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Original Article

Bioinformatics analysis of high-intensity intermittent exercise for prevention of myocardial infarction

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Abstract

The mechanism of target interaction involving high-intensity interval training (HIIT) in improving prognosis of myocardial infarction (MI) remains unclear. This study aimed to establish a visual network of "HIIT-target-disease" by referring to the methods of pharmacological disease and drug bioinformatic analysis, to explore the potential targets, and key targets and predict the potential biological mechanism of high-intensity intermittent exercise in preventing and treating myocardial infarction. Public data resources such as OMIM, NCBI and GeneCards were used to find potential targets of high-intensity intermittent exercise and myocardial infarction. Key targets of overlap between exercise and disease were determined according to the Relevance score values analyzed by GeneCards. The visual network diagram of "HIIT - Multi-target-disease" was constructed by Cytoscape. A total of 4820 disease targets and 528 high-intensity intermittent exercise targets were screened out, and 444 overlapped targets were obtained, including 425 protein targets. Five core protein targets were selected: IL10, PPARA, TNF, IL6, and STAT3. It may pass PI3K-AKT signaling pathway, Insulin resistance pathway, T-cell signaling pathway, TNF signaling pathway, and JAX-STAT signaling pathway and other pathways play a role. Our study comprehensively elucidated the potential targets, key targets and molecular mechanisms of high-intensity intermittent exercise in improving the prognosis of myocardial infarction, and proved that high-intensity intermittent exercise can act on multiple targets and multiple pathways to play a good preventive and therapeutic effect on myocardial infarction, providing scientific theoretical basis for revealing the mechanism of high-intensity intermittent exercise in the prevention and treatment of cardiovascular disease.

Keywords: A target point, Health information analysis, High-intensity interval exercise, Myocardial infarction, Mechanism of action.

1. Introduction

Ischemic heart disease remains a major disease worldwide and is one of the leading causes of death in humans [1]. In recent years, China's clinical data show that the mortality rate, fatality rate and disability rate of acute myocardial infarction remain high [2], and the disease tends to develop in young people, bringing severe tests to China's public health. Most patients with myocardial infarction are accompanied by coronary atherosclerosis, chest pain, fever, tachycardia and other disease manifestations [3], which are mostly due to lipid accumulation, excessive fatigue, arrhythmia and other causes of arterial myocardial ischemia and necrosis. ST-segment elevation and other image examinations are mainly used in clinical diagnosis, and reperfusion therapy is the main treatment method for acute ST-segment elevation myocardial infarction [4]. Reperfusion within 12 h of coronary artery occlusion can reduce the infarct size and mortality [5, 6]. However, reperfusion may further aggravate the death of cardiomyocytes. To increase the infarct size [7, 8], other treatment methods, such as taking statins or surgical treatment, have poor prognosis and high prices, which makes it difficult to improve the clinical treatment effectiveness of cardiovascular diseases.

Cardiac rehabilitation (CR) is an effective adjuvant treatment for the prognosis of patients with myocardial infarction, and exercise training is a powerful tool in CR program [9]. HIIT can enhance the physiological function of the heart and reduce metabolic abnormalities. Exercise can also reduce the risk of diseases associated with aging, such as high blood sugar [10], high blood pressure [11], dyslipidemia, cardiovascular disease, and cancer [12, 13]. In addition, active skeletal muscle can increase venous return, increase left ventricular end-diastolic volume and enhance ventricular systolic function [14]. Previous studies have shown that exercise can significantly reduce myocardial ischemia, increase the content of glutathione in myocardial tissue, and reduce the content of oxidized glutathione. Moderate-intensity exercise can lead to changes in the body's REDOX state and reduce oxidative stress [15]. HIIT can improve cardiopulmonary health, functional performance, heart rate variability, cognitive level and quality of life [16], increase the expression of vascular endothelial growth factor, reduce the expression

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of inflammatory markers (TNF-α, IL6, etc.) [17], enhance sympathetic nerve susceptibility [18], insulin sensitivity [19], and promote normal myocardial function in patients with MI. However, due to the complexity of myocardial infarction and the diversity of movement, the biological mechanism of HIit-target-myocardial infarction has not yet been clarified. This paper aims to predict the potential targets, key targets and possible mechanisms of HIIT prevention and treatment mechanism of myocardial infarction through bioinformatics analysis. It provides scientific theoretical basis for clinical application of high-intensity intermittent exercise therapy to prevent and treat myocardial infarction.

