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Original article

Herbal Diet and the Impact of Nutrition on Lipogenic Activity, a System Biology Study

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Abstract

Background and objectives: Human diet is branded with higher caloric and protein content and cooking processes in comparison with the diet of the primate species. The aim of this study was to explore the differences between human diet and chimpanzee diet which consists of fruits and vegetables, to find benefits and harmful aspects of human nutritional behavior. **Methods:** Differentially expressed genes (DEGs) of mouse liver in response to consume "human cafeteria diet" and "chimpanzee diet" were acquired form Gene Expression Omnibus (GEO) database. The DEGs were assessed based on p-adj and fold change criteria. The significant DEGs were included in a protein-protein interaction (PPI) network to form an interactome unit. Central nodes of the studied network were determined based on degree value and betweenness centrality. The identified central genes were evaluated via gene ontology. **Results:** Numbers of 150 significant DEGs that discriminated the two nutrition diet regimes were introduced. Fatty acid synthase (FASN), stearoyl-CoA desaturase (SCD), and farnesyl-diphosphate farnesyltransferase 1 (FDFT1) were pointed out as the central DEGs. "Activation of gene expression by SREBF (SREBP)" and "NR1H2 & NR1H3 regulate gene expression linked to lipogenesis" were highlighted as two classes of the biological terms that were related to the central DEGs. **Conclusion:** The findings indicated that human cafeteria diet is a lipogenic regime compared to the chimpanzee diet which is enriched with vegetables. The studied human nutrition behavior was accompanied with increased level of fatty acid synthesis enzymes beside cholesterol accumulation in body.

Keywords: fatty acid; human; mouse; network; nutrition

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Introduction

Diet is a cultural difference between human and primate species. The human diet is characterized with higher caloric and protein content and cooking processes relative to the diet of the primate species [1]. Correlation between human health and nutrition is an accepted dogma that is investigated by researcher during human life [2,3]. On the other hand drug, nutrition relationship and poisoning properties of some foods, imply development of investigation about human nutrition [4,5]. Due to importance of food effects on human health and psycho-physical well-being and in the prevention of certain diseases, producing safe foods for consumers has

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attracted the attention of experts and the related industries. There are several control parameters such as proper physico-chemical and microbiological stability, cooking methods, and conservation to achieve a safe food [6]. The positive role of vegetable diet on human health has been vastly discussed in literature [7].

The safe and the unsafe foods influence the gene expression profiles of the consumers; therefore, study of gene expression alteration of human under consuming special diet regime is a useful tool to detect the role of nutrition as a risk factor for diseases or a maintenance factor for human health [8,9]. In a genomic study, the investigator is able to detect expression pattern of thousands of genes via a single experiment. However, rate of expression is different for the evaluated genes. Bioinformatics is an associated field to genomics to interpret the findings. Bioinformatics-genomics relationship can be found in many genomic studies. This association facilitates useful application of genomic outcome [10,11].

PPI network analysis is a well-known method to detect critical genes, proteins, or metabolites among large numbers of the studied individuals. Topology analysis of a PPI network leads to introducing centrality parameters of the nodes of the assessed network. Two important centrality parameters which are used frequently to evaluate the biological and medical systems are degree value and betweenness centrality. The nodes with high value of degree are known as hub nodes. The hubs of a network play crucial role in the function of the studied system. The bottleneck nodes are characterized by high value of betweenness centrality. It has been reported that bottlenecks are critical elements of a network. The unique role of hub-bottleneck nodes in progress of the studied process has been reported in different investigations [12-14]. Another well stablished method to understand the alteration of gene expression profile is gene ontology [15].

In the present study, gene expression profiles of mice liver were extracted from GEO to highlight the difference between diet regime of primate species and human on mouse liver. It can be expected that human nutrition style be associated with a gross factor which affects human health.

Material and Methods

Ethical consideration

This project was approved by Shahid Beheshti University of Medical Sciences ethical committee (IR.SBMU.RETECH.REC.1402.265).

Data collection

Gene expression profiles of 18 mice which were grouped in three classes including H, C, and P groups were extracted from GSE6297 of GEO (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=gse6297).

