Research Article

Identification of Aberrantly Expressed IncRNAs Involved in Orthodontic Force Using a Subpathway Strategy

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Background. The aim of the study was to identify key long noncoding RNAs (lncRNA) and related subpathways in the periodontal ligament tissue following orthodontic force. Methods. We adopt a novelty subpathway strategy to identify lncRNAs competitively regulated functions and the key competitive lncRNAs in periodontal ligament disorders after undergoing orthodontic force. To begin with, patients with orthodontics in our hospital were enrolled in our research. The relationship of lncRNA-mRNA was established through shared predicted miRNA by using the hypergeometric test, Jaccard coefficient standardization, and the Pearson coefficient to determine the valid interaction relationship. After embedding screened lncRNA interactions to pathways, the significant subpathways were recognized by lenient distance and Wallenius approximation methods to calculate the false discovery rate value of each subpathway. Results. The lncRNA-mRNA intersections including 263 lncRNAs, 1,599 mRNAs, and 3,762 interacting pairs were obtained. The enriched mRNAs were further enriched into various candidate pathways such as the PI3K-Akt signaling pathway. Several subpathways were screened, including the PI3K-Akt signaling pathway, 04510_1 focal adhesion, and p53 signaling pathway, respectively. The network of pathway-lncRNA-mRNA was constructed. Several key lncRNAs including DNAJC3-AS1, WDFY3-AS2, LINC00482, and DLEU2 were screened. Conclusions. DNAJC3-AS1, WDFY3-AS2, LINC00482, and DLEU2 as aberrantly expressed lncRNAs involved in orthodontic force might play crucial roles in periodontal ligament disease pathogenesis.

1. Introduction

Orthodontic tooth movement was considered a response to remodeling processes of the alveolar bone, which are initiated by the application of orthodontic force in the periodontium [1]. Bone remodeling is interceded by the release of cytokines and growth factors in the cellular paracrine environment, which are caused by the transmission of signals from extracellular matrix leading to alteration of nuclear protein matrix and gene activation or suppression [2]. Although there is increasing clarification of the primary aberrant cellular processes responsible for orthodontic tooth movement, the underlying mechanisms of many periodontal ligament disorders are still not fully understood. However, little information is available concerning lncRNAs involved in the field of the periodontal transcriptome [3]. Improved understanding of transcriptome arose by orthodontic forces helps us deepen the understanding of periodontal ligament disease pathogenesis, nominate new biomarkers, and motivate new therapeutic strategies.

Long noncoding RNAs (lncRNAs) have longer than 200 nucleotides regulating gene expression in epigenetics and transcription at the level of posttranscriptional repression of their target genes in a sequence-specific manner [4]. In addition, a tremendous amount of lncRNAs have no biological function annotations although there has been accumulating evidence that lncRNAs are closely associated with regulating various biological and pathological processes in the past 10 years [5]. However, researchers in the field of periodontium incorporated regulatory interaction information between periodontal ligament disease and lncRNAs biology into their studies [6, 7]. lncRNAs have also...
been implicated in periodontal ligament disease, such as previously periodontal ligament disease-associated VAMP3 [8] and CCND2 [9]. However, to our knowledge, orthodontic forces-associated lncRNAs and related functions and pathways in human have little been studied.

According to the competitive endogenous RNA (ceRNA) hypothesis, lncRNAs competitively bind to microRNA sites and regulated mRNAs expression levels [10, 11]. Through microarray profiling and bioinformatics analyses, firstly, lncRNA-mRNA competitively regulated interaction was constructed by the hypergeometric test and Jaccard coefficient. Then, we converted the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways into undirected graphs where genes as nodes and regulated relations as edges. After matching lncRNA-mRNA interaction to KEGG, lncRNA competitively regulated signal pathways (LRSP) were obtained. Interesting lncRNAs and genes were mapped into LRSP and subpathways were pitched in pathways by the lenient distance similarity method [12]. Eventually, the significance of candidate subpathways was assessed according to the Wallenius approximation [13]. We noticed that the deregulated lncRNAs caused by orthodontic forces represented complex regulation networks and participated in the immune system, signal transduction, translation, periodontal ligament tissue contraction, and other pathways.

2. Materials and Methods

2.1. Samples and Treatment. A total of 16 cases of adult patients that designed for the extraction of four first molars were selected randomly (8 cases in the treatment group, 8 cases in the control group), including 10 females and 6 males, aged 20–26 years old.

