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New conceptual approaches toward dentin regeneration using the drug repositioning strategy with Wnt signaling pathways

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This study summarizes the recent cutting-edge approaches for dentin regeneration that still do not offer adequate solutions. Tertiary dentin is formed when odontoblasts are directly affected by various stimuli. Recent preclinical studies have reported that stimulation of the Wnt/β-catenin signaling pathway could facilitate the formation of reparative dentin and thereby aid in the structural and functional development of the tertiary dentin. A range of signaling pathways, including the Wnt/β-catenin pathway, is activated when dental tissues are damaged and the pulp is exposed. The application of small molecules for dentin regeneration has been suggested as a drug repositioning approach. This study reviews the role of Wnt signaling in tooth formation, particularly dentin formation and dentin regeneration. In addition, the application of the drug repositioning strategy to facilitate the development of new drugs for dentin regeneration has been discussed in this study.

Keywords: Tooth, Drug repositioning, Wnt signaling pathway

Structure and Function of Dentin

Dentin is the most spacious calcified tissues among the composition of tooth structure which is complex, porous and yellowish-hued [1]. There are three types of dentin – *Primary*, *Secondary*, and *Tertiary*. Primary dentin constitutes the most part of the dentin mass and lies between the enamel and pulp chamber, near dentinoenamel junction. It is produced relatively high rate. The outer most layer of dentin, close to enamel is known as *mantle dentin*. Mantle dentin is producedby newly differentiated odontoblasts and forms a layer consistently 15–20 micrometers wide. Unlike primary dentin, mantle dentin lacks phosphorylation which makes loosely packed collagen fibrils and less mineralized composition. Below the mantle dentin, *circumpulpal dentin* lies. Circumpulpal dentin forms major part of the dentin layer and is produced before the root formation is completed [2,3]. Secondary dentin starts immediately after completion of root formation and continues throughout the life. The only difference between primary and secondary dentin is the tubule profile in which primary dentin is straight

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and secondary dentin is curved due to the gradual restriction in the space for inward migration of odontoblasts. It causes a decrease in the size of the pulp chamber with age as it deposits matrix continuously. Tertiary dentin is formed as a reaction to external stimuli such as chemical irritants, caries, attrition or other traumatic stress. There are two types of tertiary dentin – *Reactionary and Reparative*. Reactionary dentin is formed from a pre-existing odontoblasts, whereas thereparative dentin is formed from newly differentiated odontoblast-like cells which are formed due to death of original odontoblasts. Tertiary dentin is the only dentin formed by odontoblasts which are directly affected by a stimulus [2]. Recently, studies about differentiation and regeneration of dentin are continuously investigated using various methods such as modulation of signaling pathway, application of small molecules and drug repositioning method [4-11].

Wnt Signalings in Tooth Formation

Wnt/β-catenin signaling plays an important role in morphogenesis and cellular differentiation of tissues [12]. Several studies revealed that Wnt/β-catenin signaling involves in various stages of tooth morphogenesis and differentiation in both dental epithelium and mesenchyme which was organized and listed in Table 1 [13-17]. Many studies showed Wnt/β-catenin signaling acts as a factor in stages of tooth morphogenesis [18,19]. A study by Kim et al. [20] show that Wnt/β-catenin signaling acts as a key factor in the differentiation of odontoblast in root formation. In mice with the limited expression of β-catenin, incisors and molars showed distinct abnormalities in tooth morphology. In histological analysis, the differentiation of odontoblast in the inner layer remarkedly decreased and root was not formed properly despite the extension of the Hertwig's epithelial root sheath that determines the size and shape of the root [21]. These results suggest that Wnt/β-catenin signaling control the differentiation of odontoblast in root formation. Recent study by Bae et al. [11] showed that odontoblast-specific disruption of Wntless (Wls), a chaperone protein that regulates Wnt sorting and secretion, mediates severe defects in formation of dentin and root elongation, resulted in thin den-

Table 1. Wnt signaling molecules in developmental stage of tooth and their compartmental roles