Animals

Each group contained six mice. The P group had been fed with ‘mouse pellet diet” while the C and H groups were fed with “chimpanzee diet” and “human cafeteria diet”, respectively. After two weeks gene expression profiles of mice livers were assessed. Chimpanzee diet contains some fruits and vegetables while human cafeteria diet comprises of cooked foods such as roast beef, boiled potatoes, cooked cabbage, fried vegetables and baked chicken breastMore details of experiment and combination of foods were described in the report of Somel et al. [1].

The gene expression profiles of H and C groups were evaluated versus P group separately and the results were compared with consequence of analysis of H group versus S group.

Analysis

All analyses were done via GEO2R program. Volcano plot analysis was administrated to visualize the significant DEGs beside the other expressed genes. All related DEGs were downloaded and assessed via expression value comparison. p-adj$\leq$ 0.05 and fold change$>$ 2 were considered to determine the significant DEGs. The common and uncommon significant DEGs related to the S-P and H-P analyses were pointed out for more investigations.

The significant DEGs were included in a PPI network from STRING database by Cytoscape network v.3.7.2. A considerable amount of DEGs were remained unbound. Therefore, optimum numbers of the first neighbors were added to the queried DEGs. The network was created by “protein query” application of STRING database via Cytoscape software v 3.7.2 [16]. The PPI network was analyzed via “Network Analyzer” application of Cytoscape to find centrality parameters of the nodes of network. The top 10% of nodes based on degree value and betweenness centrality were selected as hubs and bottlenecks. The common hub and bottleneck nodes were pointed out as hub-bottlenecks. The related gene ontology results for the introduced hub-

bottlenecks were identified via ClueGO v2.5.7 application of Cytoscape software [17]. The biological terms were clustered based on Kappa score value.

Statistical analysis

To find the significant DEGs p-adj < 0.05 was considered. Term p-value, term-p-value corrected with Bonferroni step down, group p-value, group p-value corrected with Bonferroni step down less than 0.01 were considered.

Results and Discussion

Assessments indicated that 44528, 44940, and 45084 expressed genes are related to C-P, H-P, and H-S groups analyses, respectively. The schematic presentation of the up and down – regulated spots of the two analyses are shown in Figure 1. As it is depicted in the figure, S and H groups were discriminated from P group by 576 and 161 DEGs, respectively. Seventeen DEGs appeared as differences between H and C groups. More screening process showed that there were 8 significant DEGs related to the H and S groups analyses (Table 1).

Among the 576 DEGs of S-P analysis, 168 individuals including 55 up-regulated genes and 113 down-regulated individuals were determined as significant DEGs. Sixty four significant DEGs including 20 up-regulated genes and 44 down-regulated DEGs were identified for H-P analysis. Numbers of 150 uncommon and 41 common DEGs were determined from comparison of H-P and C-P analyses. Among the 150 uncommon DEGs, 123 genes were recognized by STRING database. Due to high numbers of connected nodes, the network was constructed by the 123 queried DEGs plus 50 added first neighbors from STRING database. The network including 21 isolated genes, a triple and a paired sub-network, and a main connected component of 147 nodes (97 queried DEGs plus 50 added first neighbors) was shaped. The main connected component is presented in Figure 2.

The network was analyzed and the centrality parameters of nodes were determined. Three hub-bottleneck DEGs were recognized as FASN, SCD, and FDFT1. Properties of hub-bottlenecks are shown in Table 2. The biological terms related to FASN, SCD, and FDFT1 are presented in Figure 3 and Table 3.

Since human health and life style are tied together, nutrition plays a crucial role in maintenance of social health. In many references, nutrition is pointed out as the key of human health [18]. Effect of life style modification and nutrition on human health has been pointed out by researchers [19]. Somel et al. investigated the effect of diet regime change on mouse liver. Three gene expression profiles of the examined mice with “mouse pellet diet”, “chimpanzee diet”, and “human cafeteria diet” were introduced in this research project [19]. In the present study, the mentioned gene expression profiles were assessed to find the possible differences based on nutrition style of human relative to the primate species.

