Effects of DSPP Gene Mutations on Periodontal Tissues

Zhaojun Jing1 Zhibin Chen2 Yong Jiang1

1 Department of General Dentistry II, Peking University School and Hospital of Stomatology, National Clinical Research Center for Oral Diseases, National Engineering Laboratory for Digital and Material Technology of Stomatology, Beijing, People’s Republic of China
2 Department of Periodontology, Peking University School and Hospital of Stomatology & National Clinical Research Center for Oral Diseases, National Engineering Laboratory for Digital and Material Technology of Stomatology, Beijing Key Laboratory of Digital Stomatology, Beijing, People’s Republic of China

Global Med Genet 2021;8:90–94.

Abstract
Dentin sialophosphoprotein (DSPP) gene mutations cause autosomal dominantly inherited diseases. DSPP gene mutations lead to abnormal expression of DSPP, resulting in a series of histological, morphological, and clinical abnormalities. A large number of previous studies demonstrated that DSPP is a dentinal-specific protein, and DSPP gene mutations lead to dentin dysplasia and dentinogenesis imperfecta. Recent studies have found that DSPP is also expressed in bone, periodontal tissues, and salivary glands. DSPP is involved in the formation of the periodontium as well as tooth structures. DSPP deficient mice present furcation involvement, cementum, and alveolar bone defect. We speculate that similar periodontal damage may occur in patients with DSPP mutations. This article reviewed the effects of DSPP gene mutations on periodontal status. However, almost all of the research is about animal study, there is no evidence that DSPP mutations cause periodontium defects in patients yet. We need to conduct systematic clinical studies on DSPP mutation families in the future to elucidate the effect of DSPP gene on human periodontium.

Keywords
► dentin sialophosphoprotein
► genetic mutations
► periodontal defects

Introduction
The dentin sialophosphoprotein (DSPP) gene consists of five exons and four introns located on chromosome 4q21. Previously, the DSPP was believed to be expressed only in dentin.1 To date, 40 pathogenic mutations of the DSPP gene have been identified in different ethnic groups, 17 of which are located in the DSP region and 23 in the DPP region.1–7 A proposal was made in 1973, based on clinical and imaging characteristics and the expression of DSPP gene mutations in dentin, to divide hereditary dentin defects into two distinguishable groups, the dentine dysplasia (DD) and the dentinogenesis imperfecta (DGI), both of which are autosomal dominant genetic diseases.8 According to the clinical and imaging manifestations, DGI can be further classified into type I, II, and III and DD into type I and type II.8,9 The most common clinical disease is DGI-II, namely hereditary opalescent dentin.8 DGI-II, DGI-III, and DD-II are mostly caused by mutations of the same gene, the DSPP gene.1,10

The reason why DSPP gene mutations can cause abnormal tooth development is that DSPP is related to the mineralization of hydroxyapatite (HA). The mineralized tissues, such as
dentin, cementum, and bone, are developed through similar mechanisms with similar composition to each other. Odontoblasts, cementoblasts, and osteoblasts secrete unmineralized type-I collagen-rich matrices. These unmineralized organic areas are transformed into mineralized phases after the deposition of hydroxyapatite. This dynamic biomineralization process involves active interactions among several molecules, including type-I collagen and numerous noncollagenous proteins (NCPs), of which DSPP is a member of its own category. DSPP is believed to be specifically expressed in dentin in the early stage and has a significant effect on the formation and mineralization of dentin. It is also expressed in ameloblast cells at a transient level. Subsequently, DSPP is also found in other nondental tissues such as bone, periodontal tissues, kidney, salivary gland, and mammary gland. DSPP gene mutations not only cause hereditary dentine defects, but also affect the formation of other soft and hard tissues. Basing on the critical role of periodontal tissue in oral health, the periodontium defects caused by DSPP gene mutations have attracted more and more attention from researchers. Dentine defects caused by DSPP gene mutations are usually manifested as crown discoloration, enamel dislodged, dentin attrition, pulp alterations, and periapical lesions. DEFQ1 mutations are usually manifested as crown discoloration, enamel dislodged, dentin attrition, pulp alterations, and periapical lesions. DSPP gene mutations not only cause hereditary dentine defects, but also affect the formation of other soft and hard tissues. Basing on the critical role of periodontal tissue in oral health, the periodontium defects caused by DSPP gene mutations have attracted more and more attention from researchers. Dentine defects caused by DSPP gene mutations are usually manifested as crown discoloration, enamel dislodged, dentin attrition, pulp alterations, and periapical lesions. The clinical investigation in this study only involved one adult and one child, and the characteristics of alveolar bone cells was analyzed in only one adult. In addition, the details on oral clinical examination like probing depth, clinical attachment loss, bleeding on probing etc. are not shown in this study.

