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Oral microbiota shifts following tooth loss affect gut health

Ling Dong[1†], Zhaoxin Ji[1†], Jiangqi Hu[1], Qingsong Jiang[1*] and Wei Wei[1*]

Abstract

Background Tooth loss not only impairs oral function but also affects gut health by altering the host microbiota. Understanding the oral-gut axis can provide insights into systemic health implications following tooth loss.

Methods Using an animal model, we extracted the molars of C57 mice. Saliva and fecal samples were collected for 16S rRNA and metagenomic sequencing to analyze changes in the oral and gut microbiota. Pearson correlation analysis assessed the relationship between altered microbial communities.

Results The study found a significant reduction in oral microbiota diversity following tooth loss, with increased *Proteobacteria* and decreased *Muribacter*. Gut microbiota showed increased *Firmicutes* and decreased *Bacteroidota*. Correlations between oral and gut microbiota changes were observed, indicating a potential link between tooth loss and alterations in intestinal microbial balance.

Conclusion In the mouse model, tooth loss disrupted the balance of the oral-gut microbiota, with potential implications for intestinal health. Although these findings are from a murine model, considering the existence of the oral-gut axis balance in the human body, it is reasonable to postulate that following tooth loss in humans, the health of the intestinal microecology may also warrant attention.

Keywords Oral Microbiota, Gut microbiota, Oral-gut microbiome axis, Tooth Loss

Introduction

The oral cavity, composed of teeth and various soft and hard tissues, serves as a crucial component of the digestive system, where preliminary digestion and mastication occur. The integrity of teeth is essential for maintaining masticatory efficiency [1] and overall oral health [2]. The loss of teeth not only impairs oral function but is also correlated with the onset and progression of systemic diseases affecting the gastrointestinal tract [3], brain [4], and other systems [5, 6]. Particularly, the impact of tooth loss on intestinal health has become a focal point of interest for researchers.

The complexity and diversity of the oral microbiota play a significant role in sustaining the health of oral tissues and the homeostasis of microbial communities [7]. The health and presence of teeth markedly influence the balance of the oral microbial environment [8, 9]. Any disruption to this balance may trigger a cascade of effects on overall oral health. When teeth are missing, not only is masticatory efficiency reduced [10], but it also leads to an imbalance in the biomechanical environment within the oral cavity [11].

The concept of the oral-gut axis highlights the profound implications of oral microbial homeostasis on intestinal and systemic health [12, 13]. Imbalances in the microbial community caused by oral diseases such as periodontitis may lead to dysbiosis in the gut [14]. Clinical studies have

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indicated a link between tooth loss and changes in gut anti-inflammatory bacteria, suggesting a potential role in systemic inflammatory responses [15, 16]. However, the specific changes in the gut microbiota following tooth loss and the mechanisms of interaction between the oral and gut microbiotas warrant further investigation.

In this study, we utilized an animal model involving tooth extraction and employed sequencing data from the oral microbiome to deeply analyze the changes in the oral microbial community after tooth loss and their correlation with the distribution of the gut microbiota. Histological and immunohistochemical (IHC) analyses were conducted to evaluate gut inflammation in response to tooth loss and its potential impact on the oral-gut axis [17]. TNF-α and IL-6, key inflammatory markers, were selected for their roles in immune regulation [18, 19]. We aim to dissect the microbial community changes triggered by tooth loss and assess their relevance to the gut microbiota. We seek to understand how these changes may lead to intestinal damage and provide insights into the underlying mechanisms.

Methods and materials

Animals

Eight-week-old male C57 mice, free of specific pathogens, were housed in a pathogen-free environment and provided with sterile food and water. These mice were purchased from Beijing SHENRUI BIOTECHNOLOGY company. Ethical approval for this animal study was granted by the Ethics Committee of Capital Medical University (approval number: KQYY-202403–007). Mice were randomly assigned to either the control group with intact dentition (Ctrl, $n=5$) or the experimental group with tooth loss (TL, $n=5$). For tooth loss, the first molars of the maxilla were extracted [20]. Thirty days post-extraction, the mice were euthanized using CO_2.

Histological Examination (HE staining)

Tissue samples from the maxillary alveolar bone and intestines of the mice were collected and fixed. Paraffin sections were prepared and stained according to the instructions provided with the HE staining kit (Servicebio, G1076-500ML).

Immunohistochemistry (IHC)

Maxillary alveolar bone and intestinal tissues were also collected, fixed, and sectioned into 5-micron thick paraffin sections for IHC analysis. Primary antibodies specific for TNF-α (Servicebio, GB11188-100) and IL-6 (Servicebio, GB11117-100) were applied. The sections underwent antigen retrieval, serum blocking, primary antibody incubation, secondary antibody incubation, chromogenic reaction, and were then mounted for microscopic examination.

Collection of saliva and fecal samples

All procedures were conducted under sterile conditions. Samples were collected one-month post-tooth extraction, coinciding with the time of euthanasia. A total of three salivary samples and three fecal samples were collected from each group. Saliva collected using swabs inserted into the oral cavity of the mice [21]. Fresh fecal samples were also collected. Both saliva and fecal samples were stored at −80°C for future analysis [22]. Oral microbiota in saliva samples was analyzed using 16S rRNA sequencing, while gut microbiota in fecal samples was assessed using metagenomic sequencing [23, 24].