2. Materials and methods

2.1. Data Sources

"High-intensity interval Training" and "Myocardial Infarction "as keywords in OMIM (http://omim.org/), NCBI (https://www.ncbi.nlm.nih.gov/), GeneCards three main database retrieval phase (http://www.Genecards.org/) For the target, the correction target is named "Gene Symbol" and the human target and corresponding gene name are selected.

2.2. Protein-protein interaction network and core protein target Nnetwork

High-intensity intermittent exercise genes and disease genes were mapped into Bioinformatics, and the intersection of the two targets was a potential target for HIIT prevention and treatment of myocardial infarction. Excel was used to screen 444 targets of high-intensity intermittent exercise and myocardial infarction gene repeats, and 5 core protein targets (Table 1) were selected according to the Relevance score values in GeneCards, and the above targets and their upstream and downstream targets were respectively introduced into STRING. The species "Homo sapiens" was selected and "minimum required interaction score>0.90" was set to obtain the protein-protein interaction (PPI) and core protein target network. Adjust the position of nodes in the network to make them compact and orderly, so as to observe the interaction of nodes.

2.3. Gene ontology and Kyoto encyclopedia of genes and genomes enrichment analysis

Gene Ontology (GO) function and Kyto Encyclopedia of Genes and Genomes Enrichment (KEGG) pathway were analyzed using David database. biological processes (BP), Cell composition (CC), molecular function (MF) and KEGG signal pathway analysis data were obtained. Bioinformatics was introduced to draw the enriched bubble map.

3. Results

3.1. Target screening

In OMIM, NCBI and GeneCards databases, 528 genes of high-intensity intermittent exercise and 4820 genes of disease were obtained by screening and removing duplicates. A total of 3926 disease protein targets and 507 high-intensity intermittent exercise protein targets were selected after RNA, gene loci and biomarkers were removed. An intersection of high-intensity intermittent exercise targets and disease gene introduction into Bioinformatics was obtained, and 444 intersection targets were obtained, including 425 protein targets. They accounted for 0.91 and 0.89 of the combined targets respectively (Fig. 1). According to the Relevance score values in GeneCards, five core protein targets were selected: IL6, IL10, TNF, PPARA, and STAT3, which were consistent with the results of GO functional enrichment analysis.

3.2. PPI and core protein target network

528 intersection targets, 507 protein targets, 5 core protein targets and their upstream and downstream targets were respectively imported into STRING, and the "Multiple proteins" tool was selected. Organisms chose to map the intersection of target protein interaction and core protein target network for Homo sapiens (Fig. 2).

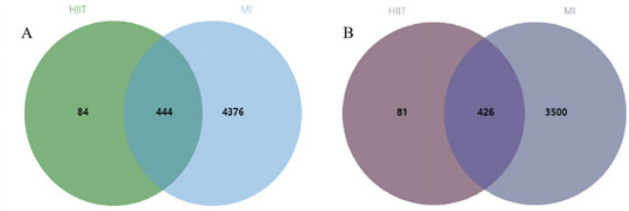

Fig. 1. Venn diagram of overlapped targets. (A) All of overlapped targets: RNA Gene, Protein Coding, Biological Region, Genetic Locus; (B) Protein Coding of overlapped targets.

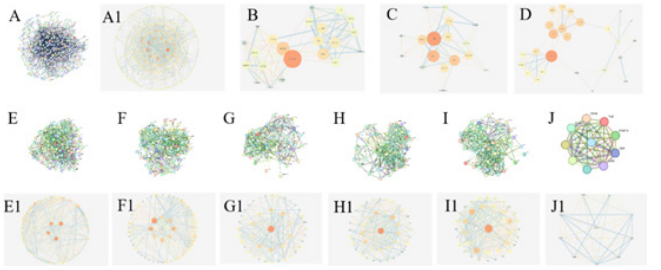

Fig. 2. PPI protein network of high-intensity interval training-myocardial infarction. (A-A1) The interactive PPI network was obtained from STRING database with the minimum required interaction score set to 0.90. PPI network imported from STRING database to Cytoscape 3.7.1. (B-D) High-density subnetwork diagram in PPI network of core proteins (E-E1) Core PPI network of core proteins. (F-F1) PPI network of PPAPA target. (G-G1) PPI network of TNF. (H-H1) PPI network of IL10. (I-I1) PPI network of IL6. (J-J1) PPI network of STAT. Higher degree values indicate larger node sizes. Red indicates a higher degree, and yellow represents a lower degree.