### Three Cleavage Fragments of DSPP and Their Functional Roles

Studies showed that DSPP exists in the extracellular matrix (ECM) as three cleavage fragments: DSP, DPP, and glycosylation dentin sialoprotein (DPG). DSP, DPP, and DPG were discovered in 1967 and 1981, respectively. The discovery of DSP and DPP in ECM was earlier than DSPP, but their effects were unclear at that time. After 13 years later in 1994, it was confirmed that DSP and DPP came from two fragments of the same protein DSPP. Later, the third fragment of DSPP, the proteoglycan form of DSP, that is, DPG, was confirmed and purified in 2005. DSP, DPP, and DPG play different roles in the formation and mineralization of mineralized tissue. The proteolytic processing of DSPP into DSP, DPP, and DPG is an essential activation step for its biological function in biomineralization. In other words, the role of DSPP in biomineralization relies on its cleaved products. Various studies have shown DPP to be an important initiator and modulator of the formation and growth of HA. DSP and DPG are involved in the maturation of mineralized dentin. In addition, DPP has been suggested to regulate the expression of the marker genes of dentin and bone via the SMAD-pathway and integrin/MAPK signaling pathway. Although DSP has been shown to regulate the initiation of mineralization, it appears not to have a functional role in the maturation of dentin. In vitro studies have demonstrated that DSP promotes human dental pulp cells to differentiate into odontoblast-like cells. In addition, DSP has been shown in the alveolar bone, cementum, and periodontal ligament (PDL). It suggested that DSP is involved in the formation of the periodontium. N-terminal DSP was shown to promote bone formation by accelerating osteoblast cell proliferation and differentiation and inducing the expression of osteogenic markers, such as COL1, Runx2, Osterix, and ATF. However, little is known about the effects of DPG.

### Clinical Study of Patients with Periodontium Defects Caused by DSPP Gene Mutation

A large number of studies have confirmed the existence of periodontal defects in DSPP-deficient mice, but little attention has been directed to the periodontal status of patients with DSPP gene mutation. At present, there are few relevant clinical studies and the only study is shown here. Pontavetevut et al suggested DSPP mutation caused alveolar bone damage by studying the characteristics of alveolar bone cells in patients with dentinogenesis imperfecta. The researchers performed basic research in a family with a DSPP heterozygous pathogenic missense mutation presented with defective dentin and periodontium. Heterogeneous cells were isolated from the human alveolar bone of patients with the DSPP mutation and compared with those of healthy donors. In comparison, DGI patients with the DSPP gene mutation showed reduced alveolar bone cell proliferation and colony formation units, delayed cell spreading, and inhibited osteogenic differentiation as well as altered expression of alkaline phosphatase (ALP), COL1, and OCN. DSPP is involved in the development of periodontal tissues. The genomic organization of the DSPP gene is very similar among mice, rats, and humans. In 2004, Baba et al were among the first group to demonstrate DSP was expressed in...
the periodontal tissues of rats. In this study, the root formation of molars in rats was systematically studied. The specific anti-DSP polyclonal and monoclonal antibodies were used to detect the DSP, and the high-sensitivity RNA probe was used to detect the DSP mRNA transcripts in situ. The expression of the DSP gene in osteoblasts, odontoblasts, and fibroblasts was confirmed. Although the gene expression level of osteoblasts was low, the staining intensity in the alveolar bone matrix was similar to that in dentin. These results suggest that DSP plays a vital role in the formation of the periodontium, especially alveolar bone.

