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Persistence of Western Diet-Associated Pathway Activity Profiles in Ventricular Tissues

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Abstract

The consumption of a Western diet (WD), characterized by high levels of fats and sugars, is strongly associated with adverse cardiovascular outcomes. In this case-control study, we evaluated long-term alterations in signaling pathway activities in the left (LV) and right (RV) ventricular tissues of C57Bl/6J mice that were exposed to WD starting at 300 days of age for 125 days before switching to a normal diet (ND). LV and RV tissues were collected at 530 days and subjected to RNA sequencing. Pathway activity for 40 signaling pathways (comprising 709 pathway branches/sinks) was calculated using the topology-aware Pathway Signal Flow (PSF) algorithm, which assesses signal propagation along a pathway based on gene expression levels of its components and their interactions. We observed significant perturbations in 14 pathway branches specifically in LV tissue of male mice, 105 days after the ND switch. These alterations included the downregulation of cardioprotective VEGF signaling and the upregulation of pro-fibrotic TGF-beta signaling, suggesting lasting cardiovascular risks. Furthermore, strong signaling was detected in the cGMP-PKG and FOXO pathways linked to cardiac failure. Finally, pro- and anti-apoptotic signals were simultaneously upregulated, accompanied by the downregulation of cell cycle inhibitors. Notably, no significant gene expression changes were detected in the left ventricular tissue of females, and no significant differences were observed in right ventricular tissue in either sex. These findings suggest that the effects of a Western diet may persist even after transitioning to a healthier diet. Further studies are needed to elucidate the diet-associated risks and develop strategies to mitigate these long-term effects.

Keywords: Western diet, left ventricle, right ventricle, RNA sequencing, transcriptomics, signaling pathways, Pathway Signal Flow

1. Introduction

The long-term impact of dietary habits on cardiovascular health remains a critical area of research, particularly in the context of metabolic memory and disease predisposition [1]. While the detrimental effects of prolonged consumption of a high-fat and high-sugar Western diet (WD) on cardiovascular function are well-documented [2], less is known about the persistence of these effects following a transition to a healthier diet. In real-world scenarios, individuals may consume a WD for extended periods, such as during early adulthood, before adopting healthier dietary patterns later in life.

We have previously demonstrated that prior WD consumption induces sex-specific alterations in cardiac function and transcriptomic profiles in the left ventricular (LV) in mice [3]. This study aims to investigate the long-term effects of WD on both heart ventricles, with a particular focus on the persistence of signaling pathway alterations following a transition to a normal diet. We applied a topology-aware Pathway Signal Flow (PSF) algorithm, a computational method for pathway activity analysis incorporating gene expression and pathway topology (interaction between pathway nodes) [4]. Using RNA sequencing data from left (LV) and right (RV) ventricular tissues of male and female mice previously subjected to a WD, we assessed whether prior dietary exposure leaves persistent imprints on signaling network activity profiles.

2. Materials and Methods

Animals and Diet

Three-month-old male and female C57BL/6J mice were stratified into two dietary groups: case - a Western diet (WD) (n=20, males/females: 10/10) received a modified Teklad diet containing 42% fat (TD.88137, Envigo, Madison, WI), and control - a standard rodent chow as a control (Normal diet, ND) (n=20, males/females: 10/10). WD was introduced at 300 days of age for 125 days, then animals switched to ND. Our previous publication extensively described animal handling, diet exposure, tissue collection, and RNA sequencing [3]. Animal protocols adhered to the National Institutes of Health guidelines and were approved by the Institutional Animal Care and Use Committees at Brookhaven National Laboratory (BNL) (Upton, NY) (BNL IACUC Protocol #502) and the Icahn School of Medicine at Mount Sinai (NY, NY) (ISMMS IACUC Protocol #2019-0017).

Pathway Signal Flow analysis of transcriptome perturbations

The PSF algorithm computes the activity state of pathway nodes (genes or gene groups) using relative gene expression values of a node in a pathway and its interactions with upstream nodes. It begins with input nodes and propagates to terminal nodes, computing node signal values based on fold changes, upstream signals, interaction weights, and activation/inhibition impacts. For each node in a pathway, a signal value is computed as the product of its expression fold change and the weighted contributions of signals arriving from upstream nodes. At each node, incoming signal from upstream nodes is combined proportionally: the contribution of an upstream node is normalized by the total incoming signal. Activating edges transmit upstream signal multiplicatively, whereas inhibitory edges invert the signal by applying a negative impact factor. The detailed description of algorithm is presented in our previous publication [4].

