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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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Содержание:

JAG2 AS A KEY MEDIATOR IN PORPHYROMONAS GINGIVALIS-INDUCED PERIODONTAL INFLAMMATION

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Abstract.

Porphyromonas gingivalis (*P. gingivalis*) is a key pathogen in chronic periodontitis, but its exact pathogenic mechanisms remain unclear. This study aimed to investigate the transcriptomic changes induced by *P. gingivalis* and identify potential key pathways involved in periodontal pathogenesis. We performed high-throughput sequencing and bioinformatic analyses on oral epithelial cell exposed to *P. gingivalis*. Differential gene expression analysis revealed 106 significantly altered genes ($p < 0.05$, $|log2FC| > 1$). KEGG pathway enrichment analysis highlighted the involvement of TNF signaling, Notch signaling, and ribosomal pathways. Protein-protein interaction network analysis identified JAG2, a Notch ligand, as a key hub gene significantly downregulated in *P. gingivalis*-treated samples. Our findings provide new insights into the molecular mechanisms of *P. gingivalis*-induced periodontal inflammation and suggest potential therapeutic targets, particularly within the Notch and IL-6 signaling pathways, for the treatment of periodontitis.

Key words. *P. gingivalis*, Periodontitis, Molecular maker, JAG2.

Introduction.

Porphyromonas gingivalis (*P. gingivalis*) is a Gram-negative anaerobic bacterium, widely recognized as one of the primary pathogens of chronic periodontitis [1]. This bacterium predominantly colonizes subgingival plaques, secreting various virulence factors such as proteases, endotoxins, and glycosidases, which directly destroy periodontal tissues and elicit host immune responses. *P. gingivalis* not only degrades connective tissue and extracellular matrix proteins but also interferes with host defense mechanisms, promoting the persistence of inflammation [2]. Moreover, it acts synergistically with other oral bacteria to form complex biofilms, enhancing its pathogenicity and antibiotic resistance [3]. Recent studies suggest that the pathogenic effects of *P. gingivalis* may extend beyond the oral cavity, potentially associating with various systemic diseases such as cardiovascular diseases and diabetes, highlighting the importance of further research on this bacterium [4].

The rapid advancement of high-throughput sequencing technologies has revolutionized microbiological research on periodontitis. Compared to traditional culture methods, sequencing technologies can detect unculturable or difficult-to-culture microorganisms and provide detailed information on community structure, species abundance, and functional genes [5,6]. In periodontitis research, these technologies have been extensively used to reveal differences in the microbiomes of healthy and diseased states, identify potential pathogenic bacterial groups, and elucidate mechanisms of host-microbe interactions [7]. Additionally, sequencing data combined with bioinformatics analysis provide crucial insights into the pathogenesis of periodontitis, the search for biomarkers, and the development of new therapeutic strategies. With the introduction of new techniques such as single-cell sequencing and long-read sequencing, we can expect to obtain higher-resolution microbiome maps, further advancing periodontological research.

Methods.

Differential Gene Acquisition: The gene expression dataset (GSE192887) was downloaded from the GEO database for analysis. It contains sequencing data from 3 sets of oral epithelial cells exposed to *P. gingivalis* and has 3 sets of untreated cells as controls. We used the limma package in R to conduct differential expression gene (DEG) analysis. We constructed a design matrix and a contrast matrix, then used the lmFit() function to fit a linear model. Adjusted p-values (FDR) < 0.05 and $|log2FC| > 1$ were used as criteria for identifying DEGs.

KEGG Pathway Enrichment Analysis:

To understand the functional significance of the DEGs, we performed KEGG pathway enrichment analysis using the clusterProfiler package in R. We employed hypergeometric testing to evaluate the enrichment of DEGs in each KEGG pathway and used the Benjamini-Hochberg method to correct p-values for multiple testing. Pathways with adjusted p-values < 0.05 were considered significantly enriched.