The PDL contains PDL stem cells (PDLSC) that have a high proliferative capacity and could differentiate into different cell lineages, such as osteoblast-like cells, cementoblast-like cells, and fibroblast-like cells. Furthermore, PDLSCs are extremely important for maintaining PDL stability, repairing cementum tissue damage, and achieving functional cell renewal. In 2013, Ozer et al studied the expression pattern and distribution of DSP fragments in mouse periodontium at the transcriptional and translational levels using in situ hybridization and immunohistochemical analyses, and confirmed that DSP was expressed in PDL and alveolar bone at various stages of root development. The recombinant COOH-terminated DSP fragment (r-C-DSP) induces cell proliferation and differentiation by promoting the expression of tooth/bone-related markers, transcription factors, and growth factors, as well as by the formation of mineralized tissue and ALP activity. DSP was proved for the first time to be able to promote the adhesion, migration, proliferation, and differentiation of PDLSC and PDL cells, thus promoting the formation, repair, and regeneration of periodontal tissue.

### The Loss of DSPP Expression or the Overexpression of the NH2 Terminal Expression Products of DSPP Caused Periodontium Defects

Gibson et al conducted a series of studies on DSPP. In addition to proving the important role and mechanism of DSPP in the process of dentin formation, they also found that DSPP was closely related to the formation and health maintenance of periodontal tissue. This paper mainly discusses the close relationship between DSPP and periodontal tissue. In 2013, Gibson et al conducted a study on DSPP gene knockout mice, which confirmed that DSPP deletion would cause severe damage to the periodontium, and suggested that DSPP plays a key role in maintaining the structural integrity of periodontium. X-ray plain film and micro-CT were used to evaluate the morphology and structure of the whole mandible of DSPP gene knockout mice, which showed that alveolar bone defects were more serious than in normal mice, especially in the furcation area of mandibular molars. Histochemical observation revealed alveolar bone loss, inflammatory cell infiltration, detachment of the PDL, and the apical migration of epithelial attachment, suggesting the occurrence and progression of periodontitis. Scanning electron microscope data further confirmed alveolar bone loss and showed a significant loss of cementum. The mineral content around osteoblasts in DSPP deficient mice was significantly reduced, which was manifested as alveolar bone and cementum defects, secondary damage to the PDL located between alveolar bone and cementum. These structural changes lead to bacterial infiltration, periodontal inflammation, further loss of alveolar bone and periodontal pocket formation, periodontal diseases occurred in the end. Gibson et al pointed out in another paper in 2013 that proteolysis of DSPP was a necessary condition for the formation and maintenance of a healthy periodontium. The results showed that transgenic mice expressing the uncleavable full-length DSPP in the DSPP knockout (DSPP-KO) background (named DSPP-KO/D452A-Tg mice) had severe alveolar bone loss and obvious inflammatory cell infiltration in the furcation area of mandibular first molars. However, the mice expressing the normal DSPP transgene in the DSPP-KO background (designated DSPP-KO/normal-Tg mice) could reverse alveolar bone damage, show epithelial attachment at the cemento-enamel junction, and promote the deposition of healthy alveolar bone. The study suggested that DSPP proteolysis was significantly associated with periodontal tissue formation and health maintenance. Gibson also suggested that the periodontal defects observed in DSPP-deficient mice are due to intrinsic defects in alveolar bone and cellular cementum due to DSPP dysfunction but are not disease secondary to chronic periodontitis. It is likely the alveolar bone loss occurs earlier than chronic periodontitis, and periodontitis can exacerbate the periodontal defects in DSPP-deficient mice as chronic periodontitis itself could also cause alveolar bone loss and PDL damage. Gibson et al mentioned it remained to be seen whether treating and preventing chronic periodontitis could slow or save periodontal defects in DSPP-deficient mice. In 2014, the Gibson et al made further research on the NH2 terminal expression products of DSPP, the DSP and DPG. Compared with DSPP knockout mice, they concluded the transgenic mice overexpressing the NH2-terminal fragment of DSPP in the DSPP knockout background (named “DSPP KO/DSP Tg” mice) showed more severe defects in the alveolar bone and cementum with remarkably altered canalicular systems around the osteocytes, and more apical migration of the epithelial attachment with severe inflammation in molar furcation region. Overexpression of NH2 end of DSPP can also aggravate the destruction of periodontal tissue, suggesting NH2 end fragment of DSPP protein may inhibit the formation and mineralization of the alveolar bone and cementum.