Genes	Developmental stage of tooth					Compartmental roles in Wnt signaling			
	Cap-bell stage		Secretory stage						
	Enamel knot/IEE	Dental pailla	Ameloblast	Odontoblast/ pre-odontoblast	Dental papilla	Ligand	Transducer	Transcription factor	Antagonist
Axin2	O	O	O	O			O		
Dkk1		O							O
Dkk2					O				O
Dkk3					O				O
Lef1	O	O						O	
Sostdc1	O	O							
Tcf1		O						O	
Tcf4	O	O						O	
Wnt3	O					O			
Wnt4	O					O			
Wnt5a	O	O		O		O			
Wnt6	O					O			
Wnt7b	O					O			
Wnt10a	O					O			
Wnt10b	O					O			
Wnt11				O	O				
β-catenin	O	O	O	O				O	

Modified from the article of Wu et al. (Int J Biol Sci 2017;13:1082-91) [16] and Tamura and Nemoto (Jpn Dent Sci Rev 2016;52:75-83) [17].
IEE, inner enamel epithelium.

tin with enlarged pulp chambers and short roots. However, the study of Lim et al. [22], showed opposite phenotype, in which the deleted Wls in odontoblasts resulted in the increase of dentin thickness and the decrease of pulp volume in incisors. The differences are likely due to arrangement of expression of the osteocalcin-Cre recombinase. In summary, Wnt/β-catenin signaling in odontoblasts involves in regulating differentiation and matrix production. During tooth development, Wnt ligands secreted from odontoblasts are required for maturation of odontoblasts, dentin deposition and root elongation.

Recent Studies in Regenerative Endodontics

1. Cell transplantation and homing

The goal of regenerative endodontics is to restore the functions of the dental pulp-dentin complex. There are two approaches of pulp-dentin regeneration - *cell transplantation* and *cell homing* [23]. Cell transplantation by delivering *ex vivo* cultivated cells in pulp-dentin regeneration is the most studied topic among pulp-dentin regeneration. When stem/progenitor cells are transplanted, not regarding their origins, they are thought to be in aid of regeneration or repair process not only by supplying cells but also by adding up growth factors or signaling molecule [24,25]. Stem and progenitor cells in dental pulp are anticipated to replenish odontoblasts upon infection or trauma in adult hood. Cell homing compared to cell transplantation has not been explored much yet. It is defined as migration or mobilization of cells involving stem/progenitor cells to the damaged tissue and this process is induced by biological signaling molecules [26,27]. The growth factors shown by Kim et al. [28] for cell homing approaches of pulp regeneration are vascular endothelial growth factor, basic fibroblast growth factor, platelet-derived growth factor, nerve growth factor and bone morphogenetic protein-7. The induction of stem/progenitor cells from periapical tissue around the apical area of the root leads to the cell homing [29]. In cell homing strategy, scaffolds filled with growth factors are inserted into root canals. The placement of those scaffold initiates migration, proliferation, and differentiation of endogenous stem/progenitor cells located around the root apex like periodontal ligament stem cells [30]. The use of biological signaling molecules for cell transplantation is not yet applied in clinical approaches because of its immune rejection, and potential contamination during cell manipulation. For cell homing, the elaborated hurdles for cell transplantation are minimized. However, growth factors used in cell homing approaches for pulp regeneration require the U.S. Food and Drug Administration approval for the clinical application [31-33].

2. Pulp revascularization

Regenerative endodontics procedures designed to replace damaged structures, including dentin and root, as well as cells of the pulp-dentin complex [34]. Revascularization is one of candidates of regenerative endodontics. Revascularization mainly focuses on development of immature tooth root with promoting of dentinal wall by deposition of hard tissue of roots [35,36]. Another approach for regenerating dentin is recombinant human proteins combined with collagen-based matrixes. The mechanism of this procedure is relevant to stimulating agents which were placed in direct contact with dental pulp, however, the induction of reparative dentin was unsuccessful because of insufficient amount of active recombinant protein; protein has relatively short half-life and faster degradation rates when the pulp is inflamed. It is found that growth/differentiation factor11 and bone sialoprotein are considered as important factor to induce reparative dentin and to stimulate differentiation of dental pulp cells into cells that can secrete extracellular matrix respectively [37,38].

