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Original Article

Predicting interactome networks of up/down regulated proteins and drug-gene interaction analysis associated with peri-implantitis

Azizeh Asadzadeh[1], Fatemeh Shams Moattar[2], Azam Moshfegh[2]

[1]Department of Biology, Faculty of Science, Nour Danesh Institute of Higher Education, Meymeh, Isfahan, [2]Department of Microbiology, Faculty of Basic Sciences, Lahijan Branch, Islamic Azad University, Lahijan, Iran

ABSTRACT

Background: Peri-implantitis is implant-associated inflammation that leads to irreversible loss of surrounding bone. Early diagnosis increases the success of peri-implantitis treatment. Despite various studies associated with this most common complication, early detection of the onset of peri-implantitis remains a major challenge. Molecular biomarkers are applicable detectors for the early detection of numerous diseases and monitoring their development. The present study aimed to predict interactome networks of up/down regulated proteins and analyze drug-gene interaction in peri-implantitis to identify the diagnostic and druggable genes.

Materials and Methods: In this *in silico* study, a suitable gene expression profile related to peri-implantitis was retrieved from Gene Expression Omnibus. Screening differentially expressed genes (DEGs) was carried out based on the cut-off criteria |log2 (fold change)|>2 and $P < 0.05$. Interactome networks were constructed and analyzed by the STRING database (Version: 12.0) and the Cytoscape software (version: 3.9.1). Finally, to investigate drug-gene interaction, detected hub genes were analyzed by DGIdb (version: 5.0.6).

Results: A total of 216 genes were identified as DEGs (129 down-regulated and 87 up-regulated genes) in peri-implantitis. Regarding Cytoscape analysis, FCGR3B, CSF3R, AQP9, TREM1, and P2RY13 were the top 5 hub nodes of up-regulated DEGs, and CXCL10, OASL, IFIT1, RSAD2, and ISG15 were the top 5 hub nodes of down-regulated DEGs. Among these key nods, AQP9, CSF3R, CXCL10, IFIT1, ISG15, OASL, and, FCGR3B were therapeutic targets and had approved drugs.

Conclusion: In this research, seven genes have been identified as druggable genes in peri-implantitis which can be used to treat and diagnose this disease. However, these results and identified genes need to be validated by clinical or experimental methods.

Key Words: Biomarkers, gene expression, peri-implantitis, protein interaction, therapeutics

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Address for correspondence:
Dr. Azizeh Asadzadeh, Department of Biology, Faculty of Science, Nour Danesh Institute of Higher Education, Meymeh, Isfahan, Iran.
E-mail: az.asadzadeh@nourdanesh.ac.ir, az.asadzsadeh@yahoo.com

INTRODUCTION

In modern comprehensive dental care, dental implant treatment is one of the best solutions for missing teeth.[1] Due to the increase in dental implant therapy, the biological complications and diseases related to implants have significantly increased. The soft and hard tissues around dental implants are impacted by the damaging inflammatory process known as peri-implantitis. With the progress of inflammation,

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the hard tissue (alveolar bone), which surrounds the implant for retention, gradually disappears. Bacterial biofilm proliferating plays a major role in the progress of this disease. Gram-negative anaerobic bacteria are the most common microorganisms in the environment of implants. Bacterial colonization occurs in the transmucosal attachment of osseointegrated dental implants. Titanium plays a pivotal role in implant material. Laboratory studies show the high affinity of several microorganisms to the titanium surface. To solve this problem, nanomaterials are used to cover titanium. Dental nanomaterials such as chlorhexidine, zinc oxide, hydroxyapatite, copper-oxide, and other metal oxide nanoparticles are used for titanium-based dental implant coatings to provide antimicrobial function and better integration of the implants into the bone. However, peri-implantitis remains one of the problems of implant treatment failure.[2-7]

