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Comparative Systems Biology Analysis of Human and Primate Diets Reveals Enhanced Lipogenic Activity

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ABSTRACT

Compared to primate species, the human diet features increased calories, higher protein levels, and the incorporation of cooking methods. This research sought to examine the variations between the human diet and the chimpanzee diet, which mainly includes fruits and vegetables, aiming to uncover both positive and negative impacts of human eating habits. Data on differentially expressed genes (DEGs) in mouse liver tissues following exposure to a "human cafeteria diet" versus a "chimpanzee diet" were retrieved from the Gene Expression Omnibus (GEO) repository. These DEGs were filtered according to adjusted p-value and fold change thresholds. The selected significant DEGs were then integrated into a protein-protein interaction (PPI) network to build an interactome model. Key hub nodes in this network were identified using metrics such as degree and betweenness centrality. Subsequently, these pivotal genes underwent gene ontology analysis. A set of 150 notable DEGs capable of distinguishing between the two dietary conditions was identified. Among them, fatty acid synthase (FASN), stearoyl-CoA desaturase (SCD), and farnesyl-diphosphate farnesyltransferase 1 (FDFT1) emerged as the most prominent central DEGs. Two prominent biological process categories associated with these key DEGs were "Activation of gene expression by SREBF (SREBP)" and "NR1H2 & NR1H3 regulate gene expression linked to lipogenesis." Evidence from this analysis points to the human cafeteria diet acting as a promoter of lipogenesis relative to the vegetable-dominant chimpanzee diet. Such human dietary practices were linked to heightened activity of enzymes involved in fatty acid synthesis, coupled with greater cholesterol buildup in tissues.

Keywords: Fatty acid, Human, Mouse, Network, Nutrition

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Introduction

A major cultural distinction separating humans from other primates lies in dietary habits. Human consumption patterns typically involve greater energy density, elevated protein intake, and food preparation through cooking, unlike those observed in primate counterparts [1]. The connection between nutritional intake and human well-being has long been recognized and extensively studied across various life stages [2, 3]. Furthermore, interactions between medications and food intake, along with the potential toxicity of certain dietary items, have prompted expanded research into human nutrition [4, 5]. Considering the profound influence of diet on physical and mental health, as well as its role in disease prevention, the development of safe consumables has become a priority for specialists and food-related sectors. Key quality controls encompass suitable physical, chemical, and microbial properties, appropriate preparation techniques, and effective preservation strategies to ensure product safety [6]. Numerous studies have highlighted the advantageous effects of plant-focused diets on overall health [7].

Foods that are either beneficial or detrimental can modify gene expression patterns in those who consume them; consequently, analyzing gene expression changes under particular dietary conditions serves as an effective method to evaluate nutrition's potential as a health promoter or disease contributor [8, 9]. Genomic approaches allow for the simultaneous assessment of expression levels across thousands of genes in one analysis, although variability

exists among genes. Bioinformatics complements genomics by aiding in data interpretation, a synergy apparent in many studies that enhances the practical utility of genomic insights [10, 11].

Analysis of protein-protein interaction (PPI) networks is a recognized approach for pinpointing essential genes, proteins, or metabolites from extensive datasets. Examining network topology reveals centrality measures for nodes. Degree and betweenness centrality are two frequently employed indicators in biological and health-related research. High-degree nodes, referred to as hubs, are vital for network operations. Nodes exhibiting elevated betweenness centrality, termed bottlenecks, are also deemed indispensable. Multiple studies have underscored the significance of combined hub-bottleneck nodes in driving biological mechanisms [12-14]. Gene ontology provides another established framework for deciphering shifts in gene expression [15].

Here, mouse liver gene expression data were sourced from GEO to illuminate how primate versus human dietary patterns impact the mouse liver. Human eating styles may involve overarching elements that broadly affect health outcomes.

Materials and Methods

Ethical consideration

Approval for this research was granted by the ethics committee at Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1402.265).

Data collection

Expression profiles from livers of 18 mice, categorized into three groups designated as H, C, and P, were obtained from the GSE6297 series in the GEO database (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=gse6297).