Table 1. Relevance score of the core target in the Genecards.

Gene	Name	High-light interval training	Myocardial infarction
IL10	Interleukin 10	11.38	26.36
IL6	Interleukin 6	13.65	29.47
TNF	Tumor Necrosis Factor	9.55	25.39
PPARA	Peroxisome Proliferator Activated Receptor Alpha	4.00	14.54
STAT3	Signal Transducer And Activator Of Transcription 3	2.95	11.94

3.3. Functional enrichment analysis and KEGG pathway analysis

1670 GO enrichment items and 161 KEGG signaling pathways were obtained by biological functional pathway analysis. The results of GO functional enrichment included BP1313, CC149 and MF208. The top 20 entries in each group of GO functional enrichment were selected to draw bar charts and bubble charts, showing BP, CC and MF with the highest gene counts (Fig. 3A-C). The KEGG pathway was selected to analyze the top 20 signaling pathways with P-value, and bar charts and bubble charts were drawn (Tables 2-5). The KEGG pathway was applied to explore the function and signaling pathways of high-intensity intermittent exercise on myocardial infarction targets (Fig. 3D). As shown in the figure, core protein targets may play a role in several signaling pathways such as Insulin resistance pathway, T-cell signaling pathway, and TNF signaling pathway.

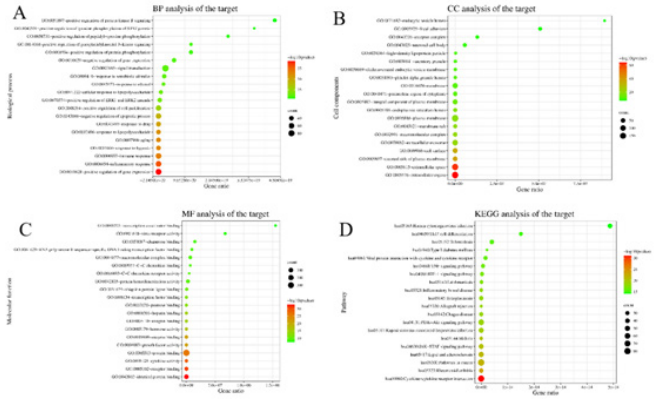

Fig. 3. The Bubble diagram of GO function and KEGG pathway analysis. High-intensity interval Training-Myocardial infarction genes, including the top 20 significant enrichment terms of BP, CC, MF and KEGG. The abscissa represents the proportion of genes of interest in the entry, and the ordinate represents each entry. The larger size of a dot indicates the larger number of genes annotated in the entry, and the redder color of a dot stands for the lower the q value. (A) BP analysis of the target (B) CC analysis of the target (C) MF analysis of the target (D) KEGG pathway analysis.

4. Discussion

The positive effects of exercise on cardiovascular health have been widely recognized, which involve several systems such as nervous, endocrine, metabolic, and immune systems. Recent studies have shown that high-intensity intermittent exercise is a training technique for all-out, rapid and explosive exercise in a short period of time, which can increase the body's vital capacity, maximum oxygen uptake, reduce insulin resistance, improve the capacity of myocardial mitochondria, etc., reshape the ventricular structure, enhance the heart function, and promote cardiovascular health. It has been proved that the process of HIIT prevention and treatment of myocardial infarction has multi-target and multi-pathway characteristics, and its mechanism of promoting myocardial infarction has not been clearly demonstrated. Therefore, in this paper, biological information analysis method was used to construct a visual network of HIIT-target-disease, in order to explore the potential targets, key targets and mechanisms of high and mild intermittent exercise to improve the prognosis of myocardial infarction. This study identified the key targets of high-intensity intermittent exercise for prevention and treatment of myocardial infarction: IL10, PPARA, TNF, IL6, STAT3, It may play a role through several signaling pathways, such as PI3K-AKT signaling pathway, Insulin resistance pathway, T-cell signaling pathway, and TNF signaling pathway.