3. Tertiary dentin formation using Wnt/β-catenin signaling

Moving on to tertiary dentin problems and facilitation, the most obvious reparative response to pulp exposure is observed by reparative dentin because it offers odontoblasts and other pulp cells as well as protects pulp from harmful stimuli [39]. Furthermore, various factors may induce formation of tertiary dentin, also called reparative dentin: occlusal attrition, trauma, carious decay, dental restoration and any external harmful stimulus. A recent preclinical study found that stimulation of Wnt/β-catenin signaling promotes formation of reparative dentin [40]. When the tissue is damaged, Wnt/β-catenin signaling is activated immediately with the addition of small molecule, Wnt agonists generates reparative dentin formation and consequently restores the lost dentin structure by producing new dentin [11,20]. These results suggest that odontoblast differentiation and Wnt signaling pathways are significant factor in consideration of dentin regeneration.

Table 2. List of approaches for regeneration of tertiary dentin

Application	Genes/Drugs		Reference
Cell homing approach	VEGF, bFGF, PDGF, NGF, BMP7		[28,38]
Pulp revascularization	GDF11, BSP		[37]
Indirect pulp capping	Molecules	CPNE7	[48]
	Drugs	Bortezomib, Tideglusib	[9,44-46]
Cell culture method	Molecules	CPNE7, TGF-β1, Wls	[5,6,11,47]
	Drugs	Midazolam	[10]

VEGF, vascular endothelial growth factor; bFGF, basic fibroblast growth factor; PDGF, platelet-derived growth factor; NGF, nerve growth factor; BMP7, bone morphogenetic protein-7; GDF11, growth differentiation factor 11; BSP, bone sialoprotein; CPNE7, copine 7; TGF-β1, transforming growth factor beta 1; Wls, Wntless.

4. Reparative dentin formation using drug repositioning

Recently, many studies employed the drug repositioning strategy, using approved drugs into other purposes from original one for saving time and cost [31–33]. In medical fields these applications were well understood and performed for overcoming various diseases, however, in dental field these approaches are limited and not well announced so far. In this study we prepared and summarized the recent reports which successfully showed the possibilities of drug repositioning in dentin regeneration.

Bortezomib is introduced as the drug for dentin regeneration. Bortezomib is known to inhibit nuclear factor kappa B activation and interleukin-6 mediated cell growth [41]. The mechanism of Bortezomib involves various signaling pathways such as Wnt/β-catenin signaling pathway [42]. Bortezomib treatment up-regulated the Nestin and CD31 expression levels in odontoblasts and pulp tissue. Furthermore, stronger positive reaction against neutrophils marker has been found after Bortezomib application. Through these results, it is assumed that Bortezomib induces blood vessel formation in response to pulpal inflammation. Examination of the molecular reactions to Bortezomib using mesenchymal tissues showed that dental pulp and odontoblast-forming mesenchymal cells indicated different expression patterns of Bmp and Wnt genes [9]. Midazolam is considered as another potential drug for dentin regeneration. Midazolam regulates inhibitory neurotransmitters in the vertebrate nervous system. The Midazolam-only treatment increased the alkaline phosphatase activity and mRNA levels of odontoblast differentiation marker genes. In contrast, combination of midazolam and PPU-7 cells exhibited high potential of dentin regeneration. These results show that the repositioning of Midazolam stimulates dentin regeneration [10,40]. Moreover, glycogen synthase kinase 3 (GSK3) is a proline/serine protein kinase ubiquitously expressed and associated with many cellular pathways such as controlling metabolism, differentiation and immunity, especially cell death and survival [43]. Interestingly, the delivery of small molecule inhibitors of GSK3 stimulates Wnt/β-catenin signaling when applied into exposed pulpal cavity and examined on dentin repair [44–46]. Other approaches are organized and listed at Table 2 [47,48]. This drug repositioning would be an effective way of providing practical solutions for dentin regeneration in near future.

Conclusions

Significant findings in regenerative endodontics (Table 2) contributes to development of treatment protocols and application of tissue engineering. As a clinical treatment strategy, regenerative endodontics has limited cases in permanent teeth and lack of robust diagnostic marker. In addition, infection control (for example, rubber dam, disinfection protocols, etc.), the extent of surgical excision of inflamed tissue and case selection in the context of preservation of tissue vitality are central features of regenerative endodontics [36]. Regenerative endodontics offers a number of exciting opportunities for preservation of pulp vitality. Treatment strategies also provides substantial clinical advantages in case of immature teeth. True pulp regeneration will arise as a practical clinical treatment. Such achievements will target recruitment of specific stem/progenitor cell populations and develop endogenous signaling molecules in order to regenerate dentin-pulp tissue with physiological characteristics.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