16S rRNA gene sequencing

Sequencing was provided by Shanghai Personal Biotechnology Co., Ltd. Total DNA was extracted using the TIANamp Bacterial DNA Kit (Tiangen, DP302). The V3 and V4 regions of the 16S rRNA gene were amplified with specific primers (Forward: ACTCCTACGGGAGGCAGC; Reverse: GGACTACHVGGGTWTCTAAT). The community DNA fragments were sequenced using the Illumina platform with paired-end technology. After sequence denoising and clustering, Operational Taxonomic Units (OTUs) were obtained and annotated using the classify-sklearn algorithm from QIIME2 (https://github.com/QIIME2/q2-feature-classifier), which employs a pre-trained Naive Bayes classifier. Further analysis was conducted using QIIME2 (2019.4) [25].

Metagenomic sequencing analysis

Sequencing was performed by Shanghai Personal Biotechnology Co., Ltd., utilizing the Illumina NovaSeq / HiSeq high-throughput sequencing platform. The metagenomic DNA was subjected to Whole Genome Shotgun sequencing strategy, where the total DNA was randomly fragmented into short segments, and libraries with appropriate insert sizes were constructed and sequenced using paired-end technology. After quality control, a subset of sequences was annotated using Kraken2 for species identification.

Pearson correlation analysis

To assess the correlation between the gut and oral microbiota, this study employed Pearson correlation analysis on the major microbial phylum and genera across the gut and oral cavity. Additionally, species-level correlation analyses have been performed and included in the supplementary materials for reference, providing further insights into the potential microbial interactions at a finer taxonomic resolution. A P-value less than 0.05

was considered to indicate statistical significance, and the analysis was conducted using the Hmisc package in R (version 4.2.1).

Statistical analysis

Differences in α-diversity were evaluated using the Wilcoxon test, a P-value less than 0.05 was considered significant. The LEfSe method was used to determine if the inter-group differences in these taxonomic units were statistically significant, based on the LDA effect size and the KW test P-value (less than 0.05). Correlation analysis was performed by calculating the Spearman correlation coefficient, and a heatmap was generated for variables with an absolute correlation coefficient greater than 0.8 and a P-value less than 0.05.

Results

Tooth loss impacts intestinal health

In our in vivo experiments, the neighboring teeth affected by tooth loss exhibited an imbalance, leading to an enlargement of the periodontal ligament (Fig. 1A) and an increase in the expression of inflammatory factors in the periodontal microenvironment (Fig. 1B).

Our in vivo research revealed that tooth loss affected not only oral health but also had profound implications for intestinal health. Following tooth loss, the mucosal structure of the intestine changed, with significant infiltration of inflammatory cells in the lamina propria (Fig. 1C), and an increase in the expression of inflammatory factors within the intestinal tissue (Fig. 1D). Maintaining the health and integrity of teeth is vital for the overall health of the digestive system [26]. Therefore, it is necessary to explore the specific mechanisms linking tooth loss to intestinal health to better prevent and treat related diseases.

Alterations in the oral microbiota following tooth loss

In our study, 16 s rRNA sequencing was performed on saliva samples from mice with tooth loss to assess the impact on the oral microbiome. The oral microbiota represents one of the largest and most diverse microbial reservoirs in the human body [27]. Pathological changes in oral tissues can significantly alter the composition of the oral microbiota [28]. To comprehensively evaluate the α-diversity of the microbial community, we utilized the Shannon and Simpson indices to characterize the diversity, and the Pielou's evenness index to represent the evenness of species distribution. The statistical results indicated a significant reduction in the α-diversity of the oral microbiota following tooth loss (Fig. 2A). The numbers under the diversity index labels represent the *p*-values obtained from the Kruskal–Wallis test. For pairwise comparisons, Dunn's test post-hoc analysis was performed, and significance was indicated with appropriate markers. Additionally, we conducted β-diversity analysis to assess the between-habitat diversity. PCoA was employed to reduce the dimensionality of the complex microbial data, revealing distinct microbial distributions between the tooth loss and control groups (Fig. 2B). Hierarchical clustering further demonstrated the similarity within groups, with samples from the tooth loss group and the control group showing dissimilarity in their microbial profiles (Fig. 2B).

Post-sequencing statistical analysis was conducted, we visualized the species composition at the phylum, class, genus, and species taxonomic levels using stacked bar charts for each sample (Fig. 2C). At the phylum level, *Proteobacteria* and *Firmicutes_D* were the dominant phyla in the control group, with a higher proportion of *Proteobacteria* in the tooth loss group. At the class level, *Bacilli* and *Gammaproteobacteria* were the predominant classes in the control group, with a higher proportion of *Bacilli* observed in the tooth loss group. At the genus level, *Muribacter* and *Streptococcus* were the most abundant genera in the control group, while in the tooth loss group, *Streptococcus* showed an increased proportion, and the proportion of *Rodentibacter_A* also significantly increased, with a corresponding decrease in the proportion of *Muribacter*.