Protein-Protein Interaction (PPI) Network Analysis:

We constructed the PPI network of DEGs-encoded proteins using the STRING database. The minimum combined score was set to 0.4, and the network was visualized using Cytoscape software (version 3.9.0). We applied the MCODE plugin to identify highly interconnected modules and the CytoHubba plugin to identify key nodes within the network.

Statistical Analysis:

All statistical analyses were performed using R software (version 4.2.3) and GraphPad Prism (version 9.5.0). Comparisons between two groups were made using an unpaired Student's t-test. All tests were two-tailed, and p-values less than 0.05 were considered statistically significant. Data are presented as mean ± standard deviation (mean±SD).

Results.

Differential gene analysis:

Differential gene expression analysis revealed significant changes in the transcriptome between the experimental conditions. As illustrated in Figure 1, a total of 106 genes were found to be differentially expressed ($p < 0.05$, $|logFC| > 1$). Among these, 44 genes were significantly upregulated (red points), and 62 genes were significantly downregulated (blue points).

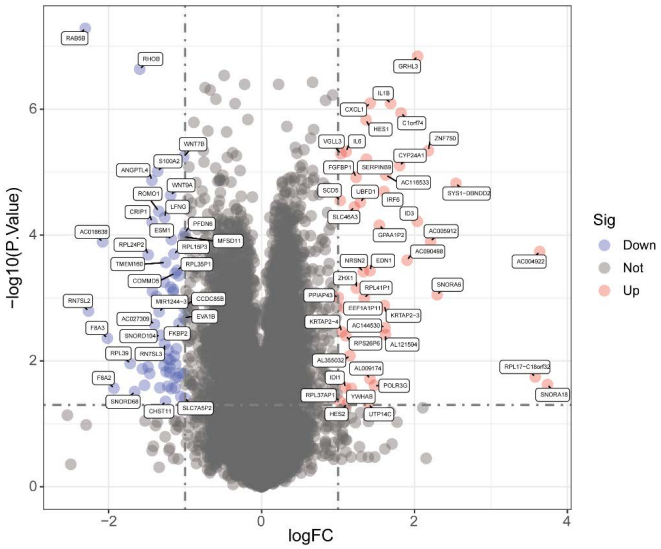

Figure 1. *Volcano plot of differentially expressed genes.*

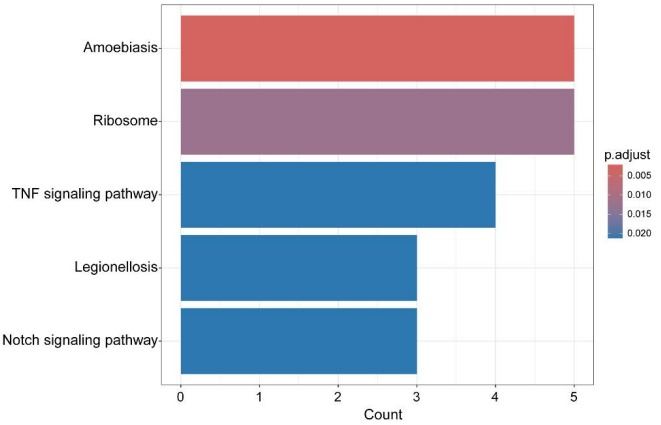

Figure 2. *Enriched pathways analysis of differentially expressed genes. The Y-axis shows the top 5 significantly enriched pathways. The X-axis represents the count of differentially expressed genes associated with each pathway*

Red points indicate significantly upregulated genes (Up), blue points indicate significantly downregulated genes (Down), and grey points represent genes with no significant change in expression (Not). Some key differentially expressed genes are labelled.