All the patients who participated in the experiment have healthy, noncarious human premolar teeth and informed consent from the hospital. The maxillary first premolar in each patient was stressed by 6 ounces of orthodontic traction interact torsion force value, then taking on the force on the maxillary first premolar; four weeks later, we gained the periodontal ligament tissue from the teeth. For this study, an approval from the Ethics Committee (the School of Stomatology Shandong University).

2.2. Microarray Assay. For the control group, the teeth were extracted individually at the same time similar to the treatment group and periodontal ligament tissue was extracted. mRNA were hybridized to Affymetrix Human U133 plus 2.0 gene chip at Shanghai Biotechnology Corporation.

2.3. lncRNA-mRNA Competitively Regulated Interaction Construction. MiRNA-mRNA interactions and lncRNA-miRNA interactions were primarily collected from starBase v2.0, TarBase, mortar base, mir2Disease, and miRecords v4.0. Based on the shared miRNAs, lncRNA-miRNA-mRNA interactions were constructed, from which the candidate lncRNA-mRNA competitively regulated interaction will be selected. Briefly, candidate lncRNA-mRNA interactions were determined by the hypergeometric test of shared miRNAs with false discovery rate (FDR) < 0.05 and Jaccard coefficient ranked at the top 20%. Hypergeometric functions were computed based on the following formula:

\[
P = 1 - \sum_{t=0}^{x} \binom{K}{t} \binom{N - K}{M - t} \binom{M}{N}^{-1}
\]

2.4. lncRNA Coexpression Network Construction. Based on the matched lncRNA and mRNA expression profiles, the Pearson correlation coefficient was used to evaluate the lncRNA-mRNA intersections. After Fisher’s Z transformation, P value < 0.01 was considered to be significant lncRNA-mRNA intersections under specific conditions in our study.

2.5. Subpathway Analysis. The lncRNA-regulated subpathway comprised two steps: mapping interested mRNAs and lncRNAs into linked pathways, and identifying lncRNA-regulated subpathways (Figure 1).

2.5.1. Screening of Candidate Different Pathways. mRNAs of lncRNA-mRNA interactions enrichment analysis was carried out based on the KEGG. Different pathways were identified by the Fisher test with the threshold of adjusted P < 0.01. In order to reconstruct the lncRNA competitively regulated signal pathways (LRSP), lncRNAs were embedded in the different pathways.

2.5.2. Different Pathways of Embedding lncRNAs. We reconstructed subways graphs by embedding lncRNAs to different pathways. lncRNA and miRNA participating in the competing regulation were deemed important nodes, which could assist us with precisely locating subpathways.

2.5.3. Identification of lncRNA Competitively Regulated Signal Subpathways. Important nodes were linked to LRSP and lenient distance similarity and network topology feature were used to identify the LRSP subways [12]. The detailed processes were described below. Firstly, the shortest path between any two important nodes of LRSP was calculated, if the count of molecules nodes between each pair of signatures was no more than k (k = 1); then, they will be merged into one node. Next, the number of nodes of the molecule sets in pathways were calculated, whose nodes count was no smaller than m (m = 8) were considered as candidate LRSP subpathways.

3. Results

3.1. Screening of Differentially Genes. Based on the platform of hgu133plus2, through systematic processing and statistics for the raw microarray data, we obtained the differentially
expressed genes and the critical differentially expressed genes (using adjusted \( P \) value \( \leq 0.05 \)). DNAJC3-AS1 (log fold change \( = -0.466 \), \( P \) adjust \( = 0.0142 \)) was downregulated while DLEU2 (log fold change \( = 0.464 \), \( P \) adjust \( = 0.0412 \)) was the most upregulated lncRNA (Figure 2).

### 3.2. lncRNA-mRNA Competitively Regulated Interaction Construction

As we know, lncRNAs contained miRNA-response elements and could competitively anchor to miRNAs, indirectly regulating mRNAs [10]. Based on the miRNA-mRNA interactions and lncRNA-miRNA intersections downloaded from multiple RNA databases, the lncRNA-mRNA interaction was obtained through shared miRNAs. A hypergeometric test was executed for each lncRNA-mRNA pair; combined with Jaccard coefficient ranking, the candidate lncRNA-mRNA interactions contained 3762 interaction pairs and 1599 mRNAs, and 236 lncRNAs were obtained. The genes of expression profiling were intersected with mRNA and lncRNA in the lncRNA-mRNA interaction, respectively. Finally, 1502 mRNAs and 169 lncRNAs were screened out for further study (Figure 3). The intersection between RNA expression profiles and candidate lncRNA-mRNA interaction was considered as lncRNA-mRNA competitively regulated interaction.