References

1. Hillson S. Tooth development in human evolution and bioarchaeology. Cambridge: Cambridge University Press; 2014. 307 p.
2. Nanci A. Ten Cate's oral histology - e-book: development, structure, and function. 9th ed. St. Louis: Elsevier Health Sciences; 2017.
3. Goldberg M, Kulkarni AB, Young M, Boskey A. Dentin: structure, composition and mineralization. Front Biosci (Elite Ed) 2011;3:711-35. doi: 10.2741/e281.
4. Lee JH, Lee DS, Choung HW, Shon WJ, Seo BM, Lee EH, Cho JY, Park JC. Odontogenic differentiation of human dental pulp stem cells induced by preameloblast-derived factors. Biomaterials 2011;32:9696-706. doi: 10.1016/j.biomaterials.2011.09.007.
5. Seo YM, Park SJ, Lee HK, Park JC. Copine-7 binds to the cell surface receptor, nucleolin, and regulates ciliogenesis and Dspp expression during odontoblast differentiation. Sci Rep 2017;7:11283. doi: 10.1038/s41598-017-11641-y.
6. Park SJ, Lee HK, Seo YM, Son C, Bae HS, Park JC. Dentin sialophosphoprotein expression in enamel is regulated by Copine-7, a preameloblast-derived factor. Arch Oral Biol 2018;86:131-7. doi: 10.1016/j.archoralbio.2017.12.004.
7. Lee YS, Park YH, Lee DS, Seo YM, Lee JH, Park JH, Choung HW, Park SH, Shon WJ, Park JC. Tubular dentin regeneration using a CPNE7-derived functional peptide. Materials (Basel) 2020;13:4618. doi: 10.3390/ma13204618.
8. Oh HJ, Choung HW, Lee HK, Park SJ, Lee JH, Lee DS, Seo BM, Park JC. CPNE7, a preameloblast-derived factor, regulates odontoblastic differentiation of mesenchymal stem cells. Biomaterials 2015;37:208-17. doi: 10.1016/j.biomaterials.2014.10.016.
9. Jung JK, Gwon GJ, Neupane S, Sohn WJ, Kim KR, Kim JY, An SY, Kwon TY, An CH, Lee Y, Kim JY, Ha JH. Bortezomib facilitates reparative dentin formation after pulp access cavity preparation in mouse molar. J Endod 2017;43:2041-7. doi: 10.1016/j.joen.2017.07.018.
10. Karakida T, Onuma K, Saito MM, Yamamoto R, Chiba T, Chiba R, Hidaka Y, Fujii-Abe K, Kawahara H, Yamakoshi Y. Potential for drug repositioning of midazolam for dentin regeneration. Int J Mol Sci 2019;20:670. doi: 10.3390/ijms20030670.
11. Bae CH, Kim TH, Ko SO, Lee JC, Yang X, Cho ES. Wntless regulates dentin apposition and root elongation in the mandibular molar. J Dent Res 2015;94:439-45. doi: 10.1177/0022034514567198.
12. Liu F, Chu EY, Watt B, Zhang Y, Gallant NM, Andl T, Yang SH, Lu MM, Piccolo S, Schmidt-Ullrich R, Taketo MM, Morrisey EE, Atit R, Dlugosz AA, Millar SE. Wnt/beta-catenin signaling directs multiple stages of tooth morphogenesis. Dev Biol 2008;313:210-24. doi: 10.1016/j.ydbio.2007.10.016.
13. Liu F, Millar SE. Wnt/beta-catenin signaling in oral tissue development and disease. J Dent Res 2010;89:318-30. doi: 10.1177/0022034510363373.
14. Järvinen E, Salazar-Ciudad I, Birchmeier W, Taketo MM, Jernvall J, Thesleff I. Continuous tooth generation in mouse is induced by activated epithelial Wnt/beta-catenin signaling. Proc Natl Acad Sci U S A 2006;103:18627-32. doi: 10.1073/pnas.0607289103.
15. He Q, Yan H, Wo D, Liu J, Liu P, Zhang J, Li L, Zhou B, Ge J, Li H, Liu S, Zhu W. Wnt3a suppresses Wnt/β-catenin signaling and cancer cell proliferation following serum deprivation. Exp Cell Res 2016;341:32-41. doi: 10.1016/j.yexcr.2015.11.025.
16. Wu X, Li Y, Wang F, Hu L, Li Y, Wang J, Zhang C, Wang S. Spatiotemporal expression of Wnt/β-catenin signaling during morphogenesis and odontogenesis of deciduous molar in miniature pig. Int J Biol Sci 2017;13:1082-91. doi: 10.7150/ijbs.20905.
17. Tamura M, Nemoto E. Role of the Wnt signaling molecules in the tooth. Jpn Dent Sci Rev 2016;52:75-83. doi: 10.1016/j.jdsr.2016.04.001.
18. Bae CH, Lee JY, Kim TH, Baek JA, Lee JC, Yang X, Taketo MM, Jiang R, Cho ES. Excessive Wnt/β-catenin signaling disturbs tooth-root formation. J Periodontal Res 2013;48:405-10. doi: 10.1111/jre.12018.
19. Kim TH, Lee JY, Baek JA, Lee JC, Yang X, Taketo MM, Jiang R, Cho ES. Constitutive stabilization of β-catenin in the dental mesenchyme leads to excessive dentin and cementum formation. Biochem Biophys Res Commun 2011;412:549-55. doi: 10.1016/j.bbrc.2011.07.116.
20. Kim TH, Bae CH, Lee JC, Ko SO, Yang X, Jiang R, Cho ES. β-catenin is required in odontoblasts for tooth root formation. J Dent Res 2013;92:215-21. doi: 10.1177/0022034512470137.
21. Zhang R, Teng Y, Zhu L, Lin J, Yang X, Yang G, Li T. Odontoblast β-catenin signaling regulates fenestration of mouse Hertwig's epithelial root sheath. Sci China Life Sci 2015;58:876-81. doi: 10.1007/s11427-015-4882-8.
22. Lim WH, Liu B, Cheng D, Hunter DJ, Zhong Z, Ramos DM, Williams BO, Sharpe PT, Bardet C, Mah SJ, Helms JA. Wnt