Shi et al study also supported that DSPP deficiency could lead to periodontal tissue defects. In addition, Shi et al focused specifically on the periodontal phenotype of DSPP heterozygotes and their age-dependent periodontal damage. The study divided mice into three groups; DSPP genotype of wild-type group (DSPP +/-), heterozygous HET group (DSPP +/-/C0), and knockout KO group (DSPP +/-/C0). The result showed, except for similar dental phenotypes to DD-II in DSPP heterozygous group, the periodontium was also affected; exhibiting apical migration of the junctional epithelium, decreased alveolar bone height and width, and inflammatory cell infiltration leading to periodontal tissue destruction. Both the dental and periodontal
phenotypes are age dependent and more severe at 18 months than at 12 months. The study showed that DSPP heterozygous mice developed severe periodontitis with age.\textsuperscript{50}

**The Relationship between Plaque Microorganism and Alveolar Bone Loss**

From the above study, we learnt the mechanisms of the alveolar bone defects caused by DSPP gene mutations include primarily the inhibition of osteoblastic differentiation of osteocytes, the reduction of bone formation, and the subsequent inflammatory infiltration leading to continuous alveolar bone destruction. Alveolar bone loss is mainly due to periodontal inflammation clinically. The etiology of periodontitis is multifactorial, among which dental plaque is the initiating factor.\textsuperscript{51,52} In particular, a group of specific gram-negative anaerobic species known as the “red complex” results in chronic inflammation.\textsuperscript{53} The subgingival plaque biofilm causes inflammation and elicits immune responses of the host, leading to irreversible destruction of the periodontal tissues eventually, especially alveolar bone and PDL of the susceptible host.\textsuperscript{51,54,55}

**Summary and Outlook**

In summary, DSPP gene mutations cannot only lead to typical hereditary dentin defects but also lead to defects of the periodontal tissue. Therefore, we need to update our understanding of the effects of DSPP gene mutations on oral health. The mechanisms for the severe periodontium defects and even teeth loss caused by DSPP gene mutations can be summarized as the following two aspects. On the one hand, the deficiency of DSPP, caused by mutations in the DSPP gene, leads to the failure of the normal formation and mineralization process of periodontal tissues, which is manifested as alveolar bone defect and the apical migration of the junctional epithelium. On the other hand, congenital PDL defects make this area a vulnerable point for the colonization and reproduction of oral microorganisms, leading to infiltration of inflammatory cells and creating suitable conditions for initiating development of periodontitis. When the periodontium of the DSPP gene mutations is doubly suppressed by genetic defects and microecology, the periodontal prognosis of the DSPP gene mutations is not optimistic. Whether the two have superimposed effects still needs to be further elucidated. However, almost all of the studies on the effect of DSPP on periodontal tissue formation are from animal studies, and there is no exact evidence that patients with DSPP gene defects have severe periodontium defects yet. More clinical studies are therefore needed in this field.

In addition, it has been reported that periodontal inflammation in DSPP mutant mice is age-dependent. We speculate periodontal defects in patients with DSPP mutations may also worsen with age. Again, this is only an animal study, and no relevant clinical studies were conducted. Because the health of periodontium is critical to tooth survival, the effect of DSPP mutations on periodontal tissue deserves our attention. Although the current research on DSPP gene mutations is mainly confined to animal experiments, the conclusions of these studies help us to clarify the direction of future research. In the future, we need to conduct systematic clinical studies on DSPP mutation families. Two questions remain to be answered through further in vivo studies. First, whether DSPP mutation causes periodontal defects in patients, even age-dependent periodontal defects? Second, whether DSPP gene mutation is associated with periodontitis?