### 3.3. lncRNA Coexpression Network Construction

In this study, the Pearson correlation coefficient was utilized to calculate the coexpression coefficient for any pair of candidate lncRNA-mRNA interactions. A total of 76 IncGenePairs, 31 lncRNAs, and 71 mRNAs were identified with \( P \) value \( < 0.05 \). The top 5 IncGenePairs were EMX2OS opposite strand/antisense RNA-ACTN3 \( (P = 0.0001) \), THAP7-AS1-C19orf70 \( (P = 0.0009) \), IQCH-AS1-PPF1BP2 \( (P = 0.0015) \), PITPN-A51-SOSTDC1 \( (P = 0.0296) \), and EP3A1-AS1-TRAPPCC9 \( (P = 0.0238) \) (Table 1).
3.4. Sub Subpathway analysis

3.4.1. Screening of Candidate Different Pathways. KEGG is a database resource that integrates genomic, chemical, and systemic functional information. In the present study, we firstly mapped mRNAs of the candidate lncRNA-mRNA interactions to KEGG, with the Fisher test P value < 0.01, a total of 8 different pathways were identified (Table 2). Enriched mRNA were enriched into various candidate pathways including pathways in cancer (FDR \(1.14 \times 10^{-4}\)), PI3K-Akt signaling pathway (FDR \(4.05 \times 10^{-4}\), and focal adhesion (FDR \(1.06 \times 10^{-3}\)).

3.4.2. Different Pathways of Embedding lncRNAs. The screened lncRNAs were embedded into candidate pathways according to the results of lncGenePairs. Then, 76 lncRNAs of the candidate lncRNA-mRNA interactions were embedded to the 8 different pathways, and 66 pairs of matched lncRNAs and genes were obtained (Table 3). LRSP included the lncRNA node and edge of lncRNA-mRNA competitive regulation. Figure 4 shows the predicted form of lncRNA-mRNA interactions.

3.4.3. Recognition of LRSP Subpathways. We reconstructed condition-specific LRSP by embedding lncRNAs to different pathways based on matched lncRNA-mRNA expression profiles and shared miRNA. LRSP subpathways including interesting lncRNA were located to pathways according to the “lenient distance” similarity method. After calculating the significance by Wallenius approximation, LRSP subpathways were ranked (Table 4).

After identification, several subpathways were screened, including the PI3K-Akt signaling pathway, focal adhesion, and pathways in cancer (Table 4). In the top 3 pathways, various lncRNAs and related genes were involved (Figure 5). For example, LINC00482 in focal adhesion pathway was closely associated with MET and ITGA3. Besides, insulin-like growth factor-1 (IGF1) involved in the PI3K-Akt signaling pathway, focal adhesion, and p53 signaling pathway. Furthermore, IGF1 in the PI3K-Akt signaling pathway was associated with DNAJC3-AS1 and FAM201A.

4. Discussion

Increasing evidence has shown that lncRNAs were important factors for regulating gene expression [14]. However, the molecular mechanism in lncRNAs driven by orthodontic force including lncRNA functions and regulatory genes remain unknown. In this study, lncRNA-regulated subpathways were identified, including the PI3K-Akt signaling pathway, as well as focal adhesion and prostate cancer.

| lncRNA     | Gene            | corValue     | P value     |
|------------|-----------------|--------------|-------------|
| EMX2OS     | ACTN3           | 9.89 \times 10^{-2} | 0.000159    |
| THAP7-AS1  | C19orf70        | 9.17 \times 10^{-2} | 0.009968    |
| IQCH-AS1   | PPFIBP2         | 8.97 \times 10^{-2} | 0.01515     |
| PITPNA-AS1 | SOSTDC1         | 8.55 \times 10^{-2} | 0.029634    |
| EPHA1-AS1  | TRAPPCK9        | 8.71 \times 10^{-2} | 0.023883    |
| RAMP2-AS1  | TYW5            | 9.72 \times 10^{-2} | 0.001201    |
| H1FX-AS1   | WDR13           | 8.24 \times 10^{-2} | 0.043405    |
| PCBP1-AS1  | PDGFR1          | 9.58 \times 10^{-2} | 0.002668    |
| PCBP1-AS1  | SIRT1           | 9.03 \times 10^{-2} | 0.013484    |
| WDFY3-AS2  | PTEN            | 8.86 \times 10^{-2} | 0.018571    |