Raw RNA-seq read counts were normalized with the DESeq2 R package (version 1.44.0). Gene expression fold changes against mean expression across all samples were computed from a normalized gene count matrix and used as an input for the PSF algorithm [4].

We calculated the PSF activity values of 40 signaling pathways (709 pathway branches/sinks) in the LV and RV tissues in the studied groups. For each pathway sink, PSF activity values were compared between experimental groups using linear regression models. A pathway sink was considered significant if the absolute log2PSF value exceeded 1 and the false discovery rate-adjusted p value (FDR) was < 0.05.

To orthogonally validate the PSF-based findings, we performed conventional differential gene expression analysis using the limma R package, followed by overrepresentation analysis (ORA) of Gene Ontology gene sets using the enrichR package. We then evaluated the concordance between ORA results and PSF sink significance.

3. Results

We performed a topology-aware analysis of pathway activity in the LV and RV heart ventricles in animals with prior exposure to WD. Our findings indicated significant (absolute log2PSF > 1 and pFDR < 0.05) perturbations of 14 pathway branch activities at 530 days (105 days after switching to ND) in the LV tissue of male rats (Figure 1A, Additional Figures S1-S11, Additional Tables S1-S4). However, we did not detect significant perturbations in female animals' LV or both sexes' RV tissues (Figure 1B-D).

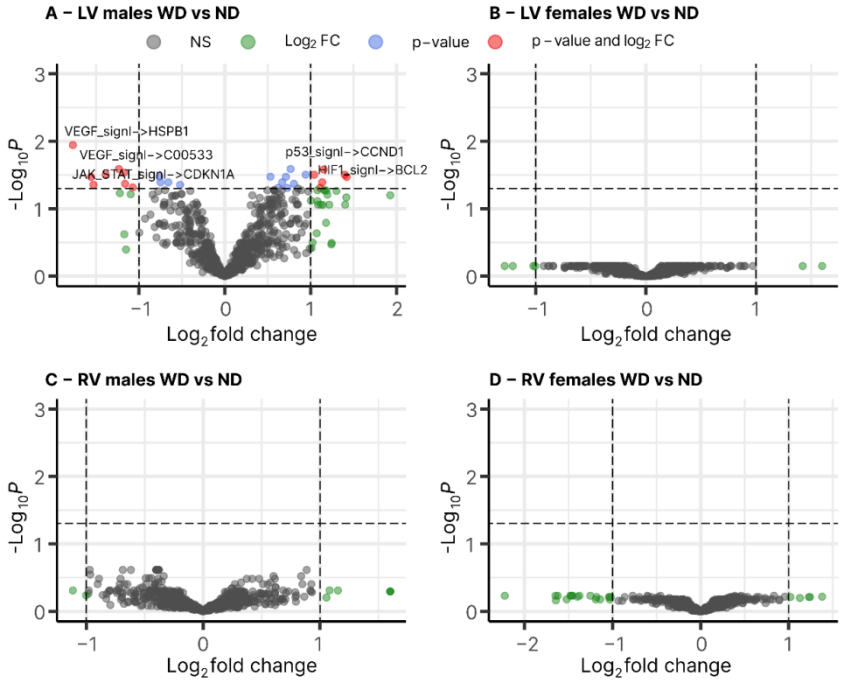

Figure 1. Signaling pathway activity perturbations (log2PSF) in LV and RV tissues associated with Western diet. The results of differential pathway deregulation analysis are presented as Volcano plots. The horizontal line represents the -log10 FDR adjusted p-value threshold equal to 0.05 (-log10(0.05) = 1.30). Vertical lines represent log2PSF = ±1 threshold. A) Pathway deregulation profiles in LV of WD-exposed male mice. B) Pathway deregulation profiles in LV of WD-exposed female mice. C) Pathway deregulation profiles in RV of WD-exposed male mice. D) Pathway deregulation profiles in RV of WD-exposed female mice.