KEGG analysis:

To elucidate the biological significance of the differentially expressed genes, we performed pathway enrichment analysis. Figure 2 illustrates the top 5 significantly enriched pathways. The TNF signalling pathway was also significantly enriched. This pathway is crucial in inflammation and immune responses, suggesting that these processes may be implicated in our observed phenotype. the Notch signalling pathway was also among the top enriched pathways. This finding suggests a potential role for Notch signalling in *P. gingivalis* conditions, which is consistent with its known functions in cell fate determination, differentiation, and tissue homeostasis. Notably, the ribosome pathway showed significant enrichment, indicating potential changes in protein synthesis machinery. This could reflect an adaptive response to the experimental conditions or a more fundamental alteration in cellular metabolism.

The Y-axis shows the top 5 significantly enriched pathways. The X-axis represents the count of differentially expressed genes associated with each pathway.

PPI analysis.

To gain deeper insights into the functional associations between differentially expressed genes, we performed protein-protein interaction (PPI) network analysis and MCODE cluster analysis. The PPI network analysis (Figure 3A) revealed complex interaction patterns among 21 differentially expressed genes. These genes are involved in various crucial cellular processes, including inflammatory responses, signal transduction, and developmental regulation. The genes in the network exhibited varying degrees of connectivity, suggesting different levels of importance in the cellular response. To identify functional modules within the network, we conducted MCODE cluster analysis (Figure 3B). This analysis revealed two significant functional clusters.

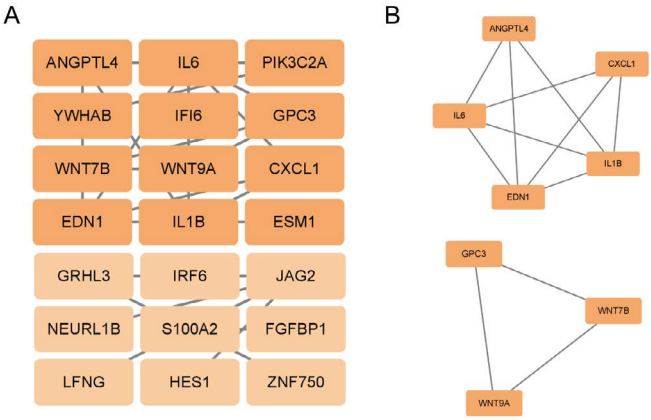

Figure 3. *Protein-Protein Interaction (PPI) network and MCODE cluster analysis of differentially expressed genes. (A) PPI network showing interactions among 21 differentially expressed genes. (B) MCODE cluster analysis results.*

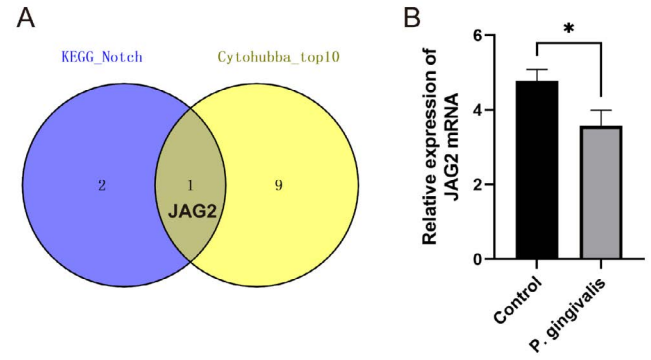

Figure 4. *Figure 4: Hub gene analysis. (A) Venn diagram showing the overlap between KEGG Notch pathway genes and top 10 hub genes identified by Cytohubba. (B) Relative expression of JAG2 mRNA in control and P. gingivalis conditions. * Indicates $p < 0.05$.*

Table 1. *The CytoHubba analysis in Cytoscape has identified the top 10 hub genes in our protein-protein interaction network.*

Rank	Name	Score
1	IL6	15
2	IL1B	13
3	EDN1	12
4	ANGPTL4	6
4	CXCL1	6
6	JAG2	5
7	GPC3	3
8	WNT9A	2
9	WNT7B	2
10	PIK3C2A	2

Analysis of key gene.

