〔Review〕

Dentin Phosphophoryn and its Possibilities in Regenerative Dentistry：A Review

Tubayesha HASSAN[1], Youjing QIU[1], Jia TANG[2], Takashi SAITO[1]

1. Division of Clinical Cariology and Endodontology, Department of Oral Rehabilitation, School of Dentistry, Health Sciences University of Hokkaido
2. Division of Biochemistry, Department of Oral Biology, School of Dentistry, Health Sciences University of Hokkaido

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Abstract

Clinical performance of current dental pulp capping agents remains questionable. This has led to researches in search for a novel dental material that possesses better biocompatibility as well as induces new dentin formation within shorter period than the materials used at present. Dentin phosphophoryn is an extracellular matrix protein (ECM), which is cleaved product of the parent gene, dentin sialophosphoprotein. Recent researches in the tissue engineering field have been utilizing the scope of variable ECM proteins to regenerate dentin from odontoblasts. This review focuses on dentin phosphophoryn as well as its characteristic domain RGD and discusses their role in inducing signals toward odontogenic cell differentiation and consequent formation of dentin with better quality and biocompatibility than calcium hydroxide, standard pulp capping agent or in shorter time period than mineral trioxide aggregate (MTA).

Introduction

For decades, calcium hydroxide had been used as the standard material for vital pulp therapy, as it induces reparative dentin formation in damaged teeth (Figure 1) (Freeman et al. 1994). But studies had been conducted evaluating its long−term functions and results state calcium hydroxide to be unpredictable and varying in performance in long term. Specific disadvantages of this material include incompatibility to biological tissues, lack of close adaptation to dental tissue (tunnel defect formation) and controversial cytotoxic effect by formation of permanent necrotic tissue (Ba−Hattab et al., 2016 ; Accorinte et al., 2008 ; Andelin et al., 2003).

Figure 1 : The standard direct pulp capping materials available at present for clinical use.

Thus, clinical success rate of vital pulp therapy using calcium hydroxide is not satisfactory to the clinicians. In 1999, Mineral Trioxide Aggregate (MTA) was introduced in clinical dentistry and applauded for its superior biocompatibility and excellent sealing property (Bortoluzzi et al., 2006 ; Tawil et al., 2015). However, there has been concerns regarding its toxic chemical components like aluminum and selenium, difficult handling characteristics and absence of any known solvent for this material (Bansal et al., 2019). The high cost is a barrier to using MTA for general population. So, the ongoing search continues to develop the ideal material. A significant number of research are being conducted to experiment with different extracellular matrix proteins (ECM) and establish their roles to induce dentin regeneration. This review discusses the role of dentin phosphophoryn, an ECM protein and its possible role to effectively induce dentin regeneration with significant quality. In addition, the specific domain of the protein structure responsible for eliciting new dentin−like structure formation is discussed.

Methodology

A review of the literature was performed by using electronic and hand-searching methods regarding the ECM protein called dentin phosphophoryn and its scopes and possibilities on the regeneration of dentin. Both *in vitro* and *in vivo* studies were selected from January 1995 to September 2019.

ECM proteins in tissue engineering

Extracellular matrix (ECM) proteins are a topic of focus in the field of tissue engineering recently. ECM constitutes the non-cellular component of tissues and is composed of structural and functional proteins (Frantz et al., 2010). At present, a number of tissue engineering studies have been conducted to replicate the composition of ECM and reported to achieve desired cellular behavior and direct towards lineage specific cell differentiation to facilitate regeneration of tissues such as bone and dental pulp tissues (Ravindran et al., 2011 ; Ravindran et al., 2013(2)). There have been reports of a number of functional ECM proteins that have significant roles in the formation of mineralized tissue ; bone and dentin (Saito et al., 2004 ; Iohara et al., 2004 ; Six et al., 2002 ; Gericke et al., 2010 ; Six et al., 2007).

The biochemical function of dentin-forming cells

Dentin is a complex mineralized tissue formed by odontoblasts. The main function is to form mineralized matrix by the secretion of different collagenous and non-collagenous proteins (Table 1) (Linde et al., 1989).

Similar to bone-forming cells, osteoblasts, odontoblasts also produce endocrine hormones named fibroblast growth factor 23 (FGF23) and osteocalcin (Yoshiko et al., 2007). However, the response of osteoblasts and odontoblasts to these growth factors are different. For example, osteoblasts express transcription factor, Runx2 when stimulated by treatment with BMP/TGF-β super-family of proteins. But the same response is elicited by odontoblasts when treated with FGFs (Balint et al., 2003).