In WD-fed males we observed downregulation of pathway signals in 4 branches of VEGF signaling pathway associated with focal adhesion (VEGF_signl → PXN log2PSF = -1.38, pFDR = 0.031), actin reorganization (VEGF_signl → HSPB1, log2PSF = -1.77, pFDR = 0.011), NO production (VEGF_signl → C00533, log2PSF = -1.23, pFDR = 0.026), angiogenic response (VEGF_signl → SHC2, log2PSF = -1.17, pFDR = 0.029). The Erbb signaling pathway converged at the downregulated signal at cyclin-dependent kinase inhibitors associated with cell cycle control (ErbB_signl → CDKN1A, log2PSF = -1.16, pFDR = 0.042) and JAK-STAT (JAK_STAT_signl → CDKN1A, log2PSF = -1.53, pFDR = 0.044). Furthermore, downregulation was observed for the pathway signal at the mitochondrial permeability transition node in the cGMP-PKG signaling pathway (cGMP_PKG_signl → PPIF, log2PSF = -1.56, pFDR = 0.034). Finally, in the Endocrine resistance

pathway, we observed downregulation of apoptosis machinery signal converged at the BIK node (Endocrine_res → BIK, log2PSF = -1.07, pFDR = 0.048).

Upregulated pathway signals in LV tissue of male mice were mostly associated with TGF-beta (TGFb_signl → ROCK1, log2PSF = 1.40, pFDR = 0.031), FOXO (FoxO_signl → ATM, log2PSF = 1.42, pFDR = 0.034), HIF-1 (HIF1_signl → BCL2, logPSF = 1.14, pFDR = 0.041), cAMP (cAMP_signl → PTCH1, log2PSF = 1.11, pFDR = 0.049), p53 (p53_signl → CCND1, log2PSF = 1.15, pFDR = 0.026), and Apoptosis (Apoptosis → TP53AIP1, log2PSF = 1.04, pFDR = 0.031).

4. Discussion

In this paper, we studied the long-term effects of WD on the signaling activity state in the ventricular tissue of the heart. Our findings show that the WD consumption, even for some time, still leaves the footprint of pathway deregulation on the left ventricular tissue of male mice (Figure 2).