Using human protein mapping website (https://www.proteinatlas.org), IL10 and PPARA, TNF, IL6 and STAT3 input, in order to get HPA map, informed by HPA map above targets in different tissues and organs of the human of RNA and protein expression level of the situation, It was found that the RNA levels of these targets were expressed to some extent in most organs, but their proteins were only expressed in a small number of organs, and their abnormal expression was associated with the occurrence of adverse cardiovascular events (Fig. 4). IL-10 is an anti-inflammatory cytokine that can play a protective role in cardiovascular diseases such as human atherosclerosis [20], acute coronary syndrome [21], unstable angina [22] and heart failure [23]. This cytokine can block NF-kappa B activity and is involved in regulating the JAK-STAT signaling pathway. STAT3 is a member of the STAT protein family. Under the action of cytokines and growth factors, STAT3 is phosphorylated to form a homologous or heterodimer that translocates into the nucleus and acts as a transcriptional activator. This protein mediates the expression of multiple genes in response to cellular stimulation and therefore plays a key role in many cellular processes, such as cell growth and apoptosis. In experiments in mice and pigs, IL10 has been shown to prevent cardiac necrosis after myocardial ischemia/reperfusion [24]. The IL6 gene encodes cytokines that play a role in inflammation and B-cell maturation. This protein is mainly expressed at the site of acute and chronic inflammation, and is subsequently secreted into the serum and induces transcriptional inflammation through the IL6 receptor. The inflammatory response mediated by M1-type pro-inflammatory factors such as TNF family and IL6 participate in the occurrence and development of myocardial infarction. Studies have shown that M1-type macrophages in rats with myocardial infarction increase and M2-type macrophages decrease, which aggravate the deterioration of new functions [25]. Regular physical exercise can up-regulate the expression of M2-type anti-inflammatory factors such as IL10, and inhibit the release and expression of M1-type pro-inflammatory factors such as TNF-α and IL6 [26]. The action of peroxisome proliferators is thought to be mediated by receptors in the PPAR family, a steroid hormone receptor that affects the expression of target genes involved in cell proliferation, cell differentiation, and immune and inflammatory responses. In patients with myocardial infarction, glucose and amino acid levels are often low, fat levels are high, and the expression of PPARA is down-regulated. These findings indicate that β-oxidation of fatty acids is reduced [27], and the expression of PPARA is activated under hypoxia, thus reducing the disorder of lipid metabolism during myocardial ischemia [28]. Experiments have shown that when PPARA is absent, exercise cannot regulate the pro-inflammatory response, and the absence of PPARA will lead to the homeostasis imbalance of anti-inflammatory response [29]. These findings once again prove that high-mild intermittent exercise can improve the prognosis of myocardial infarction by regulating the expression of multiple target proteins such as IL10, PPARA,

Table 2. BP of core targets in GO function.

BP Term	Count	P-value	Bonferroni	FDR
positive regulation of gene expression	75	3.86E-39	1.76E-35	1.51E-35
inflammatory response	66	6.48E-37	2.96E-33	1.27E-33
immune response	68	5.48E-34	2.50E-30	7.13E-31
response to hypoxia	45	2.30E-33	1.05E-29	2.25E-30
aging	46	2.97E-33	1.36E-29	2.32E-30
response to lipopolysaccharide	42	1.30E-32	5.95E-29	8.50E-30
response to drug	52	3.82E-31	1.74E-27	2.13E-28
negative regulation of apoptotic process	65	1.38E-29	6.31E-26	6.76E-27
positive regulation of cell proliferation	62	5.17E-26	2.36E-22	2.24E-23
positive regulation of ERK1 and ERK2 cascade	40	1.20E-23	5.47E-20	4.68E-21
cellular response to lipopolysaccharide	37	2.61E-23	1.19E-19	9.29E-21
response to ethanol	32	5.69E-23	2.59E-19	1.85E-20
response to xenobiotic stimulus	40	7.05E-23	3.22E-19	2.12E-20
signal transduction	89	9.22E-23	4.21E-19	2.57E-20
negative regulation of gene expression	44	2.21E-22	1.01E-18	5.76E-20
positive regulation of phosphatidylinositol 3-kinase signaling	26	5.20E-22	2.37E-18	1.20E-19
positive regulation of protein phosphorylation	37	5.21E-22	2.38E-18	1.20E-19
positive regulation of peptidyl-tyrosine phosphorylation	27	1.18E-21	5.40E-18	2.57E-19
positive regulation of tyrosine phosphorylation of STAT protein	24	1.72E-21	7.86E-18	3.54E-19
positive regulation of protein kinase B signaling	30	2.19E-21	1.00E-17	4.29E-19

Table 3. CC of core targets in GO function.