• Inorganic component	69%	
• organic component	20%	
Collagen		90 %
Dentin Phosphophoryn (DPP)		5-6 %
Others		4-5 %
DMP-1, OPN, BSP, MEPE, DSP, BGP, PG, Growth Factors, Lipids, etc.		
• water	11 %	

Table 1 : Composition of dentin extracellular matrices

Dentin Phosphophoryn

Dentin phosphoprotein, also known as phosphophoryn (DPP) is the most abundant non-collagenous protein in dentin matrix (Butler et al., 1997). It is predominantly expressed in odontoblasts (Suzuki et al., 2009). DPP belongs to a small integrin binding ligand, N-linked glycoproteins (SIBLING) family. The SIBLING protein family includes six proteins (Table 2) (Fisher et al., 2003) :

DSPP is comprised of two distinct domains, sialylated dentin sialoprotein (DSP) and phosphorylated DPP (Fisher et al., 2003). There are reports that DPP is highly acidic due the large quantity of amino acid components such as Aspartic acid and phosphorylated Serine. It is negatively charged, elucidated by its isoelectric point 1.1 (Ravindran et al., 2013 (1)). One distinct characteristic of all SIBLING family glycoproteins, including DPP is the presence of the integrin binding tripeptide Arg-Gly-Asp known as the RGD motif (D'Souza et al., 1991). In the amino acid sequence of DPP, the RGD motif is at position 26 from N-terminal and the repeating sequence of (aspartic acid- phosphoserine- phosphoserine)$_n$ as its characteristic domains (George et al., 1996). This N-terminal remains a domain that has not yet been studied as extensively as other domains of DPP.

RGD Peptide

Arginyl-glycyl-aspartic acid (RGD) peptides was firstly discovered as a specific part of the amino acid sequence of an ECM protein named fibronectin. Since then, RGD is the most common peptide motif responsible for cell adhesion to the extracellular matrix, as it acts as the recognition site for cell surface receptors. Though a significant number of extracellular matrix proteins have RGD as their cell recognition site, cells can recognize each sequence individually. This is explained by the presence of specific integrins, each one of which is capable of recognizing only a single RGD-containing sequence (Ruoslahti et al., 1987).

Dentin sialophosphoprotein (DSPP)
Osteopontin (OPN)
Bone sialoprotein (BSP)
Dentin matrix protein 1 (DMP−1)
Enamelin (ENAM)
Matrix estracellular phosphoglycoprotein (MEPE)

Table 2 : The six proteins of SIBLING glycoprotein family

Role of dentin phosphophoryn on dentin regeneration

The primary function of DPP in the matrix is to initiate nucleation of hydroxyapatite crystals (George and Hao, 2005). In a study (Saito et al., 1998), the role of phosphoprotein in mineral induction of dentin was investigated. As a portion of phosphoprotein is bound to collagen, experiments were performed with insoluble dentin collagen. Phosphoproteins were immobilized to collagen in metastable calcium phosphate solution and results showed that phosphoproteins induced the formation of crystalline structure. Moreover, when 90% of the phosphate was removed from the solution, dentin did not induce mineralization. A significant number of studies have concluded the role of DPP to induce the formation and growth of hydroxyapatite crystals of enamel (Saito et al., 2000, He et al., 2005), due to the presence of abundant negatively charged regions. This property enables DPP to bind effectively to calcium ions of hydroxyapatite crystals (Ravindran et al., 2013(1)). A study particularly found the high potential of DPP to nucleate hydroxyapatite when its covalently cross-linked on collagen fibrils (Saito et al., 2000). Moreover, DPP has been shown to act as marker of differentiation of pulp cells into odontoblasts (Wei et al., 2007). There has been reports that DPP possesses signaling functions that can initiate lineage-specific differentiation of mesenchymal stem cells (Sfeir et al., 2011). In addition to cell differentiation and calcification, DPP in the ECM can mediate cell adhesion and migration by initiating integrin-mediated signaling on the surface of pulp cells via its RGD motif *in vitro* (Yasuda et al., 2008).

Dentin phosphophoryn on dentin regeneration *in vitro*

During the initial years of research investigating the role of DPP on dental tissues, experiment was conducted by immobilizing DPP to type-I collagen fibrils and it was reported that DPP induced hydroxyapatite formation, indicating its major role in dentin calcification (Figure 2) (Saito et al., 2000). Later there was one report using human dental pulp cells and the possible contribution of DPP (as well as its RGD domain) on the migration of these cells, indicating its role in early-stage reparative dentin formation (Yasuda et al., 2008). Human dental pulp cells were cultured on DPP, DPP-RGD, DPP-RAD and fibronectin-treated tissue culture polystyrene dishes and cell migration and proliferation was assessed. Results showed that DPP induced pulp cell migration in a concentration- dependent manner. It further stated DPP-RGD peptide also promoted cellular migration (Yasuda et al., 2008). Another study observed the role of DPP on the differentiation of odontoblasts. In this experiment, DPP at different concentrations were experimented on rat dental papilla-derived cell line, MDPC-23 cells. Cell morphology, proliferation, differentiation and calcification were measured. To check the effect of DPP toward odontogenic cell differentiation and calcification, odontogenesis-related mRNA gene expressions were observed. Results showed significant increase in DMP-1 gene expression and increased expressions of alkaline phosphatase (ALPase), runt-related transcription factor-2 (Runx-2), bone sialoprotein (BSP), osteocalcin (OCN), osteopontin (OPN) and type-I collagen (Polan et al., 2014). As it had been reported *in vitro* that overexpression of DMP-1 promotes mesenchymal cell differentiation into odontoblast-like cells (Narayanan et al. 2001), and DMP-1 initiates the binding of Ca^{2+} to early stage mineral deposition, it was concluded that DPP is a signaling molecule involved in dentin formation (Polan et al., 2014). ALPase activity test was performed to check the odontogenic lineage of cell differentiation at protein level and whether DPP had a role in it. DPP induced high ALPase activity in different concentrations. In Alizarin red staining test, stronger stain was observed when cells were cultured in dishes that were treated with DPP. Quantitatively, number of stained nodules were significantly higher in DPP as compared to the control group. From the gene expression test re-