The CytoHubba analysis in Cytoscape has identified the top 10 hub genes in our protein-protein interaction network (Supplementary Table 1). This analysis helps to prioritize genes based on their network centrality and potential importance in the biological process under study. Venn diagram showing the relationship between genes involved in the KEGG Notch signalling pathway and the top 10 centred genes identified by Cytohubba analysis. JAG2 overlaps in two gene sets (Figure 4A). The sequencing results showed a significant decrease in JAG2 expression, especially considering its identification as a hub gene in our network analysis. The downregulation of JAG2, a Notch ligand, suggests a potential suppression or modulation of Notch signaling in our experimental conditions (Figure 4B).

Discussion.

This study reveals the transcriptomic changes induced by Porphyromonas gingivalis through high-throughput sequencing and bioinformatics analysis, providing new insights into the molecular mechanisms of periodontitis. Our results highlight the potential key role of the Notch signalling pathway, particularly its ligand JAG2, in the pathogenesis of periodontitis. The significant downregulation of JAG2 suggests not only the inhibition of the Notch signalling pathway but also potential impacts on cell fate determination, differentiation, and tissue homeostasis [8]. This finding is consistent with previous reports on the role of Notch signalling in inflammatory responses and tissue repair. However, it raises new questions: Is the downregulation of JAG2 a protective response of the host to *P. gingivalis* infection, or is it a pathogen-induced change that facilitates its persistent infection? These findings not only deepen our understanding of the pathogenic mechanisms of *P. gingivalis* but also provide new directions for developing targeted therapeutic strategies, particularly in regulating Notch and inflammatory signalling pathways.

Our study further confirms the critical role of the interleukin-6 (IL-6) signalling pathway in the pathogenesis of *P. gingivalis*-induced periodontitis. IL-6, a pleiotropic cytokine, activates downstream molecules such as the JAK/STAT3 and MAPK pathways through classical and trans-signalling pathways, thereby regulating inflammatory responses, bone metabolism, and tissue remodelling [9,10]. Additionally, IL-6 synergizes with other inflammatory factors (e.g., TNF-α and IL-1β) to amplify the inflammatory cascade [11]. Based on these findings, therapeutic strategies targeting the IL-6 signalling pathway, such as using IL-6 receptor antagonists or JAK inhibitors, may offer new options for treating periodontitis [12]. However, considering the importance of IL-6 in maintaining tissue homeostasis and immune defense, completely inhibiting its signalling pathway may pose potential risks. Future studies need to precisely regulate the intensity and duration of IL-6 signalling to balance inhibiting excessive inflammatory responses while preserving its physiological functions. Furthermore, exploring the interaction networks of IL-6 with other signalling pathways and its dynamic changes in different stages of periodontitis will help develop more precise and effective therapeutic approaches.

In recent years, the role of the Notch signalling pathway in the pathogenesis of periodontitis has attracted increasing attention from researchers [13]. As a highly conserved intercellular communication system, the Notch signalling pathway plays a critical role in regulating cell fate determination, proliferation, and differentiation [14]. Our results show that differentially expressed genes are significantly enriched in the Notch signalling pathway. Notably, the activation of the Notch signalling pathway is positively correlated with the exacerbation of inflammatory responses and the degree of alveolar bone resorption. This correlation may be due to the involvement of the Notch signalling pathway in regulating the production of inflammatory factors and the differentiation of osteoclasts [15,16]. Moreover, we observed complex interactions between Notch signalling and other key pathways (e.g., NF-κB and MAPK pathways), jointly affecting the inflammation and repair processes of periodontal tissues [17,18]. These findings not only deepen our understanding of the molecular mechanisms of periodontitis but also provide potential targets for developing new therapeutic strategies. However, the precise regulatory mechanisms of the Notch signalling pathway in periodontal tissues and its dynamic changes during disease progression require further investigation. In the future, targeted therapy for the Notch signalling pathway may offer new directions for the prevention and treatment of periodontitis, but its safety and efficacy need to be validated through more preclinical and clinical studies.

