from PAS in $\log_{10}$ scale. For each biological sample, we performed global median normalization across all the quantified protein groups: the median intensity within each sample was aligned to the global median across samples by subtracting the sample-specific median and adding the global median. This normalization serves as a computational loading control, correcting for run-to-run differences in total signal under the assumption that most proteins do not change between diet conditions. The normalized values were then transformed to $\log_2$ scale and used for all the downstream statistical analysis.

Analysis of differentially abundant proteins

A paired two-tailed Student's *t*-test was performed for each protein in our dataset to compare protein abundances before and after the HS diet (samples collected at 6 and 12 weeks).

For each animal, per-protein Δ was computed as HS − LS. A positive Δ indicates higher abundance at 12 weeks; a negative Δ indicates lower abundance. Deltas were computed for all seven subjects. If a value was missing in either condition for a subject, Δ was set to 'NA'; no imputation was performed.

For the two animals that showed significantly increased BP (animal 1 and animal 5) by the end of the study, proteins were called concordant when Δ had the same sign in both (same directionality of BP change). A magnitude filter of $|\Delta| \geq 0.5$ (1.4-fold change) was applied in each subject. Proteins were ranked by the smaller absolute Δ across the two subjects to prioritize changes strong in both.

Results

Nonhuman primate plasma proteome depth

Nanoparticle-based enrichment coupled to DIA LC–MS/MS was applied to 14 plasma samples from female baboons. A total of 2139 plasma proteins with gene IDs were identified across the analysed samples. The per-sample proteome depth is shown in Fig. 1A. Protein identifications showed interindividual variation across runs. Normalized protein intensities for all 14 samples are included in Supplementary Table S1. By condition, 2042 proteins were identified in LS samples, and 2132 in HS samples. Not unexpectedly, most proteins identified were shared between the LS and HS groups, with 7 proteins unique to LS and 97 proteins unique to HS (Fig. 1B). Out of these, 95 proteins were annotated as kidney-expressed in the Human Protein Atlas (HPA), and 1 as kidney-enhanced. This suggests that the HS diet leads to an increase of new proteins detected in plasma after HS exposure, suggesting a potential for cell or tissue damage leading to the release of these putative kidney-derived proteins.

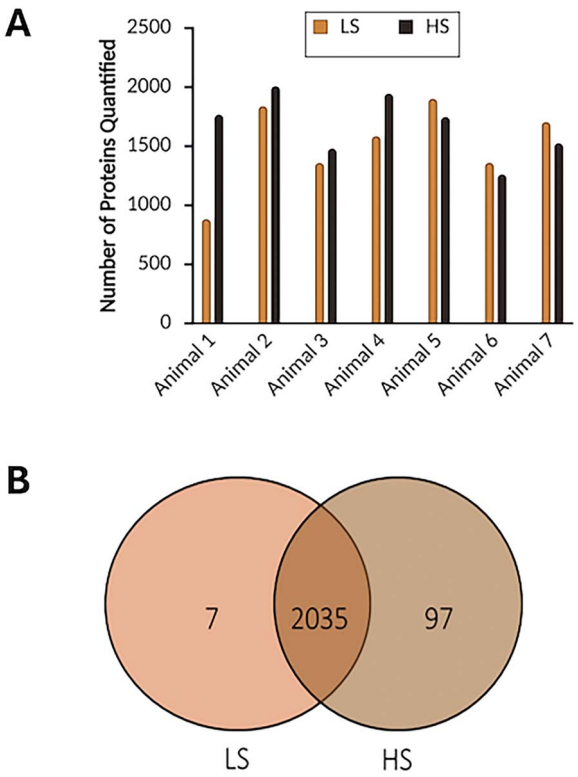

Figure 1 (A) Number of quantified plasma proteins with gene IDs per animal at both low-sodium (LS) and high-sodium (HS) time points. Bars illustrate the number of proteins identified with a gene ID. (B) Venn diagram of proteins identified at each time point. Protein IDs and gene IDs were aligned for comparison.