Figure 3: Heat maps showing the distinct lncRNA (a) and mRNA (b) expression profiles between the control group and the treatment group. Red colour represents upregulation; blue colour represents downregulation.
found that significantly inhibited the IGF1 synthesis [17]. Xiang et al.
Meanwhile, the cyclic tensile strain of high magnitude ligament cells to inflammation by the orthodontic load.

growth factor was modulated the response of periodontal possible role in periodontal regeneration. Moreover, IGF1 as growth factor was modulated the response of periodontal ligament cells to inflammation by the orthodontic load. Meanwhile, the cyclic tensile strain of high magnitude significantly inhibited the IGF1 synthesis [17]. Xiang et al. found that DNAJC3-AS1 has performed dysregulation in human periodontal ligament [18]; this is consistent with our results. Consequently, DNAJC3-AS1 was important for recovery of periodontal tissue by regulating IGF1.

WDFY3 antisense RNA 2 (WDFY3-AS2) was found to regulate two mRNAs via focal adhesion, including phosphatase and tensin homolog (PTEN) and cyclin D2 (CCND2). Both PTEN and CCND2 are protein-coding genes. PTEN encoded a phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase [19], the gene CCND2 belongs to the highly conserved cyclin family, and they were mainly present in cytosol and nucleus. In a previous study, CCND2 was confirmed to be related to the regulation of periodontal tissue [20]. As a member of the cyclin family, CCND2 is a key component for facilitating the G1-to-S-phase transition and subsequently increased cell proliferation. Besides, additional research demonstrated that PTEN might take part in the imbalance between cell proliferation and death [9, 21]. In the present study, WDFY3-AS2 was enriched into the focal adhesion signaling pathways. Consistent with the study of Molina et al. [22], mechanical stress could bring topographic changes of focal adhesion components and p125FAK activation in stretched human periodontal ligament fibroblasts. Thus, WDFY3-AS2 served as a potential key IncRNA for the recovery of periodontal ligament cells after the application of orthodontic force by regulating PTEN and CCND2.

Long intergenic nonprotein coding RNA 482 (LINC00482) was screened as IncRNA in the present study and resulted in the regulation of various genes, such as ITGA3, SNF, MET, and SERPINB5, respectively. Integrin, alpha 3 (ITGA3) belonged to the family of integrins and was mainly present in cytosol and cytomembrane. ITGA3 encodes the integrin alpha 3 chains. Alpha chain 3 undergoes posttranslational cleavage in the extracellular domain to yield disulfide-linked light and heavy chains that join with beta 1 to form an integrin that interacts with many extracellular matrix proteins [23]. Saminathan et al. [24] found that mechanical stress reduced the metabolic activity of periodontal ligament cells through effecting the expression of adhesion-related gene ITGA3. As we all know that SNF presents in mammalian as SWI/SNF complexes utilizing either Brahma (Brm) or Brahma-related gene 1 (Brg1) catalytic subunits to remodel nucleosomes in an ATP-dependent manner [25]. MET proto-oncogene, receptor tyrosine kinase (MET) associated with multiple diseases (such as lung cancer, hepatocellular carcinoma) in the focal adhesion pathway [26] is a protein-coding gene. Gene ontology notes that MET regulates physiological processes including transferase activity, transferring phosphorus-containing groups and protein tyrosine kinase activity. In adults, MET

### Table 2: 8 pathways enriched by candidate mRNAs.

| Pathway_names | Pathway_names | Pathway_names |
|---------------|---------------|---------------|
| 05200 Pathways in cancer | 04151 PI3K-Akt signaling pathway | 04510 Focal adhesion |
| 04510 Melanoma | 05218 p53 signaling pathway | 04115 Arrhythmogenic right ventricular cardiomyopathy (ARVC) |
| 05412 Prostate cancer | 05215 Melanoma | 05414 Dilated cardiomyopathy (DCM) |
| 05218 Pathways in cancer | 04115 PI3K-Akt signaling pathway | 05200 pathways enriched by candidate mRNAs. |

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| 05218 Pathways in cancer | 04115 PI3K-Akt signaling pathway | 05200 pathways enriched by candidate mRNAs. |