Animals

Each group consisted of **six mice**. The P group received a “mouse pellet diet,” whereas the C and H groups were provided with a “chimpanzee diet” and a “human cafeteria diet,” respectively. Following a two-week period, the gene expression profiles in the mice livers were evaluated. The chimpanzee diet included various fruits and vegetables, while the human cafeteria diet consisted of cooked items such as roast beef, boiled potatoes, cooked cabbage, fried vegetables, and baked chicken breast. Additional experimental details and food compositions were outlined in the study by Somel *et al*. [1].

The gene expression data from the H and C groups were compared independently against the P group, and the outcomes were contrasted with those from the H group versus the C group analysis.

Analysis

All evaluations were performed using the GEO2R tool. Volcano plots were generated to display the significant differentially expressed genes (DEGs) alongside other expressed genes. Relevant DEGs were retrieved and examined through comparisons of expression levels. Criteria of p-adj ≤ 0.05 and fold change > 2 were applied to identify significant DEGs. Both shared and distinct significant DEGs from the C-P and H-P comparisons were highlighted for further examination.

The significant DEGs were incorporated into a protein-protein interaction (PPI) network retrieved from the STRING database using Cytoscape software version 3.7.2. Many DEGs initially remained disconnected; thus, an appropriate number of first-neighbor nodes were added to the queried DEGs. The network was built via the “protein query” feature of the STRING database within Cytoscape version 3.7.2 [16]. Network topology was examined using the “Network Analyzer” tool in Cytoscape to calculate node centrality measures. The top 10% of nodes ranked by degree and betweenness centrality were designated as hubs and bottlenecks, respectively. Nodes that qualified as both were identified as hub-bottlenecks. Gene ontology annotations for these hub-bottlenecks were determined using the ClueGO version 2.5.7 plugin in Cytoscape [17]. Biological terms were grouped according to Kappa score.

Statistical analysis

Significance for DEGs was established with p-adj < 0.05. For terms, p-value, Bonferroni step-down corrected term p-value, group p-value, and Bonferroni step-down corrected group p-value below 0.01 were required.

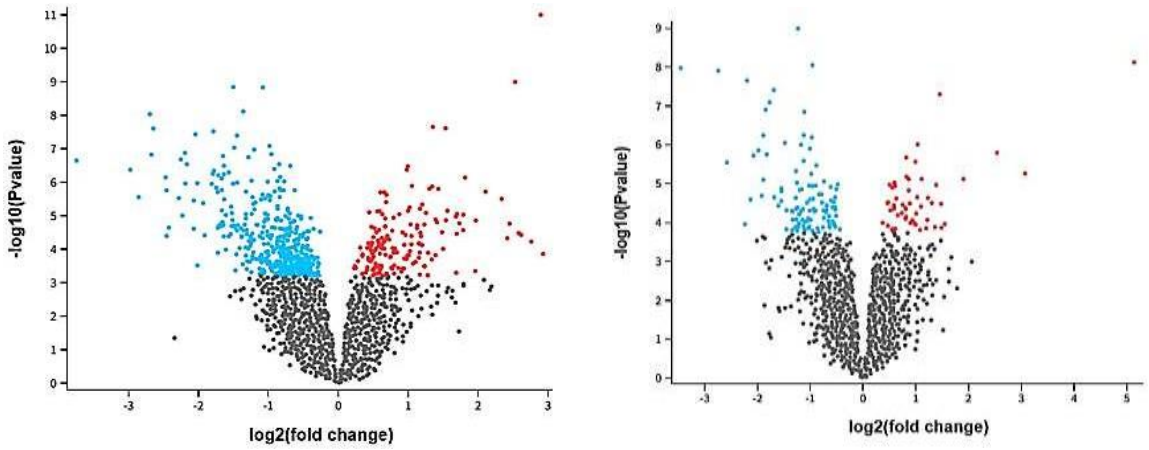
Results and Discussion

Evaluations revealed 44528, 44940, and 45084 expressed genes associated with the C-P, H-P, and H-C comparisons, respectively. A schematic illustration of upregulated and downregulated genes from the two comparisons is displayed in **Figure 1**. As shown, the C and H groups differed from the P group by 576 and 161 DEGs, respectively. Seventeen DEGs distinguished the H and C groups. Further analysis identified 8 significant DEGs common to the H and C group comparisons **(Table 1).**