Differential analysis of changes in the oral microbiota

To delve deeper into the differences in the oral microbiota following tooth loss, we employed a variety of analytical methods to achieve a comprehensive understanding. To explore the commonalities and unique characteristics between the two groups, we utilized Venn diagrams to illustrate the distinct and shared operational taxonomic units (OTUs). Specifically, we identified 249 unique OTUs in the tooth loss group, 174 unique OTUs in the control group, and 59 OTUs that were shared between the two groups (Fig. 3A).

To further visualize the abundance distribution trends of species across samples, we employed a heatmap to display the abundance of the top 20 genera based on average abundance (Fig. 3B). Continuing with our analytical approach, we utilized LEfSe to perform a differential analysis across all taxonomic levels simultaneously. Our findings revealed notable differences in the abundance of certain genera, with *Streptococcus*, *Rodentibacter_A*, and *Duncaniella* showing higher abundance in the tooth loss group, while *Muribacter* and *Ligilactobacillus* exhibited a significant decrease in the same group (Fig. 3C). Beyond the taxonomic analysis, we also predicted significant differences in metabolic pathways between the groups. Our predictions suggest that pathways such as myo-inositol degradation I, acetyl-CoA fermentation to butanoate II,

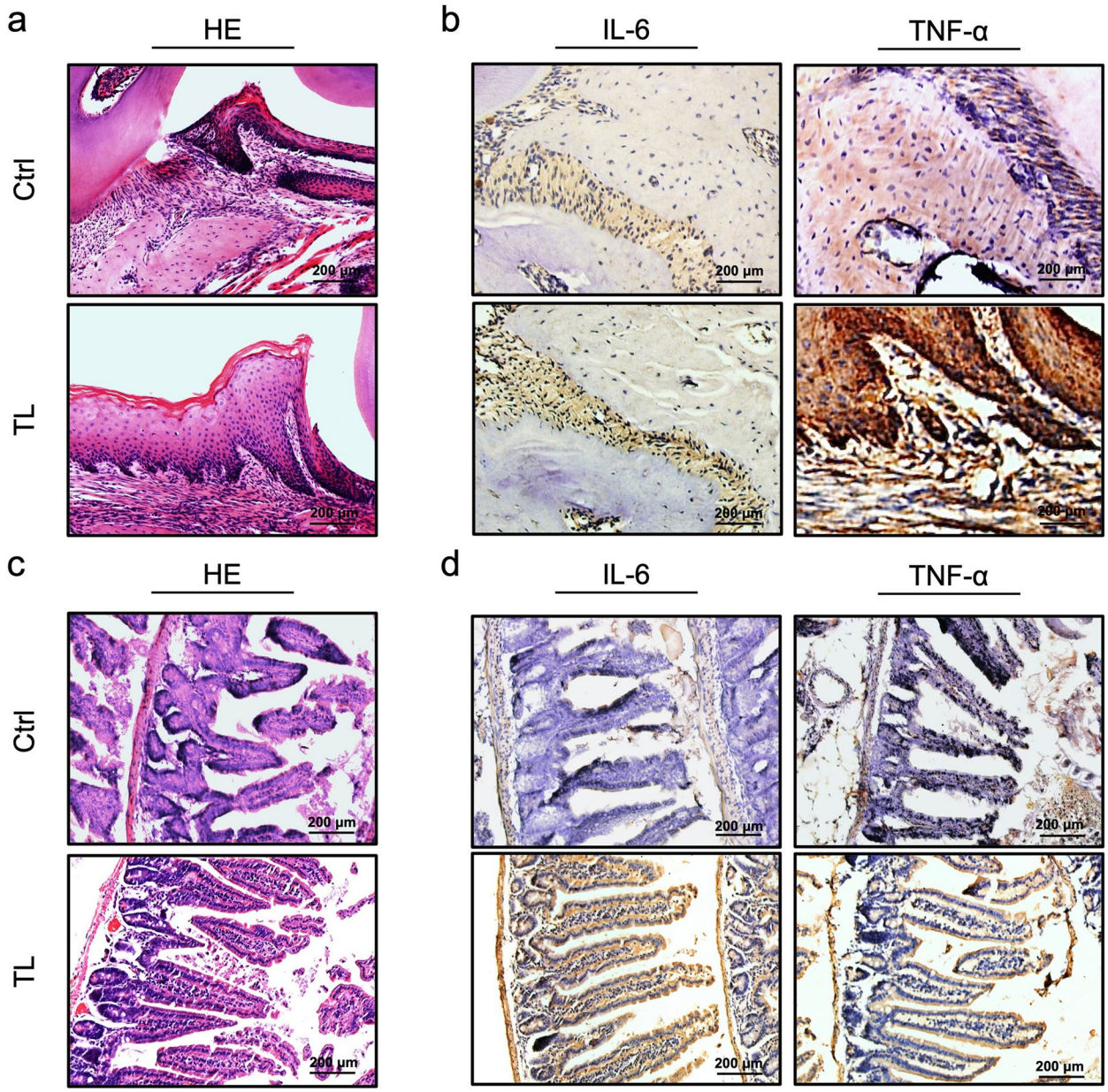

Fig. 1 The impact of oral tooth loss on intestinal health. **A** HE staining of the alveolar bone. **B** IHC staining of the alveolar bone. **C** HE staining of the intestine. **D** IHC staining of the intestine. Ctrl: the untreated and control group; TL: the tooth loss group was induced by extracting the first molars of the mice

and the superpathway of bacteriochlorophyll a biosynthesis might exhibit differences between the control and tooth loss groups (Fig. 3D).