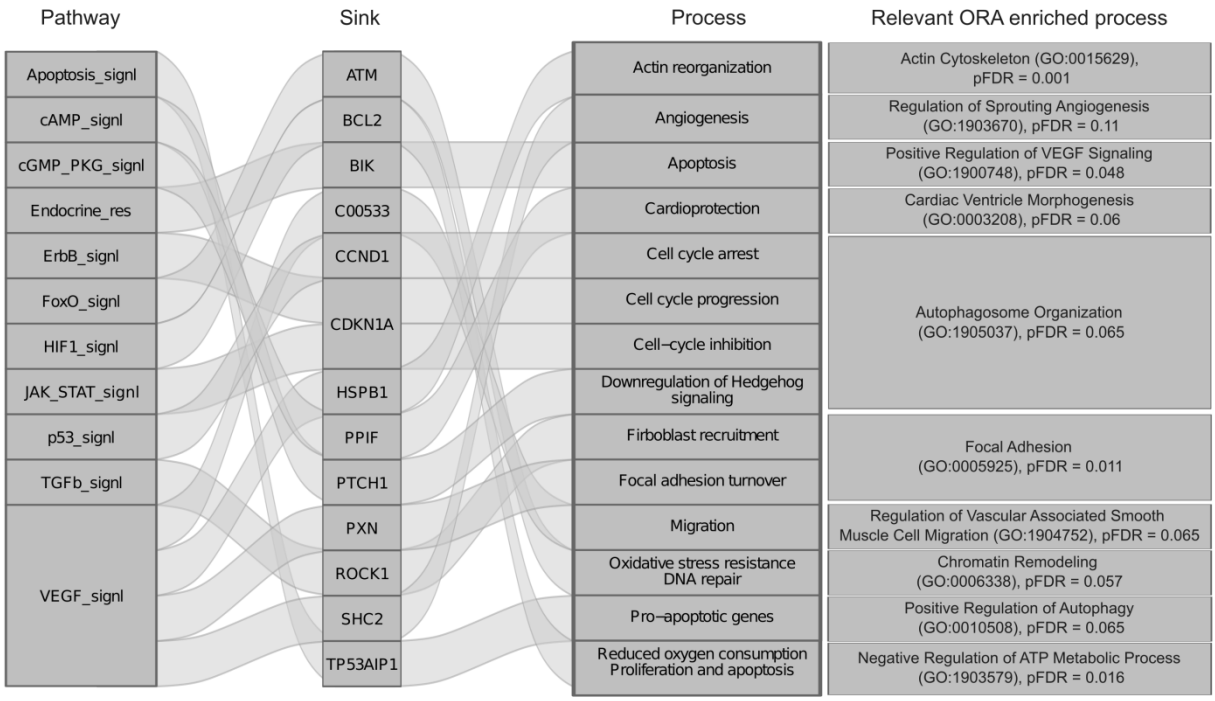

Figure 2. Association of significantly deregulated pathways with biological processes in LV tissues of WD-exposed males. The results are presented as Sankey plots connecting a pathway to its sink node and the sink node to the associated biological process. Information about pathway node-node and node-process interactions was retrieved from the KEGG Pathway database (https://www.genome.jp/kegg/pathway.html). The results of over-representation analysis with conventional differential expression analysis are also presented (right column). The full list of differentially expressed genes and enriched GO terms are presented in Additional tables S5 and S6.

Orthogonal validation using conventional differential gene expression analysis followed by functional enrichment confirmed that biological processes associated with significantly altered PSF sinks were enriched at the Gene Ontology process level (Additional Tables S5 and S6). No differences in pathway perturbation levels were observed for LV tissue in females and RV tissues in both males and females. Furthermore, neither LV in females nor RV tissues for both sexes showed significant pathway deregulation. This finding is well aligned with our previous results showing the massive deregulation in LV transcriptome at 530 days in male mice (~1500 differentially expressed genes

(DEGs) compared to females 8 DEGs), and a small number of DEGs in RV for both sexes, as it is evident from our preliminary results [3,5].

In male animals, we observed strong pathway branch deregulations promoting cardiac damage in the LV tissue. VEGF signaling pathway is known to play an important role in cardioprotection [6,7]; here we observed the downregulated pathway activity for branches associated with focal adhesion, cytoskeleton rearrangement, and NO production, all playing an important role in cardiac function recovery [8,9]. Furthermore, the activation of the TGFbeta-ROCK cascade can further exacerbate heart damage through fibrotic remodeling [10] as also shown in our previous study [3]. The cGMP-PKG pathway showed a strong inhibitory signal at *PPIF* (cyclophilin D) associated with mitochondrial permeability transition [11]. It has been shown that $Ppif^{-/-}$ mice are more prone to metabolic heart failure [12], supporting our observations. Furthermore, we also observed activation signals of IGF1 and EGF1 branches in the FOXO pathway that converged on the *ATM* gene previously implicated in cardiac failure associated with a high-fat, high-sugar diet [13].

We observed a variety of pro- and anti-apoptotic signals coming from different pathways. The observed upregulation of pro-apoptotic signals alongside anti-apoptotic signals and the downregulation of cell cycle inhibitors (Figure 2).

This balance may represent a compensatory mechanism where the tissue attempts to mitigate damage by promoting cell survival pathways, while also activating apoptotic pathways to eliminate severely damaged cells [14,15]. The net effect on cardiac function would depend on the predominance of these opposing signals and the heart's ability to manage cellular stress. These results are consistent with previously reported HFrEF phenotype in males later in life [16]. The absence of significant changes in RV and LV tissue in females can be connected to differences in sex-specific responses to a high-fat, high-sugar diet [17] and structural and functional differences between the heart’s ventricles [18].

It should be noted that we did not consider the individual levels of gene expression. Instead, we performed a systems-level analysis focusing on signal propagation through signaling pathway branches [6]. This allowed us to detect significant perturbations within pathways induced by small but orchestrated changes in expression values and affected by interactions between pathway components [19].

The apparent limitation of our study is the small number of samples in the experimental groups. Moreover, because of the limited number of pathways in the analysis, we may overlook other effects in RV tissues or in female animals associated with other pathways not included in this study. Another limitation of our study is the absence of gene expression data during the WD feeding period and immediately after switching from WD to ND, which prevents direct tracking of early diet-associated molecular events. However, previous characterization of this cohort during the active Western Diet (WD) feeding phase (14–28 days) revealed systolic dysfunction and transient hypertrophic signaling in male animals [20]. Furthermore, independent research has shown that even short-term WD exposure in male mice induces hypertrophy coordinated by repressor element 1-silencing transcription factor at the level of chromatin [21]. Finally, aligned with our results, other studies indicate that while a dietary switch causes reversal of metabolic gene signatures, structural and functional remodeling pathways are less plastic [22].