Genetic traits, history of periodontitis, smoking, systemic diseases, and oral hygiene are the risk factors for this type of infection.[4,8] Based on the progression of the disease and peri-implant defects, peri-implantitis is classified as early, moderate, and advanced stage.[9] Diagnosis of peri-implant diseases is based on analyses of peri-implant microbiota, clinical parameters such as the presence of swelling and suppuration, evaluation of peri-implant crevicular fluid or saliva, and radiographic examination of peri-implant bone loss. In this disease, untreated lesions and inflammatory processes can lead to progressive loss of peri-implant bone and implant failure. Early detection of infection, monitoring the course of inflammation, and rapid initiation of treatment are very effective for the successful treatment of peri-implantitis, which is possible through the assessment of biomarkers.[10-12]

Interactome networks are remarkably complex and diverse and play an important role in every biological process. By identifying up/down proteins and constructing protein-protein interactions, prediction of biomarkers in various diseases is possible. In recent years, biomarkers or biological markers have become increasingly important for efficient disease diagnosis, target discovery, study of drug activity and mechanisms of action, identification of toxicity and safety, assessment of efficacy signals, and understanding of disease processes.[13-15] In this research, artificial neural networks were used to detect new biological markers and drug-biomarker interaction in peri-implantitis.

Many studies have been done on peri-implantitis patients, in this field. A significant increase in levels of proinflammatory cytokines such as interleukin 1β (IL-1β), tumor necrosis factor alpha, and IL-6 was reported in peri-implantitis patients compared to individuals with healthy implants.[16] The levels of osteoprotegerin (OPG), and receptor activator of nuclear factor kappa-B ligand (RANKL) were shown to be significantly higher in peri-implantitis. Even upregulation of some enzymes such as matrix metalloproteinases, cathepsin K, and elastase have been mentioned as diagnostic biomarkers. Overactivity of these enzymes is associated with irreversible destruction of the connective tissue around the implant.[17] In addition, miRNA-142-3p and miRNA-146a were reported as potential biomarkers in the meta-analysis study on the expression of microRNAs in periodontal and peri-implant diseases.[18]

Despite numerous studies associated with identifying biomarkers of peri-implantitis, early detection of the onset of peri-implantitis remains a major challenge, and more exploratory research is needed to identify the specific biomarkers. The present study aimed to predict interactome networks of up/down regulated proteins and analyze drug-gene interaction in peri-implantitis. We used microarray data of peri-implantitis patients to detect the up-regulated and down-regulated proteins. Furthermore, we constructed protein-protein interaction networks and identified candidate hub genes as biomarkers. Finally, to find potential drug targets, a drug-gene interaction database (DGIdb) was used and drug hub genes for therapeutic targets in peri-implantitis were discovered.

MATERIALS AND METHODS

Microarray data selection for peri-implantitis

This research was done by *in silico* methods. The gene expression omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/gds) is one of the largest and most comprehensive web-based tools for the screening and analysis of various microarray data.[19] Extracted data from the GEO database are very applicable and useful in designing different interactome networks such as protein-protein interaction networks, gene regulation networks, microRNA-mRNA regulatory networks, etc. Based on the latest publication dates, the suitable microarray gene expression data set of peri-implantitis in homosapiens was selected from the GEO database.

Data processing and screening strategy

By the R language in GEO2R, up-regulated and down-regulated genes were filtered. In this tool, two groups peri-implantitis and healthy individuals were defined and then, the differentially expressed genes (DEGs)' filtration was carried out based on the cut-off criteria |log2 (fold change)|>2 and $P < 0.05$ were obtained.

Construction of protein-protein interaction network

STRING is a free computational database for investigating all kinds of physical and functional interactions between various proteins.[20] In this section, down-regulated DEGs and up-regulated DEGs were inputted into the search tool of STRING Version: 12.0 (Swiss Institute of Bioinformatics), separately. After hiding disconnected nodes in the created file, the remaining genes were saved in TSV format. The TSV output file contains the needed information on the protein-protein interaction network consisting of all nodes and all interactions between them. The Cytoscape software is a useful viewer for visualizing the protein-protein interaction network created by STRING. In the next step, Cytoscape v3.9.1 was used and two protein-protein interaction networks were constructed and visualized.