These findings underscore the intricate relationship between tooth loss and the composition of the oral microbiota. The shift in microbial composition following tooth loss might have broader implications for systemic health, suggesting the need for targeted oral health interventions to maintain a balanced oral microbiome.

Alterations in the intestinal microbiota following tooth loss

We conducted metagenomic sequencing on fecal samples from two groups of mice to assess the impact on the gut microbiome. The interplay between the oral and gut microbiota, particularly the impact of oral microbiota changes on the gut, is a burgeoning area of research [29]. The sequencing results revealed significant alterations in the intestinal microbiota, as indicated by metrics of richness, diversity, and evenness in terms of microbial

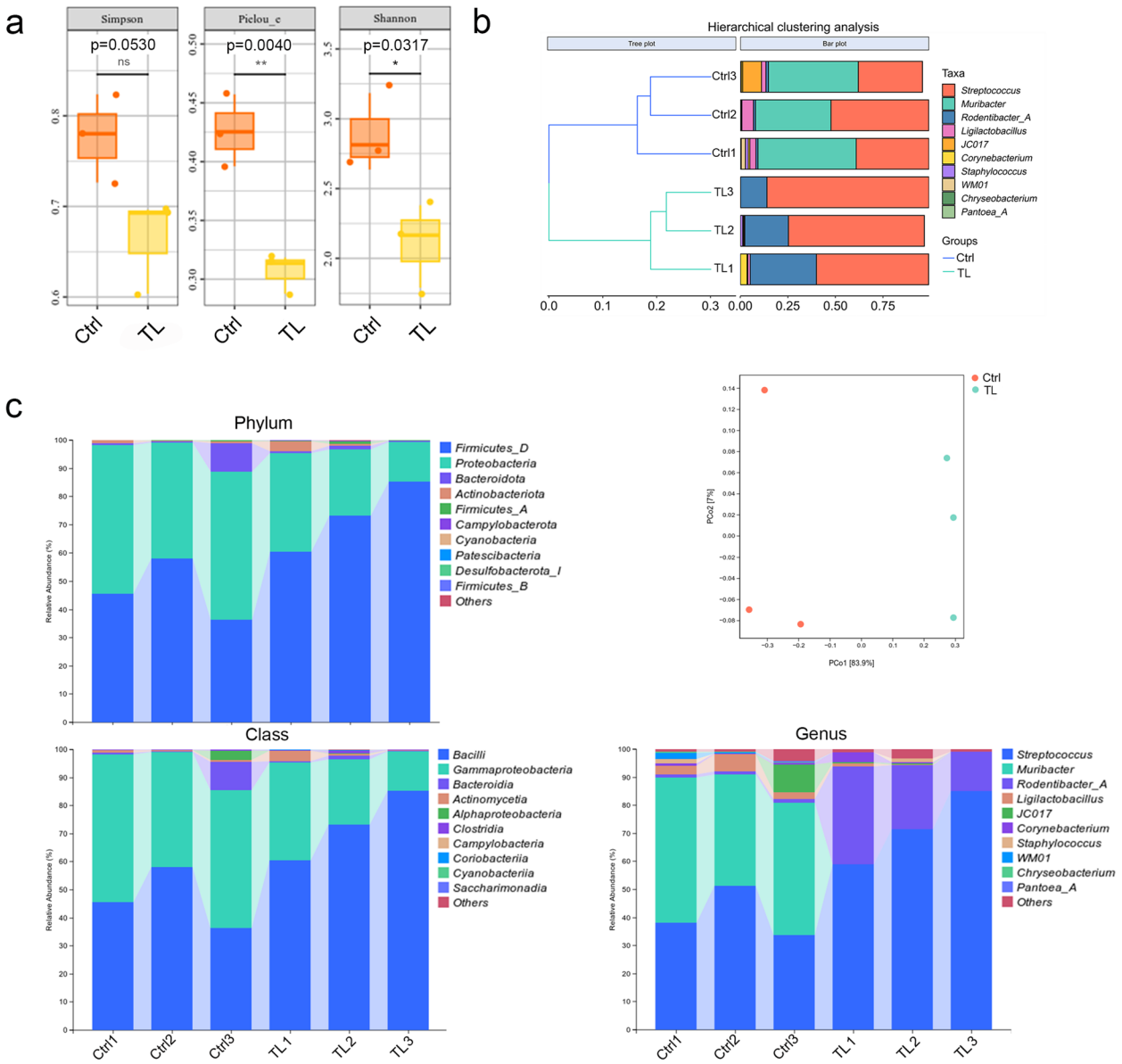

Fig. 2 Alterations in the oral microbiota following tooth loss. **A**-**B** The diversity and structure of the oral microbiota in each group. The α-diversity of the oral microbiota in each group is shown. ns, $P > 0.05$ by the Kruskal–Wallis test and Dunn's test; *, $P < 0.05$ by the Kruskal–Wallis test and Dunn's test; **, $P < 0.01$ by the Kruskal–Wallis test and Dunn's test. The β-diversity is presented as a PCoA plot based on UniFrac distances. **C** The percentages of the major phylum, classes, and genus represented in the oral microbiota. Ctrl: the untreated and control group; TL: the tooth loss group was induced by extracting the first molars of the mice

α-diversity (Fig. 4A). β-diversity analysis also demonstrated differences in the distribution of gut microbiota between the groups, indicating that tooth loss markedly alters the diversity of the gut ecological community (Fig. 4B).