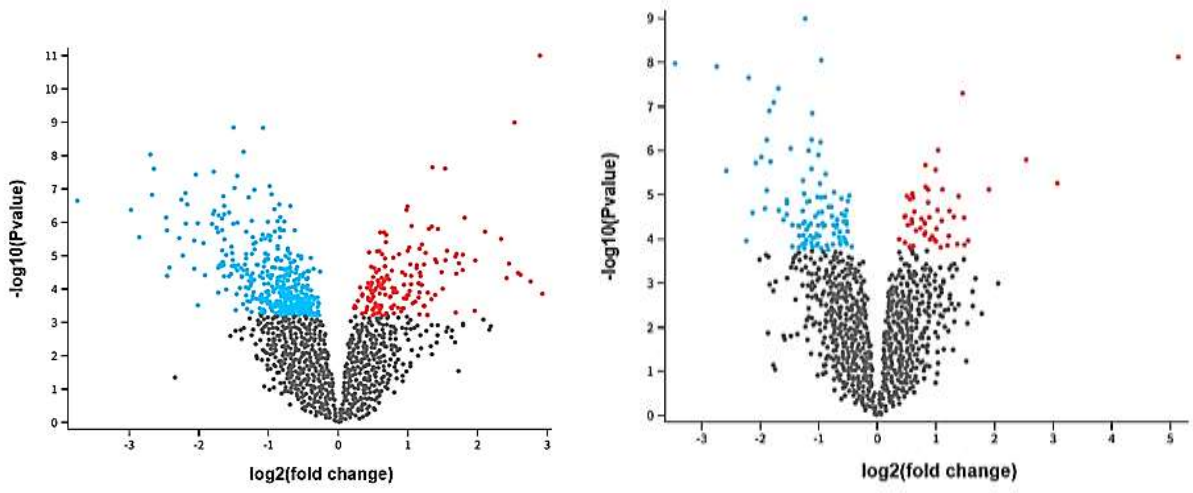

Figure 1. Volcano plot of C-P group (left) and H-P group (right) analyses. Up and down regulated DEGs are presented in red and blue colour, respectively; p-adj ≤ 0.05

Table 1. The significant DEGs which discriminate C and H groups

Gene symbol	Gene title	p-adj	LogFC
Cyp2b10	Cytochrome P450, family 2, subfamily b, polypeptide 10	0.00332	2.522
Keg1	Kidney expressed gene 1	0.02176	1.934
Id3	Inhibitor of DNA binding 3	0.01479	1.468
Id1	Inhibitor of DNA binding 1	0.02686	1.153
Pklr	Pyruvate kinase liver and red blood cell	0.03783	-1.256
Fasn	Fatty acid synthase	0.03145	-1.398
Rgs16	Regulator of G-protein signaling 16	0.01542	-2.924
Gck	Glucokinase	0.00907	-2.947

FC: fold change; p-adj ≤ 0.05

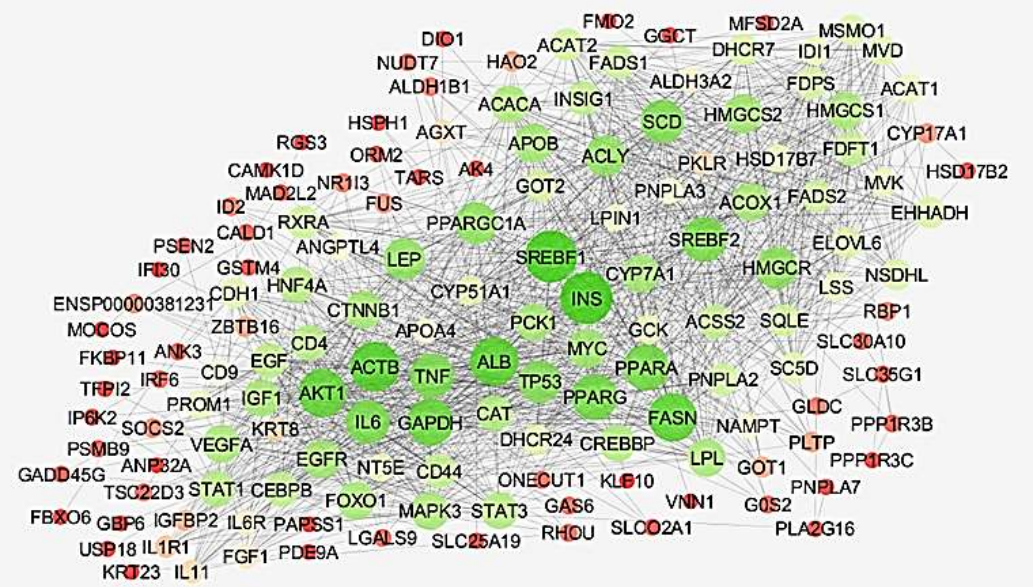

Figure 2. PPI network, main component of 123 uncommon DEGs plus 50 added first neighbors related to the compared H-P and C-P analyses; the nodes layout based on degree value; bigger size and green color refer to increase of degree value