CC Term	Count	P-value	Bonferroni	FDR
extracellular region	178	3.79E-65	2.12E-62	1.80E-62
extracellular space	167	2.99E-62	1.68E-59	7.10E-60
external side of plasma membrane	70	1.28E-39	7.16E-37	2.03E-37
cell surface	77	3.26E-36	1.83E-33	3.87E-34
extracellular exosome	116	1.58E-21	8.84E-19	1.50E-19
macromolecular complex	61	4.78E-21	2.68E-18	3.78E-19
membrane raft	37	4.01E-20	2.25E-17	2.72E-18
plasma membrane	188	5.21E-19	2.92E-16	3.10E-17
endoplasmic reticulum lumen	38	3.55E-18	1.99E-15	1.87E-16
integral component of plasma membrane	80	1.01E-14	5.66E-12	4.81E-13
perinuclear region of cytoplasm	50	1.91E-12	1.07E-09	8.26E-11
membrane	105	3.23E-12	1.81E-09	1.28E-10
platelet alpha granule lumen	16	5.27E-12	2.95E-09	1.92E-10
clathrin-coated endocytic vesicle membrane	16	1.04E-11	5.82E-09	3.52E-10
secretory granule	18	1.88E-11	1.05E-08	5.96E-10
high-density lipoprotein particle	11	7.71E-11	4.32E-08	2.29E-09
neuronal cell body	31	2.05E-09	1.15E-06	5.73E-08
receptor complex	22	5.02E-09	2.81E-06	1.32E-07
focal adhesion	30	2.04E-08	1.14E-05	5.09E-07
endocytic vesicle lumen	8	3.95E-08	2.21E-05	8.93E-07

Table 4. MF of core targets in GO function.

MF Term	Count	P-Value	Bonferroni	FDR
identical protein binding	125	1.16E-33	1.12E-30	1.01E-30
receptor binding	60	1.39E-31	1.35E-28	6.10E-29
cytokine activity	43	1.25E-29	1.21E-26	3.65E-27
protein binding	376	4.48E-27	4.33E-24	9.81E-25
enzyme binding	49	3.60E-22	3.48E-19	6.14E-20
growth factor activity	34	4.20E-22	4.06E-19	6.14E-20
hormone activity	25	1.71E-17	1.66E-14	2.14E-15
integrin binding	27	2.46E-15	2.36E-12	2.66E-13
heparin binding	28	2.73E-15	2.68E-12	2.66E-13
protease binding	21	5.19E-13	5.02E-10	4.55E-11
transcription factor binding	27	1.38E-12	1.34E-09	1.10E-10
ubiquitin protein ligase binding	30	6.38E-11	6.17E-08	4.65E-09
protein homodimerization activity	46	4.24E-10	4.10E-07	2.86E-08
C-C chemokine receptor activity	10	7.96E-10	7.70E-07	4.98E-08
macromolecular complex binding	33	1.20E-09	1.16E-06	6.84E-08
C-C chemokine binding	10	1.25E-09	1.21E-06	6.84E-08
RNA polymerase II sequence-specific DNA binding transcription factor binding	22	1.85E-09	1.79E-06	9.53E-08
chaperone binding	17	3.02E-09	2.92E-06	1.47E-07
virus receptor activity	14	1.46E-08	1.41E-05	6.74E-07
transcription coactivator binding	11	3.54E-08	3.42E-05	1.55E-06

Table 5. KEGG of core targets in GO function.

KEGG Term	Count	P-value	Bonferroni	FDR
Cytokine-cytokine receptor interaction	70	7.79E-32	2.29E-29	1.18E-29
Rheumatoid arthritis	36	5.95E-24	1.75E-21	4.53E-22
Pathways in cancer	80	1.38E-22	4.07E-20	7.01E-21
Lipid and atherosclerosis	50	4.04E-22	1.19E-19	1.54E-20
JAK-STAT signaling pathway	43	2.37E-21	6.97E-19	7.20E-20
Malaria	26	4.04E-21	1.19E-18	1.02E-19
Kaposi sarcoma-associated herpesvirus infection	45	7.55E-20	2.22E-17	1.64E-18
PI3K-Akt signaling pathway	60	2.68E-19	7.89E-17	5.10E-18
Chagas disease	33	3.24E-19	9.52E-17	5.47E-18
Allograft rejection	22	4.02E-19	1.18E-16	6.11E-18
Inflammatory bowel disease	27	7.41E-19	2.18E-16	9.70E-18
Toxoplasmosis	34	7.66E-19	2.25E-16	9.70E-18
Leishmaniasis	28	8.51E-18	2.50E-15	9.95E-17
HIF-1 signaling pathway	32	2.81E-17	8.26E-15	3.05E-16
TNF signaling pathway	32	6.60E-17	3.26E-14	6.69E-16
Viral protein interaction with cytokine and cytokine receptor	30	1.73E-16	6.53E-14	1.64E-15
Type I diabetes mellitus	21	2.42E-16	6.53E-14	2.16E-15
Tuberculosis	39	4.76E-16	1.31E-13	4.02E-15
Th17 cell differentiation	30	1.88E-15	5.55E-13	1.50E-14
Human cytomegalovirus infection	42	6.41E-15	1.89E-12	4.87E-14

TNF, IL6, and STAT3.