Upon analyzing the microbiota composition at the phylum, genus, and species taxonomic levels for each sample, we observed the following: At the phylum level, *Bacteroidota* was the most dominant in both groups, but following tooth loss, there was an increase in the proportion of *Firmicutes*, with a decrease in *Bacteroidota* and *Campylobacterota*. At the genus level, *COE1* was the most abundant in the control group, whereas *Choladocola* was the most prevalent in the tooth loss group. At the species level, *COE1 sp009774245* and *Schaedlerella sp910575475* were the most dominant in the control group, while *Choladocola sp009774145* was the most abundant in the tooth loss group (Fig. 4C). Additionally,

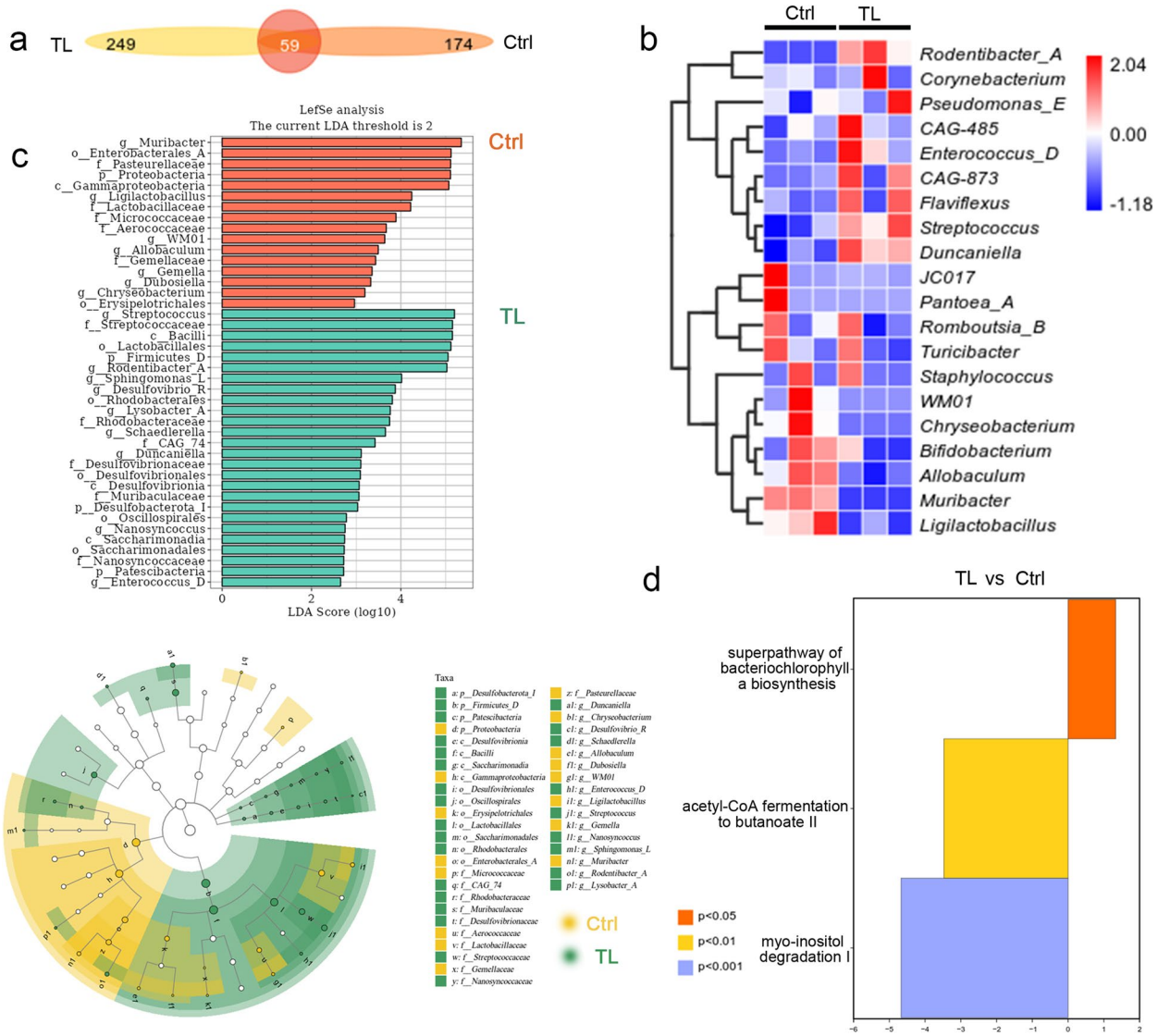

Fig. 3 Differential analysis of changes in the oral microbiota. **A** The Venn diagram intuitively shows the number of common OTUs among groups. **B** The heatmap clustering displays the distribution trends of top 20 genus abundance in each sample. **C** LEfSe differential analysis at all taxonomic levels. The bar chart shows significantly different taxa between groups on the vertical axis, and the horizontal axis displays the logarithmic LDA score for each taxon. The cladogram illustrates the taxonomic hierarchy from phylum to genus in the sample communities. Node size corresponds to the average relative abundance of the taxon; hollow nodes represent taxa with no significant difference between groups. **D** Prediction of functional units in the microbiota. Ctrl: the untreated and control group; TL: the tooth loss group was induced by extracting the first molars of the mice

we utilized LEfSe to perform a differential analysis across all taxonomic levels simultaneously (Fig. 4D). Alterations in the gut microbiota might be the major cause of intestinal damage following tooth loss.