JAG2, a Notch ligand, is critical for maintaining epithelial barrier integrity, regulating immune responses, and suppressing inflammation via inhibition of NF-κB and pro-inflammatory cytokines (e.g., IL-6, TNF-α) [19]. In *P. gingivalis*-infected cells, JAG2 downregulation disrupts Notch signalling, leading to epithelial dysfunction, amplified inflammation, and impaired tissue repair. This suppression may stem from bacterial virulence factors targeting Notch pathways, exacerbating alveolar bone loss by enhancing osteoclast activity. Restoring JAG2/Notch signalling (e.g., via agonists or gene therapy) could stabilize barrier function and mitigate inflammation, though precise modulation is needed to balance pro- and anti-inflammatory effects [20]. These insights position JAG2 as a pivotal mediator and potential therapeutic target in periodontitis.

Our study reveals a complex network of gene interactions in the pathogenesis of *P. gingivalis*-induced periodontitis, with JAG2 emerging as a key player at the intersection of multiple signalling pathways. The identification of JAG2 as both a hub gene in our network analysis and a component of the Notch

signalling pathway underscores its potential significance in our experimental system. JAG2, encoding Jagged2, a ligand for Notch receptors [21], showed a significant downregulation in our experimental conditions. This finding is particularly intriguing given the well-established role of Notch signalling in various cellular processes, including cell fate determination, differentiation, and tissue homeostasis [22]. The reduced expression of JAG2 suggests a potential attenuation of Notch signalling, which could have far-reaching implications for cellular behavior in our model.

While this study focused on transcriptomic changes in oral epithelial cells, the interplay between epithelial and immune cells is critical to periodontal pathogenesis. *P. gingivalis* is known to subvert macrophage polarization toward a pro-inflammatory M1 phenotype while impairing phagocytic clearance [23], and it modulates neutrophil extracellular trap (NET) formation to evade immune detection [24]. Our findings on JAG2 downregulation and Notch signalling suppression may indirectly influence immune cell recruitment (e.g., via altered chemokine secretion) or macrophage-epithelial crosstalk. Future studies should investigate whether JAG2 restoration in epithelial cells mitigates *P. gingivalis*-driven immune dysregulation, such as excessive TNF-α production or defective bacterial clearance, to holistically address periodontal inflammation and tissue destruction.

Declarations.

Ethics approval and consent to participate.

Not applicable.

Consent for publication.

Not applicable.

Data availability.

The datasets presented in this study can be found in online repositories GEO database (GSE192887).

Competing interests.

The authors declare that they have no competing interest.

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Authors' contributions.

Data curation and Formal analysis: WWJ; Funding acquisition, Project administration and Supervision: LR; Visualization: ZPP; Writing—original draft: LR; Writing—review and editing: WWJ. All authors have read and agreed to the published version of the manuscript.

REFERENCES

1. Miranda-López DC, Pérez-Rueda E, Rojas-Vargas J, et al. Comprehensive comparative analysis of the periodontal pathogen Porphyromonas gingivalis: exploring the pan-genome, the reconstruction of the gene regulatory network and genome-scale metabolic network. Letters in applied microbiology. 2024:77.

2. Muñoz-Medel M, Pinto MP, Goralsky L, et al. Porphyromonas gingivalis, a bridge between oral health and immune evasion in gastric cancer. Front Oncol. 2024;14:1403089.

3. Iwasaki M, Taylor GW, Manz MC, et al. Serum antibody to Porphyromonas gingivalis in chronic kidney disease. J Dent Res. 2012;91:828-833.

4. Mei F, Xie M, Huang X, et al. Porphyromonas gingivalis and Its Systemic Impact: Current Status. Pathogens (Basel, Switzerland). 2020:9.