Of the 576 DEGs in the C-P comparison, 168 were deemed significant, comprising 55 upregulated and 113 downregulated genes. In the H-P comparison, 64 significant DEGs were found, including 20 upregulated and 44 downregulated. Comparison between H-P and C-P revealed 150 unique and 41 shared DEGs. From the 150 unique DEGs, 123 were recognized in the STRING database. To enhance connectivity, the network was formed using these 123 queried DEGs along with 50 additional first neighbors from STRING. The resulting network featured 21 isolated genes, one triplet, one pair of sub-networks, and a primary component with 147 nodes (97 queried DEGs plus 50 added neighbors). The main component is illustrated in **Figure 2.**

Centrality analysis of the network identified three hub-bottleneck DEGs: FASN, SCD, and FDFT1. Characteristics of these hub-bottlenecks are detailed in **Table 2.** Associated biological terms for FASN, SCD, and FDFT1 are shown in **Figure 3 and Table 3.**

Given the close connection between human health and lifestyle, dietary habits play a vital role in sustaining overall well-being. Numerous studies emphasize nutrition as a fundamental factor in human health [18]. Researchers have explored the impacts of lifestyle changes and diet on health outcomes [19]. Somel *et al*. examined how switching dietary regimens affected mouse liver gene expression, presenting profiles from mice on "mouse pellet diet," "chimpanzee diet," and "human cafeteria diet" [19]. In this work, those profiles were reanalyzed to detect potential variations arising from human dietary patterns compared to those of primates.



a) b)

Figure 1. Volcano plots for the C-P group comparison (a) and H-P group comparison (b). Upregulated and downregulated DEGs are shown in red and blue, respectively; p-adj ≤ 0.05

Table 1. Significant DEGs distinguishing the C and H groups

Gene symbol	Gene description	p-adj	LogFC
Cyp2b10	Cytochrome P450, family 2, subfamily b, member 10	0.00332	2.522
Keg1	Kidney-enriched gene 1	0.02176	1.934
Id3	Inhibitor of DNA binding 3, HLH protein	0.01479	1.468
Id1	Inhibitor of DNA binding 1, HLH protein	0.02686	1.153
Pklr	Pyruvate kinase, liver and RBC isoform	0.03783	-1.256
Fasn	Fatty acid synthase	0.03145	-1.398
Rgs16	Regulator of G-protein signalling 16	0.01542	-2.924
Gck	Glucokinase (hexokinase 4)	0.00907	-2.947