Correlation between altered oral microbiota and intestinal microbiota distribution following tooth loss

To further elucidate the specific mechanisms by which tooth loss affects intestinal health, we conducted a correlation analysis between the significantly altered microbes in the oral cavity following tooth loss and the high-abundance intestinal microbiota. Our analysis revealed significant correlations at the phylum level, with an increase in post-tooth loss oral *Firmicutes_D* positively linked to elevated levels of *Cyanobacteria*, *Thermoproteota*, and *Myxococcota* in the intestine. In contrast, the reduction of oral *Proteobacteria* showed a significant inverse relationship with the presence of *Thermoproteota*

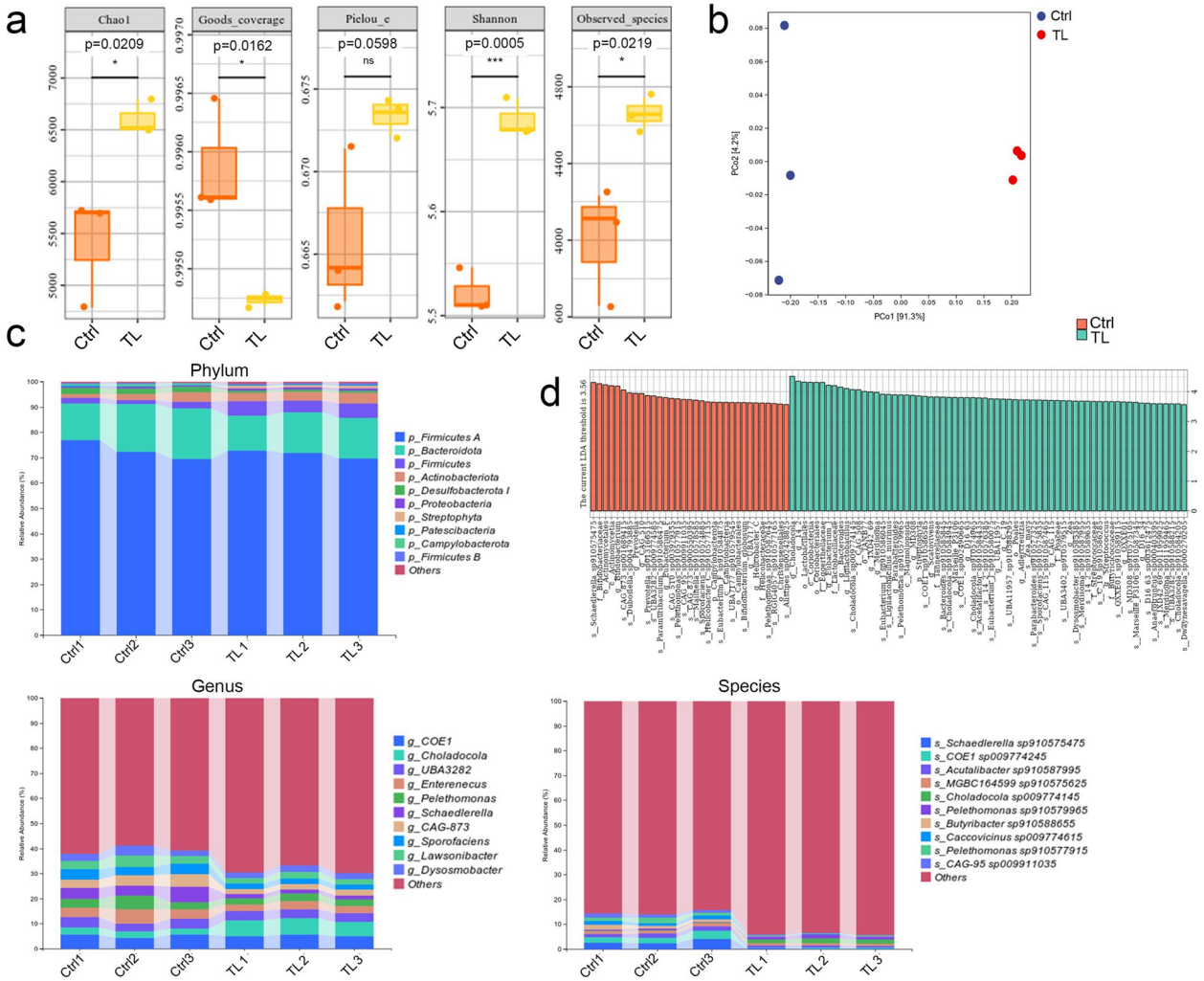

Fig. 4 Alterations in the intestinal microbiota following tooth loss. **A**-**B** The diversity and structure of the intestinal microbiota in each group. The α-diversity of the intestinal microbiota in each group is shown. ns, $P > 0.05$ by the Kruskal–Wallis test and Dunn's test; *, $P < 0.05$ by the Kruskal–Wallis test and Dunn's test; ***, $P < 0.001$ by the Kruskal–Wallis test and Dunn's test. The β-diversity is presented as a PCoA plot based on UniFrac distances. **C** The percentages of the major phylum, genus, and species represented in the intestinal microbiota. **D** LEfSe differential analysis at all taxonomic levels. The bar chart shows significantly different taxa between groups on the vertical axis, and the horizontal axis displays the logarithmic LDA score for each taxon. Ctrl: the untreated and control group; TL: the tooth loss group was induced by extracting the first molars of the mice