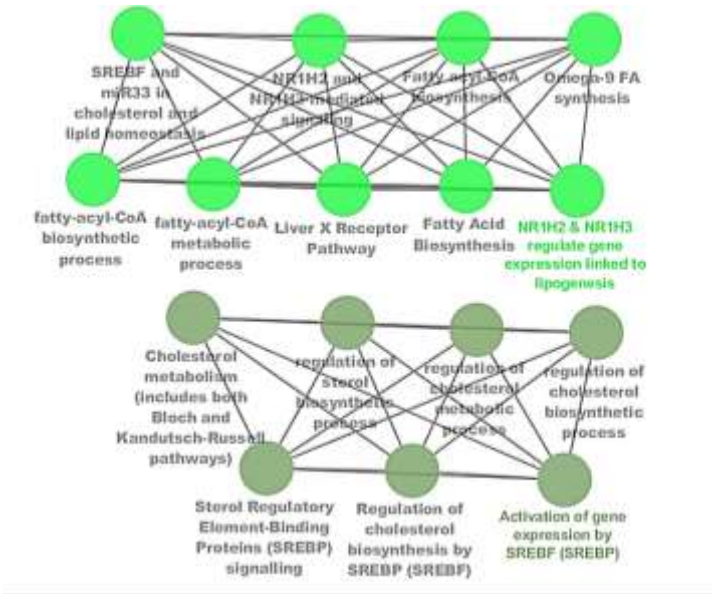

Figure 3. Gene ontology results of the hub-bottlenecks enrichments; term p-value, term p-value corrected with Bonferroni step down, group p-value, and group p-value corrected with Bonferroni step down were less than 0.001; REACTOME_Pathways_08.05.2020, WikiPathways_08.05.2020, GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_08.05.2020_00h00 were used as ontology sources

Table 2. The hub-bottlenecks query DEGs of the main connected component of the PPI network related to the compared H-P and C-P analyses

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: fed with mouse pellet diet; C and P groups were fed with "chimpanzee diet" and "human cafeteria diet", respectively.

Table 3. Gene ontology results related to FASN, SCD, and FDFT1 hub-bottlenecks

Group	GO term	Associated Genes
1	Regulation of cholesterol biosynthesis by SREBP (SREBF)	[FASN, FDFT1, SCD]
	Activation of gene expression by SREBF (SREBP)	[FASN, FDFT1, SCD]
	Sterol Regulatory Element-Binding Proteins (SREBP) signaling	[FASN, FDFT1, SCD]
	Cholesterol metabolism (includes both Bloch and Kandutsch-Russell pathways)	[FASN, FDFT1, SCD]
	Regulation of cholesterol metabolic process	[FASN, FDFT1, SCD]
	Regulation of cholesterol biosynthetic process	[FASN, FDFT1, SCD]
	Regulation of sterol biosynthetic process	[FASN, FDFT1, SCD]
2	Fatty acyl-CoA biosynthesis	[FASN, SCD]
	NR1H2 and NR1H3-mediated signaling	[FASN, SCD]
	NR1H2 & NR1H3 regulate gene expression linked to lipogenesis	[FASN, SCD]
	SREBF and miR33 in cholesterol and lipid homeostasis	[FASN, SCD]
	Liver X Receptor Pathway	[FASN, SCD]
	Fatty Acid Biosynthesis	[FASN, SCD]
	Omega-9 FA synthesis	[FASN, SCD]
	Fatty-acyl-CoA metabolic process	[FASN, SCD]
	Fatty-acyl-CoA biosynthetic process	[FASN, SCD]

Term p-value, term p-value corrected with Bonferroni step down, group p-value, and group p-value corrected with Bonferroni step down were less than 0.001; The bold terms are names of groups.