Hub genes detection and drug-gene interaction analysis

CytoHubba is a helpful application in the menu bar of Cytoscape software that predicts and explores important nodes. CytoHubba plugin in Cytoscape v3.9.1 software (Institute for Systems Biology, Seattle, Washington) was used for detecting the top 5 hub genes in each network. The screening of nods is based on degree, maximum neighborhood component, and other topological analysis parameters. The DGIdb shows interactions based on different valid sources. To investigate drug interactions with hub genes, 10 hub genes (up-regulated and down-regulated) were inserted into DGIdb v.5.0.6 at https://www.dgidb.org/.

RESULTS

Microarray data selection for peri-implantitis

Gene expression profile of peri-implantitis with accession number: GSE224044 (Public on Feb 01, 2024) was selected for further analysis. This microarray profile consists of two types of tissues, peri-implantitis samples, and healthy samples as control. This dataset was based on GPL16791 Illumina HiSeq 2500. In the GSE224044 dataset, there are 6 profiles. GSM7010225, GSM7496778, and GSM7010226 were peri-implantitis inflammatory tissues. GSM7010227, GSM7010228, and GSM7496777 were as healthy gingival tissues.

Data processing and screening strategy

After data processing by the R language in GEO2R, 129 DEGs were analyzed as down-regulated mRNAs, and 87 DEGs were analyzed as up-regulated mRNAs. The volcano plot and normalization plot of DEGs in the GSE224044 dataset are shown in Figure 1.

Construction of protein-protein interaction network

Protein interactomes help to identify key genes and main modules involved in the development and progression of peri-implantitis. Protein-protein interaction network of down-regulated differentially expressed mRNAs of GSE224044 by Cytoscape software was shown, with 19 nods and 43 edges. But about up-regulated differentially expressed mRNAs, 15 nods and 23 edges were detected [Figures 2 and 3].

Hub genes detection and drug-gene interaction analysis

Based on CytoHubba plugin results, FCGR3B, CSF3R, AQP9, TREM1, and P2RY13 are the top 5 hub genes of up-regulated differentially expressed mRNAs. CXCL10, OASL, IFIT1, RSAD2, and ISG15 are the top 5 hub genes of down-regulated differentially expressed mRNAs [Figure 4]. Based on the results of the DGIdb 3.0 database, the approved drugs related to hub genes with interaction scores were introduced [Table 1].

DISCUSSION

Peri-implantitis is a common problem in dental implant treatment and a major cause of dental implant loss. Inflammatory conditions and the presence of harmful microorganisms cause this site-specific infectious disease.[21,22] However, even with current diagnostic criteria, identifying the precise underlying cause and detecting the early stages of peri-implantitis remains challenging. Determination of disease status or response to therapy is a common use of molecular biomarkers in medicine.[23] In previous studies, we worked on the use of bioinformatics methods in drug identification and vaccine design for various diseases.[24-27] The objective of the present investigation was to predict potential key biomarkers