and *Myxococcota* in the intestinal microbiota. Additionally, we discovered a positive association between *Proteobacteria* and both *Firmicutes C* and *Apicomplexa* within the intestine (Fig. 5A).

At the genus level, the oral abundance of *Rodentibacter_A* was inversely related to *CAG-95* levels but showed a positive association with *UBA3402*. *Streptococcus*, with its increase, exhibited negative correlations with *MGBC164599*, *Caccovicinus*, and *Butyribacter*, contrasting with its significant positive correlation with *Ventrimonas*. Conversely, the diminished oral levels of *Muribacter* correlated positively with *CAG-95*, *Caccovicinus*, and *Butyribacter*, yet negatively with both *Ventrimonas* and *UBA3402*. Notably, the oral reduction in *Ligilactobacillus* demonstrated a significant negative correlation with *Bacteroides* (Fig. 5B).

In summary, the dysbiosis of the oral-gut axis following tooth loss suggests a potential mechanism by which tooth loss could impact intestinal health (Fig. 5C). This ecological imbalance in the microbiota may play a crucial role in the systemic health implications observed following tooth loss, potentially influencing the development or exacerbation of conditions such as cardiovascular diseases [30, 31], diabetes [32], and Alzheimer's disease [33–35]. Disruption of the oral-gut microbiota axis could alter immune responses, inflammation, and