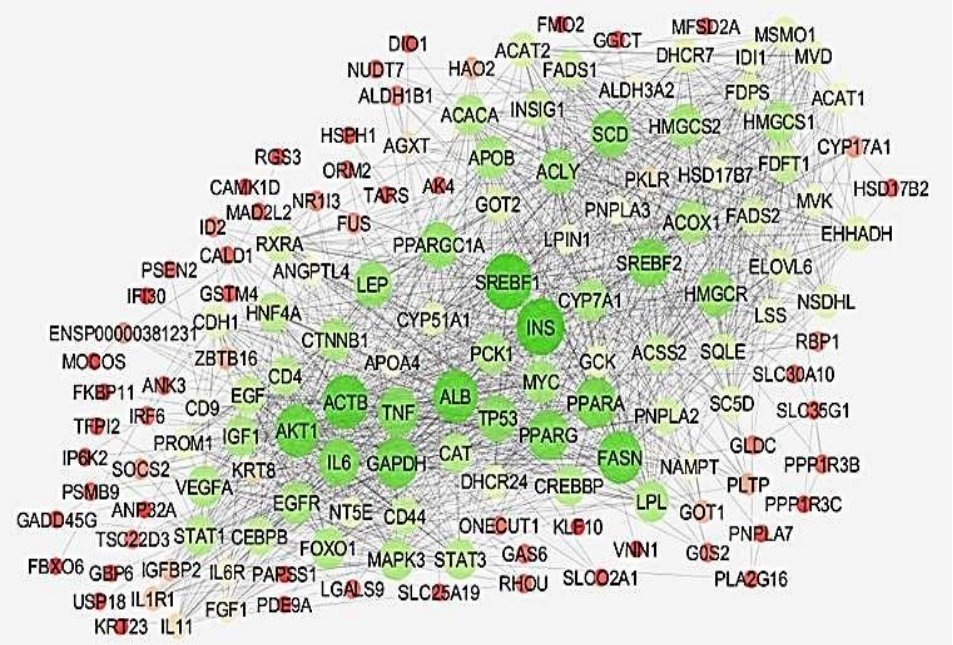


Figure 2. Main component of the PPI network constructed from 123 unique DEGs plus 50 added first neighbors, derived from the H-P and C-P comparisons; node layout is determined by degree value, with larger size and greener color indicating higher degree

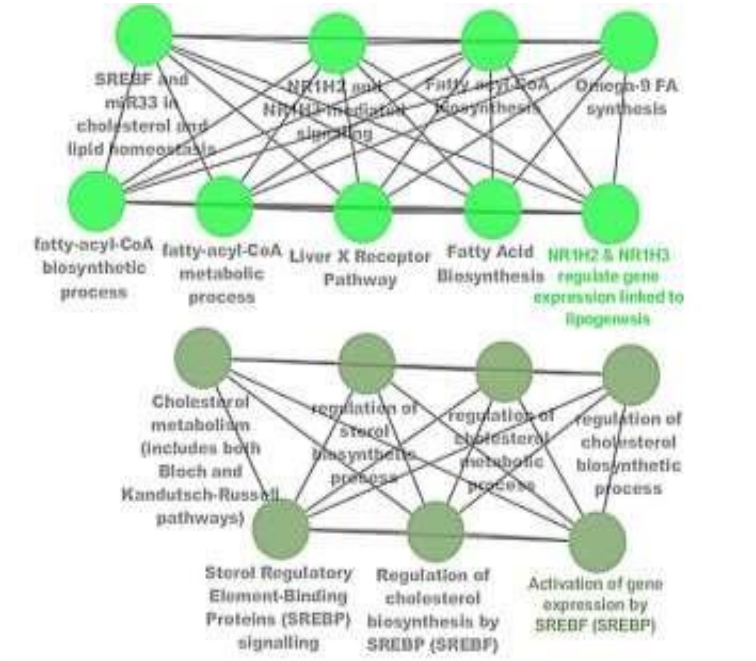


Figure 3. Gene ontology enrichment results for the hub-bottlenecks; term p-value, Bonferroni step-down corrected term p-value, group p-value, and Bonferroni step-down corrected group p-value were all below 0.001; ontology sources included REACTOME_Pathways_08.05.2020, WikiPathways_08.05.2020, and GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_08.05.2020_00h00

Table 2. Hub-bottleneck queried DEGs in the primary connected component of the PPI network from the H-P versus C-P comparisons

Display name	Degree	Betweenness centrality	Closeness centrality	Stress
FASN	60	0.032	0.59	14860
SCD	51	0.015	0.55	8902
FDFT1	34	0.019	0.46	4320

P group: received mouse pellet diet; C and H groups received “chimpanzee diet” and “human cafeteria diet,” respectively.

Table 3. Gene ontology enrichment associated with the FASN, SCD, and FDFT1 hub-bottlenecks

Group	Pathway or GO Term Description	Associated Genes
1	SREBP (SREBF)-mediated regulation of cholesterol biosynthesis	[FASN, FDFT1, SCD]
	SREBF (SREBP)-dependent activation of gene transcription	[FASN, FDFT1, SCD]
	Signaling cascade involving Sterol Regulatory Element-Binding Proteins (SREBP)	[FASN, FDFT1, SCD]
	Cholesterol metabolic pathway (encompassing Bloch and Kandutsch-Russell branches)	[FASN, FDFT1, SCD]
	Control of cholesterol metabolism	[FASN, FDFT1, SCD]
	Control of cholesterol biosynthesis	[FASN, FDFT1, SCD]
	Control of sterol biosynthesis	[FASN, FDFT1, SCD]
	Synthesis of fatty acyl-CoA	[FASN, SCD]
	Signaling mediated by NR1H2 and NR1H3	[FASN, SCD]
	Regulation of lipogenesis-related gene expression by NR1H2 and NR1H3	[FASN, SCD]
	Role of SREBF and miR33 in maintaining cholesterol and lipid balance	[FASN, SCD]
2	Liver X Receptor (LXR) signaling pathway	[FASN, SCD]
	Biosynthesis of fatty acids	[FASN, SCD]
	Synthesis of omega-9 fatty acids	[FASN, SCD]
	Metabolism of fatty-acyl-CoA	[FASN, SCD]
	Biosynthetic process for fatty-acyl-CoA	[FASN, SCD]