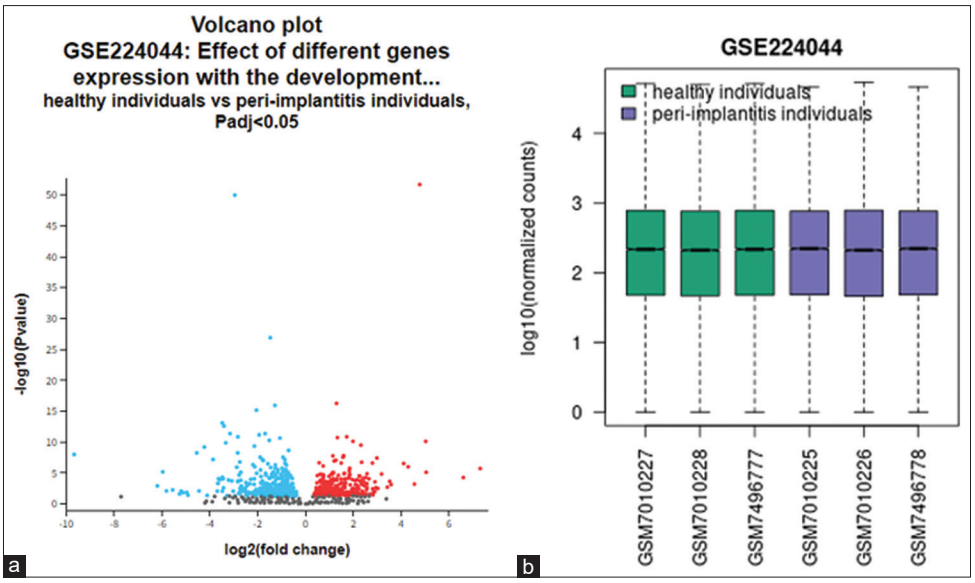

Figure 1: The volcano plot (a) and normalization plot (b) of differentially expressed genes in the GSE224044 dataset.

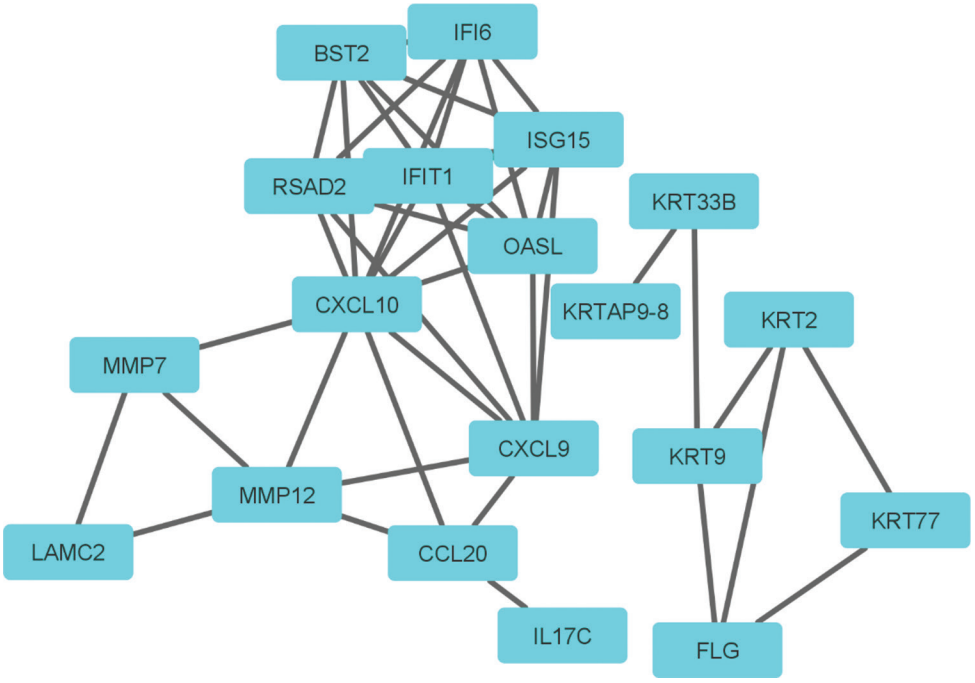

Figure 2: Protein-protein interaction network analysis of down-regulated differentially expressed mRNAs. This figure was created by cytoscape software (3.9.1).

associated with peri-implantitis by constructing interactome networks of up/down regulated proteins and drug-gene interaction analysis. Eighty-seven upregulated DEGs and 129 downregulated DEGs were successfully identified when comparing the gene expression matrix of peri-implantitis, and healthy samples. After further analysis of detected genes, 10 hub genes (5 up-regulated genes: FCGR3B, CSF3R, AQP9, TREM1, and P2RY13 and 5 down-regulated genes: CXCL10, OASL, IFIT1, RSAD2, and ISG15) were identified that may play a crucial role in the occurrence and development of peri-implantitis. Most of the obtained hub genes were consistent with previous peri-implantitis biomarker studies.