signaling regulates pulp volume and dentin thickness. J Bone Miner Res 2014;29:892–901. doi: 10.1002/jbmr.2088.
23. Kim SG, Zheng Y, Zhou J, Chen M, Embree MC, Song K, Jiang N, Mao JJ. Dentin and dental pulp regeneration by the patient's endogenous cells. Endod Topics 2013;28:106–17. doi: 10.1111/etp.12037.
24. Mao JJ, Prockop DJ. Stem cells in the face: tooth regeneration and beyond. Cell Stem Cell 2012;11:291–301. doi: 10.1016/j.stem.2012.08.010.
25. Barzilay R, Melamed E, Offen D. Introducing transcription factors to multipotent mesenchymal stem cells: making transdifferentiation possible. Stem Cells 2009;27:2509–15. doi: 10.1002/stem.172.
26. Lee CH, Cook JL, Mendelson A, Moioli EK, Yao H, Mao JJ. Regeneration of the articular surface of the rabbit synovial joint by cell homing: a proof of concept study. Lancet 2010;376:440–8. doi: 10.1016/S0140–6736(10)60668–X.
27. Quesenberry PJ, Becker PS. Stem cell homing: rolling, crawling, and nesting. Proc Natl Acad Sci U S A 1998;95:15155–7. doi: 10.1073/pnas.95.26.15155.
28. Kim JY, Xin X, Moioli EK, Chung J, Lee CH, Chen M, Fu SY, Koch PD, Mao JJ. Regeneration of dental–pulp–like tissue by chemotaxis–induced cell homing. Tissue Eng Part A 2010;16:3023–31. doi: 10.1089/ten.TEA.2010.0181.
29. Morotomi T, Washio A, Kitamura C. Current and future options for dental pulp therapy. Jpn Dent Sci Rev 2019;55:5–11. doi: 10.1016/j.jdsr.2018.09.001.
30. Duncan HF, Kobayashi Y, Shimizu E. Growth factors and cell homing in dental tissue regeneration. Curr Oral Health Rep 2018;5 z:276–85. doi: 10.1007/s40496–018–0194–y.
31. Wada N, Menicanin D, Shi S, Bartold PM, Gronthos S. Immunomodulatory properties of human periodontal ligament stem cells. J Cell Physiol 2009;219:667–76. doi: 10.1002/jcp.21710.
32. Yamaza T, Kentaro A, Chen C, Liu Y, Shi Y, Gronthos S, Wang S, Shi S. Immunomodulatory properties of stem cells from human exfoliated deciduous teeth. Stem Cell Res Ther 2010;1:5. doi: 10.1186/scrt5.
33. Ding G, Wang W, Liu Y, An Y, Zhang C, Shi S, Wang S. Effect of cryopreservation on biological and immunological properties of stem cells from apical papilla. J Cell Physiol 2010;223:415–22. doi: 10.1002/jcp.22050.
34. Jung C, Kim S, Sun T, Cho YB, Song M. Pulp–dentin regeneration: current approaches and challenges. J Tissue Eng 2019;10:2041731418819263. doi: 10.1177/2041731418819263.
35. Araújo PRS, Silva LB, Neto APDS, Almeida de Arruda JA, Álvares PR, Sobral APV, Júnior SA, Leão JC, Braz da Silva R, Sampaio GC. Pulp revascularization: a literature review. Open Dent J 2017;10:48–56. doi: 10.2174/1874210601711010048.