Term p-value, Bonferroni step-down corrected term p-value, group p-value, and Bonferroni step-down corrected group p-value were all below 0.001; bold terms denote group names.

As illustrated in **Figure 1**, both the "chimpanzee diet" and "human cafeteria diet" triggered alterations in gene expression within mouse liver tissue. However, the patterns of change differed between the two, suggesting that identifying these distinctions could reveal potential advantages and disadvantages of human dietary practices. A direct comparison **(Table 1)** identified eight significant DEGs that separated the two dietary regimens. The use of PPI network analysis in nutritional studies has been documented previously, with emphasis on its effectiveness for elucidating molecular mechanisms in biological systems [20, 21]. The outcomes of the PPI network analysis in this work are displayed in **Figure 2 and Table 2**.

Fatty acid synthase (FASN) emerged as the leading hub-bottleneck in the PPI network analysis. FASN is recognized as a vital enzyme responsible for de novo fatty acid synthesis and is considered a central regulator in lipid metabolism. Its involvement in cancer-associated signaling pathways has been investigated extensively [22]. According to **Table 1,** FASN expression was reduced in mouse liver under the chimpanzee diet relative to the human cafeteria diet.

Gene ontology enrichment results for the hub-bottleneck genes are shown in **Figure 3 and Table 3**. Two prominent categories—"Activation of gene expression by SREBF (SREBP)" (also known as activation of gene expression by sterol regulatory element-binding proteins) and "NR1H2 & NR1H3 regulated gene expression linked to lipogenesis"—encompassing 16 biological terms, stood out as the primary clusters influenced by the shift from primate to human dietary patterns. All identified terms pertained to cholesterol and fatty acid metabolism. The top two hub-bottlenecks, FASN and SCD, participated in every term. Stearoyl-CoA desaturase (SCD) catalyzes the desaturation of stearic acid to oleic acid [23]. SCD expression was lower in the livers of mice on the chimpanzee diet. Overall, these findings demonstrate that the chimpanzee diet suppressed the expression of enzymes involved in fatty acid and cholesterol synthesis and metabolism.

Zhou *et al*. demonstrated a marked increase in FASN protein levels in mice consuming a high-fat diet [24]. The contribution of FASN to obesity development and body weight control has been underscored in research. Studies show that elevated FASN in adipose tissue correlates with reduced insulin sensitivity, greater visceral fat deposition, and higher circulating levels of fasting insulin, RBP4, IL-6, and leptin. Such evidence highlights a key link between lipogenic pathways activated by surplus energy consumption and the onset of obesity and type 2 diabetes [25]. Given that obesity and diabetes pose major threats to human health, the elevated FASN expression induced by the human cafeteria diet versus the chimpanzee diet likely carries multiple adverse effects. This observation may help explain the prevalence of cancers in human populations. Experimental data indicate that fatty acid synthesis enzymes are overexpressed in cancers, with FASN playing a central role. Inhibiting FASN has been proposed as a promising therapeutic strategy for cancer [26]. Carroll *et al*. reported that FASN activity promotes cholesterol biosynthesis [27].

Conclusion

In summary, the human cafeteria diet promotes lipogenesis and is linked to higher levels of fatty acid synthesis enzymes as well as cholesterol buildup in the body. Elevated fatty acid and cholesterol levels are associated with numerous conditions, including diabetes, cancers, and cardiovascular and renal diseases. Accordingly, it is recommended to adjust human dietary habits by incorporating more fruits and vegetables into daily meals while limiting high-risk components typical of cafeteria-style diets. A fundamental shift in human nutritional practices appears warranted.

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