Our topology-aware pathway analysis reveals long-term perturbations in signaling pathway branches that influence cardiac function in the left ventricular tissue of male mice exposed to a Western diet. These findings suggest that the impact of diet may persist even after transitioning to a healthier diet, warranting further studies to elucidate diet-associated risks and develop strategies for their mitigation.

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Supplementary Materials: Additional tables and figures associated with this study are deposited in the Zenodo repository (See Data Availability Section).

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Informed Consent Statement: Not applicable.

Data and Code Availability Statement: The raw sequencing data is available in the Gene Expression Omnibus (Accession: GSE272168). Additional tables and figures associated with this study are deposited in the Zenodo repository (https://zenodo.org/records/17879619).

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Conflicts of Interest: All authors declare no conflict of interest.

ԱՄՓՈՓԱԳԻՐ

«Արևմտյան» սննդակարգով պայմանավորված կենսաբանական ուղիների երկարատև ակտիվությունը սրտի փորոքային հյուսվածքներում

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«Արևմտյան սննդակարգը» (ԱՍ), որը բնորոշվում է ճարպերի և շաքարների բարձր պարունակությամբ, սերտորեն ասոցացված է սրտանոթային հիվանդությունների բարձր ռիսկի հետ: Սույն հետազոտությունում գնահատվել են կենսաբանական ազդանշանային ուղիների ակտիվությունների երկարատև փոփոխությունները 125 օր ԱՍ-ով կերակրված, ապա նորմալ սննդակարգի (ՆՍ) անցած C57Bl/6J մկների ձախ (ՁՓ) և աջ (ԱՓ) փորոքների հյուսվածքներում: ՁՓ և ԱՓ հյուսվածքները հավաքվել են 530-րդ օրը՝ ՆՍ-ին անցնելուց 105 օր անց, և ենթարկվել ՌՆԹ սեքվենավորման: Քառասուն ազդանշանային ուղիների ակտիվությունը հաշվարկվել է մեր կողմից մշակված Pathway Signal Flow (PSF) ալգորիթմի միջոցով, որը գնահատում է կենսաբանանական ազդակի տարածումը ուղու երկայնքով՝ հիմնվելով ուղու բաղադրիչների գենային էքսպրեսիայի մակարդակների և այդ բաղադրիչների փոխազդեցությունների վրա: Արդյունքների համաձայն՝ ՆՍ-ին անցնելուց 105 օր անց արու մկների ՁՓ հյուսվածքում հայտնաբերվել են ակտիվության էական շեղումներ ազդանշանային ուղիների 14 ճյուղերում: Մասնավորապես, նկատվել է կարդիոպրոտեկտոր VEGF ազդանշանային ուղու ակտիվության նվազում և ֆիբրոզ խթանող TGF-beta ուղու ակտիվացում, ինչը վկայում է սրտանոթային ռիսկերի երկարաժամկետ պահպանման մասին: Բացի այդ, հայտնաբերվել է cGMP-PKG և FOXO ուղիներում ազդանշանի ակտիվացում, ինչը կարող է կապված լինել սրտային անբավարարության հետ: Միաժամանակ նկատվել է ինչպես հարապոպտոտիկ, այնպես էլ հակաապոպտոտիկ ուղիների ակտիվացում, որն ուղեկցվում է բջջային ցիկլի արգելակիչների ակտիվության նվազմամբ: Հատկանշական է, որ էական փոփոխություններ չեն հայտնաբերվել էգ մկների ՁՓ հյուսվածքում և երկու սեռերի ԱՓ-ի հյուսվածքում: Ստացված արդյունքները ցույց են տալիս, որ ԱՍ-ի բացասական

ազդեցությունները կարող են պահպանվել նույնիսկ առողջ սննդակարգի անցնելուց հետո: Անհրաժեշտ են հետագա ուսումնասիրություններ՝ սննդակարգի հետ կապված ռիսկերը պարզաբանելու և այդ երկարաժամկետ ազդեցությունները մեղմելու արդյունավետ ռազմավարություններ մշակելու համար:

Բանալի բառեր՝ արևմտյան սննդակարգ, ձախ փորոք, աջ փորոք, ՌՆԹ սեքվենավորում, տրանսկրիպտոմիկա, ազդանշանային ուղիներ, Pathway Signal Flow