5. Slobodianyk-Kolomoiets M, Khlebas S, Mazur I, et al. Extracellular host DNA contributes to pathogenic biofilm formation during periodontitis. Front Cell Infect Microbiol. 2024;14:1374817.

6. Xue F, Zhao J, Gao X, et al. Potential susceptibility genes in patients with stage III and IV periodontitis: A whole-exome sequencing pilot study. Biomolecules & biomedicine. 2024;24:73-81.

7. Bostanci N, Belibasakis GN. Precision periodontal care: from omics discoveries to chairside diagnostics. Clin Oral Investig. 2023;27:971-978.

8. Coppens S, Barnard AM, Puusepp S, et al. A form of muscular dystrophy associated with pathogenic variants in JAG2. American journal of human genetics. 2021;108:840-856.

9. Rose-John S, Jenkins BJ, Garbers C, et al. Targeting IL-6 trans-signalling: past, present and future prospects. Nat Rev Immunol. 2023;23:666-681.

10. Huang B, Lang X, Li X. The role of IL-6/JAK2/STAT3 signaling pathway in cancers. Front Oncol. 2022;12:1023177.

11. Purwaningrum M, Giachelli CM, Osathanon T, et al. Dissecting specific Wnt components governing osteogenic differentiation potential by human periodontal ligament stem cells through interleukin-6. Scientific reports. 2023;13:9055.

12. Nolde M, Alayash Z, Reckelkamm SL, et al. Downregulation of interleukin 6 signaling might reduce the risk of periodontitis: a drug target Mendelian randomization study. Front Immunol. 2023;14:1160148.

13. Sachan N, Sharma V, Mutsuddi M, et al. Notch signalling: multifaceted role in development and disease. The FEBS journal. 2024;291:3030-3059.

14. Siebel C, Lendahl U. Notch Signaling in Development, Tissue Homeostasis, and Disease. Physiol Rev. 2017;97:1235-1294.

15. Yu J, Canalis E. Notch and the regulation of osteoclast differentiation and function. Bone. 2020;138:115474.

16. Cao J, Wei Y, Lian J, et al. Notch signaling pathway promotes osteogenic differentiation of mesenchymal stem cells by enhancing BMP9/Smad signaling. Int J Mol Med. 2017;40:378-388.

17. Amjad E, Asnaashari S, Jahanban-Esfahlan A, et al. The role of MAPK, notch and Wnt signaling pathways in papillary thyroid cancer: Evidence from a systematic review and meta-analyzing microarray datasets employing bioinformatics knowledge and literature. Biochemistry and biophysics reports. 2024;37:101606.

18. Maniati E, Bossard M, Cook N, et al. Crosstalk between the canonical NF-κB and Notch signaling pathways inhibits Pparγ expression and promotes pancreatic cancer progression in mice. J Clin Invest. 2011;121:4685-4699.
19. Liu J, Sato C, Cerletti M, et al. Notch signaling in the regulation of stem cell self-renewal and differentiation. Curr Top Dev Biol. 2010;92:367-409.
20. Long J, Wang X, Du X, et al. JAG2/Notch2 inhibits intervertebral disc degeneration by modulating cell proliferation, apoptosis, and extracellular matrix. Arthritis Res Ther. 2019;21:213.
21. Cereseto A, Tsai S. Jagged2 induces cell cycling in confluent fibroblasts susceptible to density-dependent inhibition of cell division. Journal of cellular physiology. 2000;185:425-431.
22. Wang H, Zang C, Liu XS, et al. The role of Notch receptors in transcriptional regulation. Journal of cellular physiology. 2015;230:982-988.
23. Moutsopoulos NM, Konkel JE. Tissue-Specific Immunity at the Oral Mucosal Barrier. Trends Immunol. 2018;39:276-287.
24. Hirschfeld J, White PC, Milward MR, et al. Modulation of Neutrophil Extracellular Trap and Reactive Oxygen Species Release by Periodontal Bacteria. Infect Immun. 2017:85.