**Funding**

None.

**Conflict of Interest**

None declared.

**Acknowledgments**

The authors thank Fang Yao Stephen Hou for English language editing.

**References**

1. McKnight DA, Suzanne Hart P, Hart TC, et al. A comprehensive analysis of normal variation and disease-causing mutations in the human DSPP gene. Hum Mutat 2008;29(12):1392–1404
2. Li F, Liu Y, Liu H-C, Feng H-L. Genetic variants analysis and histological observation of teeth in a patient with hereditary opalescent dentin. J Peking Univ 2018;50(04):666–671
3. Li F, Liu Y, Liu H, Yang J, Zhang F, Feng H. Phenotype and genotype analyses in seven families with dentinogenesis imperfecta or dentin dysplasia. Oral Dis 2017;23(03):360–366
4. Zhang X, Zhao J, Li C, et al. DSPP mutation in dentinogenesis imperfecta Shields type II. Nat Genet 2001;27(02):151–152
5. Rajpar MH, Koch MJ, Davies RM, Mellody KT, Kiely TM, Dixon MJ. Mutation of the signal peptide region of the bicistronic gene DSPP affects translocation to the endoplasmic reticulum and results in defective dentine biominalerization. Hum Mol Genet 2002;11(21):2559–2565
6. Malmgren B, Lindskog S, Elgadi A, Norgren S. Clinical, histopathologic, and genetic investigation in two large families with dentinogenesis imperfecta type II. Hum Genet 2004;114(05):491–498
7. Maciejewska I, Chomik E. Hereditary dentine diseases resulting from mutations in DSPP gene. J Dent 2012;40(07):542–548
8. Shields ED, Bixler D, Al-Kafrawy AM. A proposed classification for heritable human dentine defects with a description of a new entity. Arch Oral Biol 1973;18(04):543–553
9. de L Lare-Moll M, Philippe Fournier B, Berdal A. Isolated dentinogenesis imperfecta and dentin dysplasia: revision of the classification. Eur J Hum Genet 2015;23(04):445–451
10. Liu Y, Huang Y, Gao J, Li S, Zhao X, Zhang X. Identification of a novel mutation of DSPP gene in a Chinese family affected with dentinogenesis imperfecta shields type II. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 2016;33(01):34–37
11. Prasad M, Butler WT, Qin C. Dentin sialophosphoprotein in biominalerization. Connect Tissue Res 2010;51(05):404–417
12. MacDougall M, Simmons D, Luan X, Nydegger J, Feng J, Gu TT. Dentin phosphoprotein and dentin sialoprotein are cleavage products expressed from a single transcript coded by a gene on human chromosome 4. Dentin phosphoprotein DNA sequence determination. J Biol Chem 1997;272(02):835–842
13. Linde A. Dentin matrix proteins: composition and possible functions in calcification. Anat Rec 1989;224(02):154–166
14. Bègue-Kirn C, Krebsbach PH, Bartlett JD, Butler WT. Dentin sialoprotein, dentin phosphoprotein, enamelysin and ameloblastin: tooth-specific molecules that are distinctively expressed.
DSPP Gene Mutations on Periodontal Tissues

Jing et al.

during murine dental differentiation. Eur J Oral Sci 1998;106(05):963–970

15 Qin C, Brunn JC, Cadena E, et al. The expression of dentin sialophosphoprotein gene in bone. J Dent Res 2002;81(06):392–394

16 Chen Y, Zhang Y, Ramachandran A, George A. DSPP is essential for normal development of the dental–craniofacial complex. J Dent Res 2016;95(03):302–310

17 Baba O, Qin C, Brunn JC, et al. Detection of dentin sialoprotein in rat periodontium. Eur J Oral Sci 2004;112(02):163–170