The enrichment results of KEGG pathway showed that high-intensity intermittent exercise and myocardial infarction interacted with core protein targets on the endocrine, metabolic and immune systems of the body, mainly in response to lipid metabolism, oxidative stress and inflammation. Cell proliferation, survival, metabolism, and angiogenesis are associated with normal protein expression in the PI3K-AKT signaling pathway. Although the anti-inflammatory effects of IL10 are not mediated by PI3K, the ability of IL10 to promote astrocyte survival or induce mast cell proliferation depends on PI3K activation. M2 macrophages induced by IL10 can induce fibroblast mediated extracellular matrix generation, cell proliferation and angiogenesis, and promote damaged tissue repair. In the JAK-STAT signaling pathway, IL-10 binds to the IL-10 receptor to trigger downstream signaling that phosphorylates JAK1 and further activates the intracellular domain of IL-10R-a, where STAT3 is recruited and phosphorylated to ultimately regulate anti-inflammatory gene expression. By activating STAT3, high-intensity intermittent exercise can up-regulate the expression of immune factors, participate in the regulation of mitochondrial function, and then improve energy metabolism to achieve the protective effect on myocardial infarction. Myocardial infarction puts the body in a state of chronic inflammation, and increases the expression of inflammatory markers such as TNF-α, IL6 and CRP. Stimulated by high-intensity intermittent exercise, the collective chronic inflammation can be improved, and the number, polarization type and proportion of M1/M2 macrophages [30] can be adjusted to play an anti-inflammatory role and promote cardiovascular health. This can be achieved primarily by inhibiting the overactivation of the TNF signaling pathway. In the T-cell signaling pathway, high-intensity intermittent exercise promotes the differentiation of CD4+ T cells into T regulatory cells, thereby increasing anti-inflammatory factors such as IL10 and decreasing pro-inflammatory factors such as IL6, thereby alleviating the inflammatory response of myocardial infarction and achieving protective effects on myocardial infarction (Fig. 4).

5. Conclusion

Based on bioinformation technology and molecular docking methods, this study preclinically clarified that high-intensity intermittent exercise can improve the prognosis of myocardial infarction with multi-target and multi-pathway characteristics. The results of this study provide a theoretical reference for the clinical application of exercise therapy for the prevention and treatment of cardiovascular diseases and need to be further verified by in vitro experiments, aiming at providing theoretical support for individual prevention and treatment of cardiovascular diseases and health promotion.

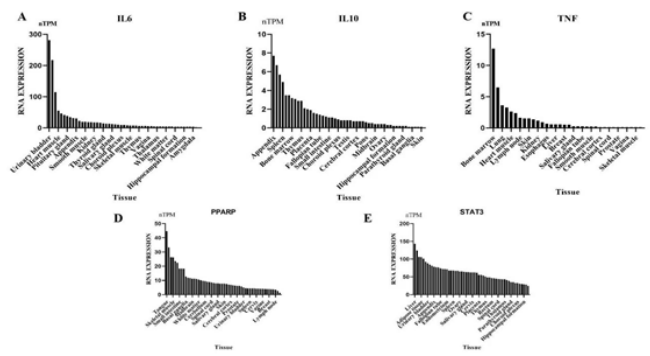

Fig. 4. RNA Expression of core proteins. (A) RNA Expression of IL6 in different tissue enriched; (B) RNA Expression of IL10 in different tissue enriched; (C) RNA Expression of TNF in different tissue enriched; (D) RNA Expression of PPARA in different tissue enriched; (E) RNA Expression of STAT3 in different tissue enriched.

Conflict of interests

The authors declare no competing interests.

Consent for publications

The author read and approved the final manuscript for publication.

Ethics approval and consent to participate

Not applicable.

Informed consent

Not applicable.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

TS and LH designed the experiments. TS, LC and LH performed the data analyses. PF helped perform the analysis with constructive discussions. TS wrote the draft manuscript. PF and TS revised the manuscript.

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Not applicable.

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