36. Simon S, Smith AJ. Regenerative endodontics. Br Dent J 2014;216:E13. doi: 10.1038/sj.bdj.2014.243.
37. Rutherford RB, Gu K. Treatment of inflamed ferret dental pulps with recombinant bone morphogenetic protein–7. Eur J Oral Sci 2000;108:202–6. doi: 10.1034/j.1600–0722.2000.108003202.x.
38. Chatzistavrou X, Papagerakis S, Ma PX, Papagerakis P. Innovative approaches to regenerate enamel and dentin. Int J Dent 2012;2012:856470. doi: 10.1155/2012/856470.
39. Nowicka A, Wilk G, Lipski M, Kołecki J, Buczkowska–Radlińska J. Tomographic evaluation of reparative dentin formation after direct pulp capping with Ca(OH)2, MTA, Biodentine, and dentin bonding system in human teeth. J Endod 2015;41:1234–40. doi: 10.1016/j.joen.2015.03.017.
40. Babb R, Chandrasekaran D, Carvalho Moreno Neves V, Sharpe PT. Axin2–expressing cells differentiate into reparative odontoblasts via autocrine Wnt/β–catenin signaling in response to tooth damage. Sci Rep 2017;7:3102. doi: 10.1038/s41598–017–03145–6.
41. Chen D, Frezza M, Schmitt S, Kanwar J, Dou QP. Bortezomib as the first proteasome inhibitor anticancer drug: current status and future perspectives. Curr Cancer Drug Targets 2011;11:239–53. doi: 10.2174/156800911794519752.
42. Boccadoro M, Morgan G, Cavenagh J. Preclinical evaluation of the proteasome inhibitor bortezomib in cancer therapy. Cancer Cell Int 2005;5:18. doi: 10.1186/1475–2867–5–18.
43. Beurel E, Grieco SF, Jope RS. Glycogen synthase kinase–3 (GSK3): regulation, actions, and diseases. Pharmacol Ther 2015;148:114–31. doi: 10.1016/j.pharmthera.2014.11.016.
44. Neves VC, Babb R, Chandrasekaran D, Sharpe PT. Promotion of natural tooth repair by small molecule GSK3 antagonists. Sci Rep 2017;7:39654. doi: 10.1038/srep39654.
45. Zaugg LK, Banu A, Walther AR, Chandrasekaran D, Babb RC, Salzlechner C, Hedegaard MAB, Gentleman E, Sharpe PT. Translation approach for dentine regeneration using GSK–3 antagonists. J Dent Res 2020;99:544–51. doi: 10.1177/0022034520908593.
46. Birjandi AA, Suzano FR, Sharpe PT. Drug repurposing in dentistry; towards application of small molecules in dentin repair. Int J Mol Sci 2020;21:6394. doi: 10.3390/ijms21176394.
47. Hwang YC, Hwang IN, Oh WM, Park JC, Lee DS, Son HH. Influence of TGF–beta1 on the expression of BSP, DSP, TGF–

beta1 receptor I and Smad proteins during reparative dentinogenesis. J Mol Histol 2008;39:153-60. doi: 10.1007/s10735-007-9148-8.
48. Choung HW, Lee DS, Lee JH, Shon WJ, Lee JH, Ku Y, Park JC. Tertiary dentin formation after indirect pulp capping using protein CPNE7. J Dent Res 2016;95:906-12. doi: 10.1177/0022034516639919.