18 Gibson MP, Jani P, Liu Y, et al. Failure to process dentin sialophosphoprotein into fragments leads to periodontal defects in mice. Eur J Oral Sci 2013;121(06):545–550

19 Gibson MP, Zhu Q, Liu Q, D’Souza RN, Feng JQ, Qin C. Loss of dentin sialophosphoprotein leads to periodontal diseases in mice. J Periodontal Res 2013;48(02):221–227

20 Ozer A, Yuan G, Yang G, et al. Domain of dentin sialoprotein mediates proliferation and differentiation of human periodontal ligament stem cells. PLoS One 2013;8(12):e81655

21 Gibson MP, Jani P, Wang X, Lu Y, Qin C. Overexpressing the NH2-terminal fragment of dentin sialophosphoprotein (DSPP) aggravates the periodontal defects in DSPp knockout mice. J Oral Biosci 2014;56(04):143–148

22 Porntaveetus T, Nowwarote N, Osathanon T, et al. Compromised alveolar bone cells in a patient with dentinogenesis imperfecta caused by DSPP mutation. Clin Oral Investig 2019;23(01):303–313

23 Alvares K, Kanwar YS, Veis A. Expression and potential role of dentin phosphophoryn (DPP) in mouse embryonic tissues involved in epithelial–mesenchymal interactions and branching morphogenesis. Dev Dyn 2006;235(11):2980–2990

24 Ogubrele KU, Fisher LW, Fishe KU. Expression of SIBLINGs and their partner MMPs in salivary glands. J Dent Res 2004;83(09):664–670

25 Prasad M, Zhu Q, Sun Y, et al. Expression of dentin sialophosphoprotein in non-mineralized tissues. J Histochim Cytochem 2011;59(11):1009–1021

26 Koli K, Saxena G, Ogubrele KU. Expression of matrix metalloproteinase (MMP)-20 and potential interaction with dentin sialophosphoprotein (DSPP) in human major salivary glands. J Histochim Cytochem 2015;63(07):524–533

27 Aseervatham J, Geetu S, Anunobi CC, Koli K, Ogubrele KU. Survey of isolated dentin sialophosphoprotein and its cognate matrix metalloproteinase-20 in human cancers. Cancer Med 2019;8(05):2167–2178

28 Xiao S, Yu C, Chou X, et al. Dentinogenesis imperfecta 1 with or without progressive hearing loss is associated with distinct mutations in DSPP. Nat Genet 2001;27(02):201–204

29 Liu Q, Gibson MP, Sun H, Qin C. Dentin sialophosphoprotein (DSPP) plays an essential role in the postnatal development and maintenance of mouse mandibular condylar cartilage. J Histochim Cytochem 2013;61(10):749–758

30 Gibson MP, Zhu Q, Wang S, et al. The rescue of dentin matrix protein 1 (DMP1)-deficient tooth defects by the transgenic expression of dentin sialophosphoprotein (DSPP) indicates that DSPP is a downstream effector molecule of DMP1 in dentinogenesis. J Biol Chem 2013;288(10):7204–7214

31 Zhu Q, Sun Y, Prasad M, et al. Glycosaminoglycan chain of dentin sialoprotein proteoglycan. J Dent Res 2010;89(08):880–812

32 Yamakoshi Y, Hu JC, Fukae M, Zhang H, Simmer JP. Dentin glycoprotein: the protein in the middle of the dentin sialophosphoprotein chimera. J Biol Chem 2005;280(17):17472–17479

33 Veis A, Perry A. The phosphoprotein of the dentin matrix. Biochemistry 1967;6(08):2409–2416

34 Butler WT, Bhawn M, Dimuzio MT, Linde A. Noncollagenous proteins of dentin. Isolation and partial characterization of rat dentin proteins and proteoglycans using a three-step preparative method. Coll Relat Res 1981;1(02):187–199

35 Ritchie HH, Wang LH. Sequence determination of an extremely acidic rat dentin phosphoprotein. J Biol Chem 1996;271(36):21695–21698