### Table 3: 10 pairs of matched lncRNA and genes embedded into the 8 different pathways.

| Path_name | Matched_lnc | Matched_gene | Path_name | Matched_lnc | Matched_gene |
|-----------|-------------|--------------|-----------|-------------|--------------|
| 4115      | LINC00482   | SNF          | 5412      | EMX2OS      | ACTN3        |
| 4115      | WDFY3-AS2   | PTEN         | 5414      | LINC00482   | ITGA3        |
| 4151      | FAM201A     | AKT2         | 5215      | DNAJC3-AS1  | IGF1         |
| 4151      | WDFY3-AS2   | PTEN         | 5218      | WDFY3-AS2   | PTEN         |
| 4510      | EPB41L4A-AS1| PTEN         | 5200      | LINC00482   | ITGA3        |

FDR, false discovery rate.
participates in wound healing as well as organ regeneration and tissue remodeling in order to promote differentiation and proliferation of hematopoietic cells [27]. Mammary serine protease inhibitor encoded by Serpin family B member 5 (SERPINB5) belongs to the serine protease inhibitor (serpin) superfamily [28]. Serpins regulate a number of cellular processes including phagocytosis, coagulation, and fibrinolysis [29]. Consequently, LINC00482 may be involved in the mechanism following periodontal ligament cell by regulation of the immune response and inflammation process.

Moreover, it is not difficult to see that deleted in lymphocytic leukemia 2 (DLEU2) directly regulated ITGA4 and YWHAE in the PI3K-akt signaling pathway (see Fig. 5). Yu et al. [30] found that integrin alpha 4 (ITGA4) may play key roles in mesenchymal stem cells derived from periodontal ligament. The product of gene ITGA4 belongs to the integrin alpha chain family of proteins, like ITGA3. Interestingly, this gene encodes an alpha 4 chain associated with either beta 1 chain [31] or beta 7 chains. Tyrosine 3-monoxygenase/tryptophan 5-monoxygenase activation protein epsilon (YWHAE) encoded 14-3-3 protein epsilon belonging to the

![Diagram](image-url)
14-3-3 family of proteins which mediate signal transduction by binding to phosphoserine-containing proteins [32]. Notably, Abbaszadeh et al. [33] demonstrated that yttrium aluminum garnet laser irradiation on human gingival fibroblasts lead to significantly changed expression proteins produced by YWHAE, UBA52, SNF, and so on. Based on this information, we inferred that DLEU2 was an important lncRNA for the recovery of periodontal ligament cells after the application of orthodontic force by regulating ITGA4 and YWHAE.

In conclusion, the strategy of subpathways is feasible to predict marker pathways for periodontal ligament disorders.

### Table 4: LRSP subpathways.

| Pathway_Id | Pathway_Name | Molecule ratio (m2/x) | Molecule list |
|------------|--------------|-----------------------|---------------|
| 04151_1    | PI3K-Akt signaling pathway | 12/69 | LAMC3; ITGA3; CSF1R; YWHAE; AKT2; IRS1; CCND2; CDKN1B; ITGA4; IGF1; CASP9; PDGFRα; KIT; AKT3; PTEN; FOXO3; FGF2; MET |
| 04510_1    | Focal adhesion | 8/69 | ITGA3; ACTN3; AKT2; CCND2; PIK3R5; ITGA4; IGF1; PDGFRα; PTEN; FLNA; MET |
| 05200_1    | Pathways in cancer | 7/69 | ITGA3; GRB2; AKT2; PIK3R5; CASP9; PDGFRα; KIT; AKT3; PTEN |
| 05215_1    | Prostate cancer | 5/69 | AKT2; PIK3R5; IGF1; CASP9; PDGFRα; AKT3; PTEN |
| 04115_1    | P53 signaling pathway | 4/69 | CCND2; SERPINB5; SFN; TP53; PTEN |
| 05218_2    | Melanoma | 4/69 | IGF1; PDGFRα; EGF; EGFR; FGF2; MET |

Id, identity.

By integrating the expression profiles of lncRNA and mRNA, several screened lncRNAs including DNAJC3-AS1, WDFY3-AS2, LINC00482, and DLEU2 in the subpathways of PI3K-Akt signaling pathway, focal adhesion, and prostate cancer might play crucial roles in orthodontic forces pathogenesis.

### Data Availability

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

### Conflicts of Interest

The authors declare that they have no conflicts of interest.

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