In this study results, Fc gamma receptor IIIb (FCGR3B) also known as cluster of differentiation 16b was identified as one of the hub genes involved in peri-implantitis. In a study conducted by Saremi *et al*., to evaluate the relationship between Fc gamma-receptor gene polymorphisms and peri-implantitis 50 cases of

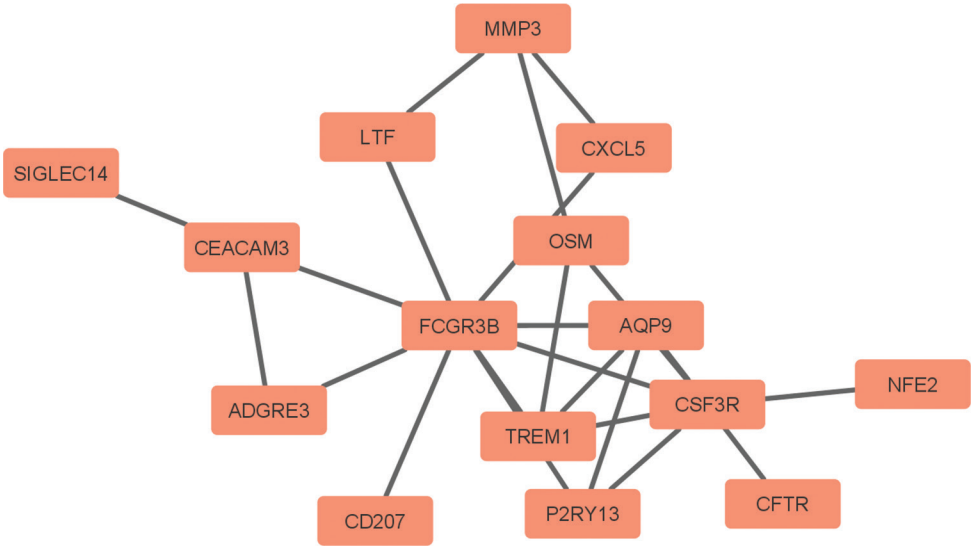

Figure 3: Protein-protein interaction network analysis of up-regulated differentially expressed mRNAs. This figure was created by cytoscape software (3.9.1).

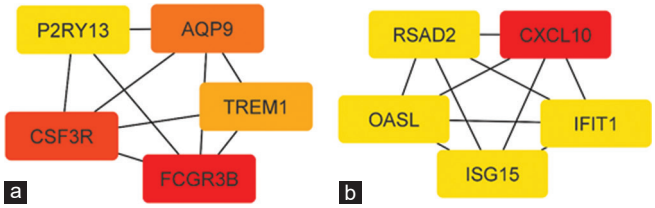

Figure 4: The top 5 hub genes of up-regulated differentially expressed mRNAs (a) and down-regulated differentially expressed mRNAs (b).

this disease were studied. Based on the results of their study, a significant association between FCGR3B and peri-implantitis was proven.[28] Suzuki *et al*., analyzed 3 microarray gene expression data sets (GSE10334, GSE16134, and GSE23586) to identify molecular biomarker candidates for the diagnosis and prognosis of chronic periodontitis. Based on their results, the gene FCGR3B was introduced as a key gene along with other genes.[29] The presence of the CSF3R gene in the protein network obtained based on the analysis of the GSE33774 microarray dataset was confirmed.[30] Aquaporin-9 (AQP-9) is an integral membrane protein that facilitates water transport. This hydrophobic membrane protein plays important roles in tissue homeostasis, the specialized functions of leukocytes such as immune response and activity against bacteria. Studies have described the involvement of AQPs in pathological conditions in various organs. In the study by Buffoli *et al*., tissue samples from six patients, comprising paired peri-implant soft tissue and periodontal gingiva tissue, were procured to analyze DEGs. In this research, 3549 genes were detected as DEGs among them AQP9, which has been confirmed to exhibit upregulation in the soft tissue surrounding the implant site.[31,32] P2Y purinoceptor 13 with 354 amino acids encoded by the P2RY13 gene belongs to the G protein-coupled receptor. This receptor increases the release of pro-inflammatory factors and is involved in various pathophysiological processes such as apoptosis, autophagy, proliferation, and metabolism. Based on the study of Cai *et al*., P2RY13 is the common gene signature among 5 key genes in both diseases, obesity and periodontitis.[33]