Putative kidney-derived proteins in plasma

We annotated our plasma proteome dataset with the HPA kidney expression information [14]. A list of 14 844 proteins was downloaded from the HPA (proteinatlas.org v24.0) as their kidney-expressed protein dataset based on existing RNA-Seq and immunohistochemistry information for the human kidney. This was performed by including normal_expression:Kidney; Any; Low,Medium,High as the search parameter for the Tissue Expression (IHC) field and downloading the results. We conducted a different search within the HPA for the Tissue Category (RNA) field with parameters: tissue_category_rna:Liver; Tissueenriched, Groupenriched, Tissue enhanced, Low tissue specificity, Detected in all, Detected in many, Detected in some, Detected in single. The two lists were combined and duplicate entries were removed from the dataset. Similarly, a separate list of 459 elevated genes for kidney was downloaded from the HPA.

Across the 2139 plasma proteins quantified, 1969 proteins were annotated by the HPA as kidney-expressed, and 37 proteins were reported as kidney-elevated. Within these 37 proteins, there are 3 tissue-enriched, 22 tissue-enhanced, and 12 group-enriched proteins (HPA categories). The data is summarized in Table 1. As LS and HS group protein abundances were compared, a total of 35 nominally significant differentially abundant proteins (DAPs) were detected at $P < .05$. A detailed list of these proteins is provided in Supplementary Table S2.

Figure 2 shows the combined principal component analysis (PCA) of the 35 DAPs before (LS) and after (HS) the salt exposure for each

Table 1 Counts of total, condition-specific, and differentially abundant plasma proteins (DAPs), and Human Protein Atlas kidney annotations

	Total protein number
Plasma proteins	2139
Proteins annotated in HPA as kidney-expressed	1969
Proteins annotated in HPA as kidney-elevated	37
Plasma protein count at LS	2042
Plasma protein count at HS	2132
DAP in LS vs HS	35
DAP annotated in HPA as kidney-expressed	33

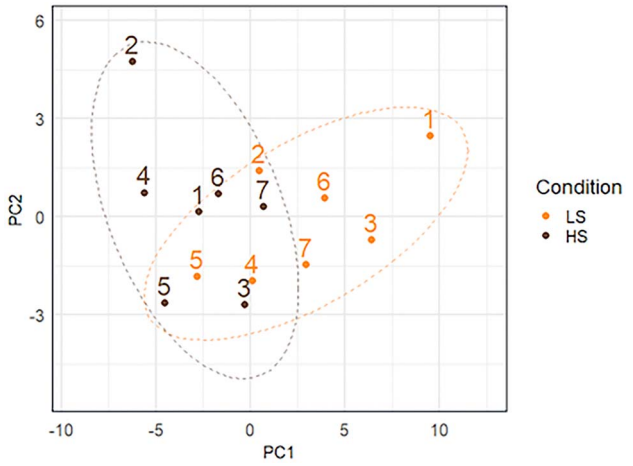

Figure 2 PCA of the 35 DAPs that are different between LS and HS samples. Samples from individual animals are annotated by number for each diet condition. Overall, the PCA shows only marginal separation and significant cluster overlap between the LS and HS samples.

animal. As the graph shows, for some animals (e.g. animal 1) the protein abundance change between LS and HS was large, but overall the quantitative changes in the abundance of the 35 DAPs were relatively small.

Of the 35 DAPs, 33 were annotated as kidney-expressed by the HPA. Of these, 28 (84%) were detected at higher abundance in samples collected after the HS exposure, suggesting that the diet exposure may have resulted in some kidney cell damage, resulting in a significantly higher release of these kidney-derived proteins into plasma.

To further interpret the protein annotation and the specificity of the reported kidney expression, we extended the analysis of our plasma proteins to also annotate liver-specific proteins for comparison using the same approach as that described above. A combined list of 14 056 liver-expressed proteins was generated from RNA and IHC data. Among the 2139 plasma proteins quantified, 2005 were annotated as liver-expressed. Out of these, 85 proteins were annotated as expressed in the liver but not in the kidney, and 49 were annotated as expressed in the kidney but not in the liver. Elevated protein expression was more frequent in the liver (224 proteins) than in the kidney (37 proteins), consistent with the liver's role in secreting proteins into circulation. Notably, among the 35 DAPs identified in our study, 34 were liver-expressed (1 liver-elevated), and 33 were kidney-expressed (1 kidney-elevated), suggesting that diet-induced changes may affect protein expression in both organs.