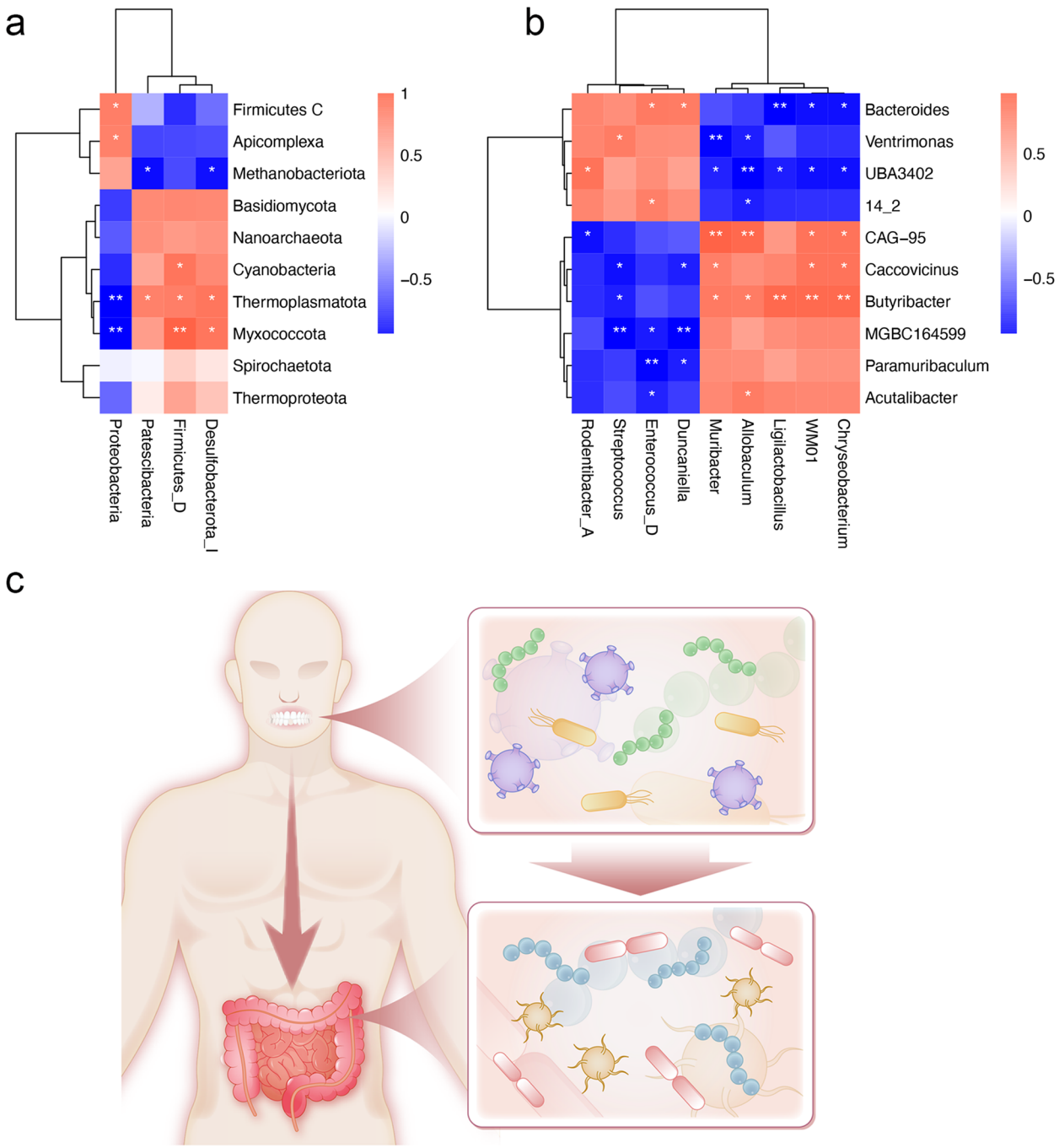

Fig. 5 Correlation between altered oral microbiota and intestinal microbiota distribution following tooth loss. **A** Correlation analysis between significantly altered phylum in the oral microbiota and the top 10 phylum in the intestinal microbiota. **B** Correlation analysis between significantly altered genus in the oral microbiota and the top 10 genus in the intestinal microbiota. **C** Hypothetical mechanism diagram. Ctrl: the untreated and control group; TE: the tooth loss group was induced by extracting the first molars of the mice

metabolic processes, which are known to play significant roles in the onset and progression of these diseases. Further research is needed to fully elucidate the mechanisms through which these microbial changes may affect systemic health.

Discussion

The concept of the oral-gut axis, which refers to the bidirectional relationship between oral and gut health [36], is at the core of our research. The diversity of the oral microbiota is crucial for maintaining overall health

[37]. In our mouse model, we observed that tooth loss led to changes in the oral microbiota, which were linked to a reduction in gut microbiota diversity. Metagenomic sequencing data indicated that tooth loss led to an increase in the proportion of certain bacterial phyla while decreasing others, potentially disrupting the balance of the gut microbiota. This dysbiosis of the gut flora might have profound effects on digestive system health [38], as it could lead to the development of gastrointestinal diseases [39] and affect nutrient absorption and metabolism [40].

Furthermore, our animal experiments have shown signs of imbalance in the extraction site, such as an increase in the expression of inflammatory factors. These oral changes were correlated with changes in the gut microbiota, indicating that the oral and gut were closely connected through a complex microbial network. It is necessary to analyze the impact of tooth loss on host immunity [41], metabolism, and the possible development of chronic diseases from multiple dimensions [42].

While our study offers valuable insights into the relationship between tooth loss and changes in the oral and gut microbiota, we recognize the limitations inherent in the mouse model used. In humans, tooth loss is often accompanied by significant dietary changes, including alterations in the types and characteristics of food consumed. These dietary changes likely have a profound impact on the oral microbiome. However, the mouse model in this study does not fully capture this aspect of human health, as the dietary patterns in mice may differ from those seen in humans, particularly following tooth loss. Given these limitations, while the findings from this model provide important preliminary data on the impact of tooth loss on the microbiota, further research involving human subjects is necessary to better understand the broader implications of tooth loss for both oral and systemic health. The mouse model was designed to isolate the effects of tooth loss on the microbiota, without the confounding influence of dietary changes or pre-existing dysbiosis. Although it does not fully replicate the complexity of human health and disease, it serves as a foundational step in exploring the relationship between tooth loss and microbiome alterations, paving the way for future studies in human populations. Further studies using human samples and more clinically relevant models are necessary to validate these findings and clarify their connection to specific systemic diseases.

Our findings, though based on a mouse model, highlight the potential impact of tooth loss on the oral-gut microbiota axis and its implications for systemic health [43, 44]. These results suggest the need for future research focusing on gut health in patients with tooth loss and exploring targeted interventions [27].

Conclusions

In summary, our research highlights the significant impact of tooth loss in mice on the oral and gut microbiota, underlining its potential implications for health. This study demonstrates that tooth loss in mice is not an isolated event but exerts broader effects on gut health and overall well-being. These findings suggest that future human studies should consider the potential consequences of tooth loss on gut health.

Abbreviations

HE	Staining: Histological Examination
IHC	Immunohistochemistry
OTUs	Operational taxonomic units

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12903-025-05581-7.

Supplementary Material 1.

Acknowledgements

Not applicable.

Authors' contributions

W. Wei and Q. Jiang conceived the study. L. Dong and Z. ji performed laboratory assays and experiments. L. Dong, Z. ji and J. Hu analyzed the laboratory data. L. Dong and Z. ji produced the tables and figures. L. Dong, Z. ji and W. Wei wrote the first draft with assistance from Q. Jiang. All authors critically reviewed and approved the final manuscript.

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Data availability

The raw sequence data reported in this paper have been deposited in the Genome Sequence Archive (Genomics, Proteomics & Bioinformatics 2021) in National Genomics Data Center (Nucleic Acids Res 2022), China National Center for Bioinformation / Beijing Institute of Genomics, Chinese Academy of Sciences (CRA018763, Shared URL: https://ngdc.cncb.ac.cn/gsa/s/9Bjbi8tS; CRA018760, Shared URL: https://ngdc.cncb.ac.cn/gsa/s/ebSeNfWh).

Declarations

Ethics approval and consent to participate

Ethical approval for this animal study was granted by the Ethics Committee of Capital Medical University (approval number: KQYY-202403–007).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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