The DGIdb database was employed to investigate the interactions between hub genes and related potential therapeutic drugs. This platform facilitates precise medical diagnosis and drug discovery. According to the results of this DGIdb, 7 genes among 10 hub genes were druggable and had approved drugs. Forty-nine potential drugs/compounds for peri-implantitis treatment were detected. Among them, 4 targeted drugs for AQP9, 12 targeted drugs for CSF3R, 11 targeted drugs for CXCL10, 2 targeted drugs for IFIT1, 1 targeted drug for ISG15, 2 targeted drugs for OASL, and 17 targeted drugs for FCGR3B.

The main difficulty in developing new drugs is identifying target proteins. Detected genes have potential applications beyond pri-implantitis screening. They may offer fresh perspectives on future directions in therapeutic drug development for clinical use. The current research has some limitations, we use available gene expression profiles and *in silico* approaches for data analysis. However, this study

Table 1: The approved drugs related to hub genes based on the drug-gene interaction database 3.0 database

Gene	Drug	Regulatory approval	Interaction score
AQP9	Flutamide	Approved	0.776053
	Urea	Approved	1.638335
	Cisplatin	Approved	0.09896
	Testosterone	Approved	0.58204
CSF3R	Pegfilgrastim-JMDB	Approved	9.436809
	Tbo-filgrastim	Approved	4.718404
	Lipegfilgrastim	Approved	2.359202
	Ruxolitinib	Approved	1.814771
	Dasatinib anhydrous	Approved	0.132913
	Lenograstim	Approved	0.262134
	Tofacitinib	Approved	0.47184
	Imatinib	Approved	0.067406
	Eflapegrastim	Approved	1.179601
	Pexidartinib	Approved	0.3932
	Ibrutinib	Approved	0.277553
	Trametinib dimethyl sulfoxide	Approved	0.160855
CXCL10	Atropine	Approved	0.630803
	Testosterone	Approved	0.182601
	Stavudine	Approved	0.495631
	Ritonavir	Approved	0.277553
	Zidovudine	Approved	0.247815
	Methylprednisolone	Approved	0.462589
	Peginterferon alfa-2B	Approved	0.108419
	Atorvastatin calcium trihydrate	Approved	0.113751
	Human chorionic gonadotropin	Approved	0.365202
	Peginterferon alfa-2A	Approved	0.204083
	Oxaliplatin	Approved	0.216838
IFIT1	Ribavirin	Approved	1.594056
	Peginterferon alfa-2B	Approved	1.843127
ISG15	Irinotecan hydrochloride	Approved	0.999662
OASL	Ribavirin	Approved	1.594056
	Peginterferon alfa-2B	Approved	1.843127
FCGR3B	Sodium chloride	Approved	0.127662
	Cyclosporine	Approved	0.047034
	Progestin	Approved	0.324959
	Methotrexate	Approved	0.036475
	Doxorubicin hydrochloride	Approved	0.024823
	Chondroitin sulfates	Approved	0.397172
	Thalidomide	Approved	0.096609
	Cholecalciferol	Approved	0.297879
	Epoetin alfa	Approved	0.10832
	Tinzaparin sodium	Approved	0.105134
	Prednisolone	Approved	0.155415
	Dimethyl sulfoxide	Approved	0.223409
	Fentanyl citrate	Approved	0.142982
	Cytarabine	Approved	0.052567
	Lactulose	Approved	0.893637
	Indomethacin	Approved	0.10213
	Methimazole	Approved	0.210268

provides new insights into the understanding of genes involved in diagnosing and treating pri-implantitis.

CONCLUSION

In conclusion, seven genes, including AQP9, CSF3R, CXCL10, IFIT1, ISG15, OASL, and FCGR3B, have been identified as druggable genes in pri-implantitis, which play a crucial role in the progression and prognosis of this disease. However, due to the lack of *in vivo* and *in vitro* validation in this study, our results and identified genes need to be validated by clinical or experimental methods.

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Conflicts of interest

The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial or non-financial in this article.

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