Protein trends in blood pressure increase

As described in a prior study [6], two animals in our cohort showed significantly increased BP in response to the HS diet. We measured the within-animal change for each protein. Δ was computed to determine shared protein abundance trends between the two animals showing a BP increase (animal 1 and animal 5). One protein with concordant abundance decrease was identified in both BP animals: (matrix Gla protein, MGP). Two proteins with a concordant abundance increase were identified in both BP animals: RASGRP2 (RAS guanyl releasing protein 2) and CHGA (chromogranin-A). The abundance changes for each of these proteins for each animal are illustrated in Fig. 3. This paired-line plot representation emphasizes condition-dependent shifts while controlling the interanimal baseline variability.

It is important to emphasize that the PCA does not reveal consistent differences between LS and HS for both animal 1 and 5 that are distinct from all other animals, suggesting that the change in BP is likely not the primary factor altering the abundance of putative kidney-derived proteins in plasma in response to this short-term high salt exposure. A similar lack of clustering can be observed using a heatmap of clustered protein data (Supplementary Fig. S1). As in the PCA, no consistent patterns emerge, and samples from animals with BP increase or samples collected before or after salt exposure do not consistently cluster.

Discussion

Only a few studies to date have described plasma proteomics analyses in nonhuman primate species. Examples include the combination of gel electrophoresis and LC–MS analysis in rhesus macaques [15], Luminex-based targeted analyses in vervets [16], and affinity-based platforms adapted for use in nonhuman primates (Olink in cynomolgus monkeys [17] and SomaScan in rhesus macaques [18]). Only two studies have reported on the application of DIA-based MS approaches to the proteomic analysis of NHP samples and biomarker discovery [19, 20].

We explored the adaptation of advanced DIA protocols to the analysis of baboon plasma, in combination with a nanoparticle-based enrichment strategy. As we describe, this approach allowed the identification and quantification of 2139 proteins across the 14 samples from female baboons. This number is significantly higher than our previous findings for MS-based direct analysis of depleted baboon plasma (106 proteins) and for an isobaric labelling approach developed by our lab (820 proteins in baboons) [21], suggesting that the DIA approach coupled with nanoparticle enrichment significantly increases the number of plasma proteins that can be quantified in a sample. This matches well with data reported for the analysis of human plasma [7], suggesting that the combination of the Proteograph enrichment strategy with DIA-based MS analysis provides a powerful tool for the comprehensive characterization of NHP plasma.

We applied the analysis platform to a pilot project to assess whether we can detect putative kidney-derived proteins in plasma after exposure of animals to a short-term high-salt diet. By using this technology, we quantified several subsets of proteins that indicate potentially different molecular responses to a HS diet. The first subset are the 35 proteins that are nominally significantly different between the LS and HS samples. Within this subset, 28 proteins significantly increased after the HS diet challenge. The second subset consists of 97 proteins that were only present in the HS diet samples. Lastly, a third