As it is depicted in Figure 1, both "chimpanzee diet" and "human cafeteria diet" induce gene expression changes in mouse liver. The pattern of alterations was not similar; therefore, detection of differences of the two nutrition styles can lead to prospective of possible benefits and harmful aspects of human life style. A simple comparison (Table 1) revealed that eight significant DEGs discriminated the two assessed nutrition styles. Application of PPI network analysis in nutrition has been reported by researchers before. It has been emphasized that network analysis is a suitable tool to understand molecular event in the studied systems [20,21]. The results of PPI network analysis of the present study are shown in Figure 2 and Table 2.

Fatty acid synthase (FASN) is appeared as the top hub-bottleneck from PPI network analysis. FASN is known as a critical enzyme which is involved in de novo synthesis of fatty acids. It has been reported that FASN is the key player in lipid metabolism. Role of this enzyme in tumor-related signaling pathways has been evaluated by scientist [22]. As it is shown in Table 1, FASN was down-regulated in mouse liver under consuming chimpanzee diet compared to human cafeteria diet.

Results of gene ontology enrichment of the hub-bottleneck genes are presented in Figure 3 and Table 3. "Activation of gene expression by SREBF (SREBP)" or "activation of gene expression by sterol regulatory element-binding proteins" and "NR1H2 & NR1H3 regulated gene expression linked to lipogenesis" containing 16 biological terms appeared as the key classes of the biological terms that were affected by change of diet regime of human relative to the primate species. All terms were involved in cholesterol and fatty acid metabolism. FASN and SCD the first and second ranked hub-bottlenecks are involved in all biological terms. stearoyl-CoA desaturase (SCD) activity leads to rise desaturation of stearic acid to oleic acid [23]. SCD was down-regulated in liver of mice that were fed with chimpanzee diet. The results indicated that chimpanzee diet decreased the expression of enzymes that were involved in metabolism and synthesis of fatty acids and cholesterol.

Zhou et al. showed that protein expression level of FASN gene increases significantly in mice that were fed with high-fat diet [24]. Role of FASN in the development of obesity and regulation of body weight is highlighted by researchers. Investigations indicate that up-regulation of FASN in adipose tissue is associated with

impaired insulin sensitivity, visceral fat accumulation, increased circulating fasting insulin, RBP4, IL-6, and leptin. These findings indicate that there is a critical relationship between lipogenic pathways in response to excess energy intake which leads to development of obesity and type 2 diabetes [25]. Since obesity and diabetes are two important risk factors for the human health, it seems that up-regulation of FASN in response to human cafeteria diet compared to chimpanzee diet is accompanied by several harmful consequences in human body. This finding may describe the development of cancers in human population. Based on the results of the experiments, overexpression of fatty acid synthesis enzymes happens in cancer. Also, it is pointed out that up-regulation of FASN plays pivotal role in this process. It is suggested that targeting FASN can be a suitable method in cancer therapy [26]. Based on the investigation of Carroll et al., promotion of cholesterol production is facilitated by FASN activity [27].

Conclusion

In conclusion, human cafeteria diet is a lipogenic regime and is associated with increased level of fatty acid synthesis enzymes beside cholesterol accumulation in the body. The correlation between arisen levels of fatty acid and cholesterol in body results in many diseases such as diabetes, cancers and kidney and heart diseases. Therefore, modifying the human diet and increasing the amount of fruits and vegetables in daily nutrition routines along with reducing the high risk food items (as in the cafeteria diet) is suggested. It seems that human nutrition behavior should be modified basically.

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Author contributions

Mostafa Rezaei Tavirani designed and supervised the study; Reza Mohamoud Robati, Alireza Ahmadzadeh and Mohammad Rostami Nejad contributed to data collection and analysis; all authors approved the final draft of the manuscript.

Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the accuracy and integrity of the paper content.

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Abbreviations

DEGs: differentially expressed genes; GEO: gene expression omnibus; PPI: protein-protein interaction; FASN: fatty acid synthase; SCD: stearoyl-CoA desaturase; FDFT1: farnesyl-diphosphate farnesyltransferase 1; P: pellet; C: chimpanzee; H: human