36 Zhu Q, Gibson MP, Liu Q, et al. Proteolytic processing of dentin sialophosphoprotein (DSP) is essential to dentinogenesis. J Biol Chem 2012;287(36):30426–30435

37 Suzuki S, Sreenath T, Haruyama N, et al. Dentin sialoprotein and dentin phosphoprotein have distinct roles in dentin mineralization. Matrix Biol 2009;28(04):221–229

38 Ritchie H. The functional significance of dentin sialoprotein-dentin phosphophoryn and dentin sialoprotein. J Oral Sci 2018;10(04):31

39 Saito T,Arsenault AL, Yamauchi M, Kuboki Y, Creshaw MA. Mineral induction by immobilized phosphoproteins. Bone 1997;21(04):305–311

40 Milan AM Sr, Sugars RV, Emberry G, Waddington R, Adsortion and interactions of dentine phosphoprotein with hydroxyapatite and collagen. J Oral Sci 2006;114(03):223–231

41 Jadlowiec JA, Zhang X, Li J, Campbell PG, Sfeir C. Extracellular matrix-mediated signaling by dentin phosphophoryn involves activation of the Smad pathway independent of bone morphogenic protein. J Biol Chem 2006;281(09):5341–5347

42 Jadlowiec J, Koch H, Zhang X, Campbell PG, Seyedain M, Sfeir C. Phosphophoryn regulates the gene expression and differentiation of NIH3T3, MC3T3-E1, and human mesenchymal stem cells via the integrin/MAK signaling pathway. J Biol Chem 2004;279(51):53323–53330

43 Jaha H, Husein D, Ohyama Y, et al. N-terminal dentin sialoprotein fragment induces type I collagen production and upregulates dentinogenesis marker expression in osteoblasts. Biochem Biophys Acta 2016;186:190–196

44 Lim WH, Liu B, Cheng D, Williams BO, Mah SJ, Helms JA. Wnt signaling regulates homeostasis of the periodontal ligament. J Periodontal Res 2014;49(06):751–759

45 Zhang L, An Y, Chen F, Jin Y. Progress in the study of dental tissue-degenerated stem cells. J Pract Stomatol 2015;31(03):425–431

46 Gu K, Chang S, Ritchie HH, Clarkson BH, Rutherford RB. Molecular cloning of a human dentin sialophosphoprotein gene. Eur J Oral Sci 2000;108(01):35–42

47 Ritchie HH, Wang LH, Knudtson K. A novel rat 523 amino acid phosphophoryn: nucleotide sequence and genomic organization. Biochem Biophys Acta 2001;1520(03):212–222

48 Feng F, Akiyama K, Liu Y, et al. Utility of PDL progenitors for in vivo tissue regeneration: a report of 3 cases. Oral Dis 2010;16(01):20–28

49 Nie F, Zhang W, Cui Q, Fu Y, Li H, Zhang J. Kaempferol promotes proliferation and osteogenic differentiation of periodontal ligament stem cells via Wnt/β-catenin signaling pathway. Life Sci 2020;258:118143

50 Shi C, Ma N, Zhang W, et al. Haploinsufficiency of DSPP gene causes dentin dysplasia type II in mice. Front Physiol 2020;11:593626

51 Hienz SA, Paliwal S, Ivanovski S. Mechanisms of bone resorption in periodontitis. J Immunol Res 2015;2015:615486

52 Luo Y, Feng X, Duan D, Liu C, Xu Z, Zhou X. Epigenetic regulations in the pathogenesis of periodontitis. Curr Stem Cell Res Ther 2018;13(02):144–150

53 Kwon T, Lamster IB, Levin L. Current concepts in the management of periodontitis. Int Dent J 2020;5(Dec)

54 Murakami S, Mealey BL, Mariotti A, Chapple ILC. Dental plaque-induced gingival conditions. J Clin Periodontol 2018;45(Suppl 20):S17–S27

55 Könönen E, Gusroy M, Gursoy UK. Periodontitis: a multifaceted disease of tooth-supporting tissues. J Clin Med 2019;8(08):E1135