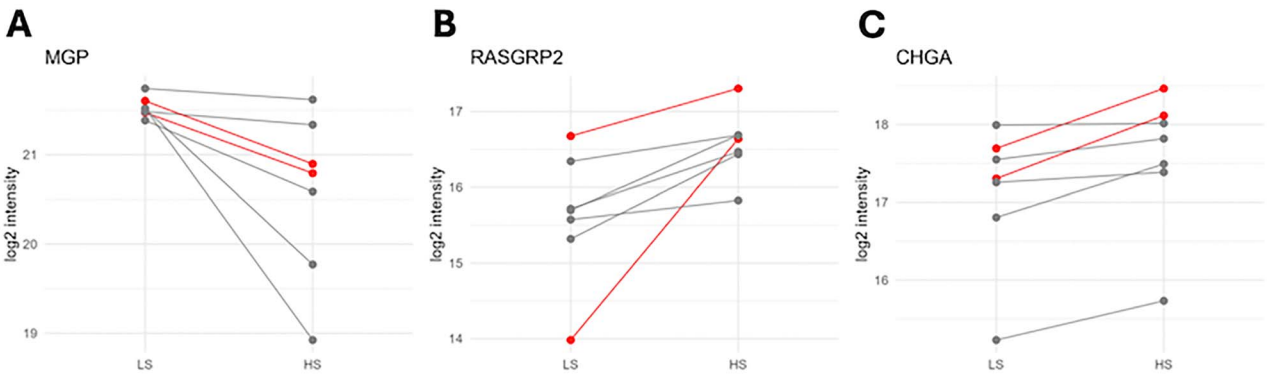

Figure 3 Paired-line plot illustrating the changes in protein abundance from LS to HS exposure. Animals with significant changes in BP are highlighted in red. (A) Matrix Gla protein (MGP); (B) RAS guanyl releasing protein 2 (RASGRP2); (C) Chromogranin-A (CHGA).

subset of three proteins was found specifically in the two animals with increased BP. The MGP is a small, secreted protein related to protective vascular effects in kidney injury [22]. RASGRP2 (also known as 'CalDAG-GEFI') has a variety of intracellular and extracellular functions, including signal integration in platelets [23]. The relationship between BP, kidney injury, and platelet formation is complex and requires more study. High levels of serum CHGA have been linked to patients with HT and cardiac or renal failure [24]. Overall, our findings suggest that HS diet exposure alone may lead to the release of putative kidney-derived proteins into the plasma, with potentially additional release of proteins in response to the BP increase. Since the proteins identified in plasma are not kidney-specific, our study cannot effectively answer whether HS diet exposure truly leads to tissue and cell damage in the kidney. Also, quantitative differences between the two samples (after LS diet and after HS diet) for each animal show high variability between animals, and changes in BP in two animals do not seem to dramatically alter the protein profile of the plasma samples collected from these animals.

While the overall results from this preliminary study are encouraging, and demonstrate the utility of the new proteomics platform, the limited suggestive evidence for potential kidney cell damage and protein release will need to be validated in future studies, and may require longer exposure to an HS diet to trigger consistent effects across animals. However, if confirmed, our results suggest that an HS diet alone and the HS-induced BP increase both contribute to the potential for cell damage in the kidney, even after short-term exposure (6 weeks).

Conclusions

The combined approach of nanoparticle enrichment (Seer Proteograph™ platform) and DIA LC–MS proteomics for NHP plasma analysis allows the effective identification and quantification of plasma proteins. Our initial application to samples collected from female baboons before and after a HS diet challenge suggest that the HS diet increases the number and/or the abundance of putative kidney-derived proteins in plasma after sodium exposure, and additional proteins can be detected in animals that show a BP increase after the short-term HS diet. These plasma proteomic changes may be early indicators of kidney cell and tissue damage in response to the diet challenge.

Supplementary material

Supplementary material is available at *Molecular Omics* online.

Author contributions

Daniela Alejandra Key Planas (Data curation [equal], Formal analysis [equal], Methodology [equal], Writing—original draft [equal]), Sumaiya Nazli (Conceptualization [equal], Methodology [lead]), Angelica M. Riojas (Resources [equal]), Arisbeth Camarillo Reyes (Methodology [equal]), Avinash Jadhav (Methodology [equal]), Kip Zimmerman (Formal analysis [equal], Software [equal], Writing—review & editing [equal]), Laura A. Cox (Funding acquisition [equal], Resources [equal], Writing—review & editing [equal]), and Michael Olivier (Conceptualization [lead], Funding acquisition [equal], Project administration [equal], Writing—review & editing [equal]).

Conflicts of interest

There are no conflicts to declare.

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Data availability

All the mass spectrometry data is available through the PRIDE Data Repository (https://www.ebi.ac.uk/pride/) and ProteomeXchange, accession number PXD071248.

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