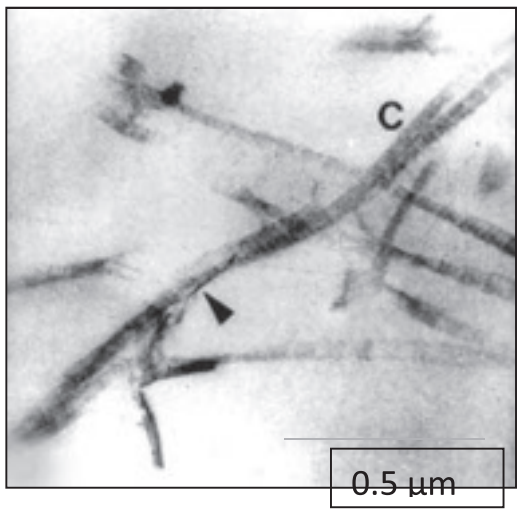

Figure 2 : Mineral induction on collagen fibrils immobilized with dentin phosphophoryn *in vitro* C : type I collagen fibrils, Arrow head : mineral crystal

sults, it was suggested that DPP might bind integrin receptors on the surface of MDPC-23 cells via its RGD motif.

In a recent study, the effect of dentin phosphophoryn-derived RGD peptides on odontoblast differentiation and mineralization was experimented. Tissue culture polystyrene dishes were treated with RGD-1 (SESDNNSSSRGDASYN SDES), RGD-2 (ANSESDNNSSSRGDA) and RGD-3 (SRG DASYNSDESKD) and rat dental papilla call line, MDPC-23 cells were cultured onto them. Based on the results of a previous study (Yasuda et al., 2005) that reported RGD-1, RGD -2 and RGD-3 stimulated human mesenchymal stem cells to differentiate into osteoblasts, these specific peptides were selected for this study. Cell morphology, proliferation, differentiation and calcification were measured. ALP activity was measured to determine the presence of odontogenic lineage cell differentiation at early stage. All the RGD groups had significantly higher ALP activity than the control. Odontogenic gene mRNA expressions were assessed by conducting conventional and real-time RT-PCR, and the result stated high mRNA expressions of DMP-1 and ALP in certain RGD groups compared to the controls. To evaluate the effect of RGD on mineralization of cells, alizarin red staining was done. The RGD groups exhibited strong staining for mineralized matrix, compared to the negligible stain of the control (Tang and Saito, 2016).

Dentin phosphophoryn on dentin regeneration *in vivo*

For an *in vivo* study, DPP was crosslinked on type-I atelocollagen fibrils and applied on exposed vital pulp of porcine molar teeth. It was reported that the rate of reparative dentin forma-tion was significantly higher in DPP-col group compared to the control group at 1st and 2nd weeks. The reparative dentin in experimental group also had significantly higher compactness, the exposed pulp was completely covered by reparative dentin by 3rd week (Figure 3). Also, tunnel defects were not present in DPP-col group. Thus, it was concluded that DPP promote reparative dentin formation with better quality than standard calcium hydroxide *in vivo* (Koike et al., 2014).

Dentin phosphophoryn and dental anomalies and diseases

Studies show that mutations in the dentin sialophosphoprotein (DSPP) gene cause severe dentin anomalies e.g. dentinogenesis imperfecta and dentin dysplasia, characterized by hypomineralized thin dentin with poor functionality (Kim and Simmer, 2007). Absence of DSPP gene expression is correlated with dentinogenesis imperfecta type II (Kim et al. 2004) and type III (Sreenath et al. 2003). DSPP- knockout mice were experimented in a study and reported that absence of DSPP gene renders them susceptible to periodontal disease (Gibson et al., 2013).

Conflict of interest

The authors declare no conflicts of interest associated with the manuscript.

Conclusion

It has been reported in clinical studies that the success rate of direct pulp capping with calcium hydroxide that has been used conventionally is approximately 60%, even though it has been considered the standard therapy (Mejare, 2003). The clinical failures of direct pulp capping have led to the search for new therapeutic agents. After its approval from FDA in 1998, mineral trioxide aggregate (MTA) was found to be an excellent pulp-capping agent because of its high biocompatibility (Bortoluzzi et al., 2006, Tawil et al., 2015). However, MTA-induced dentin bridge formation has been reported to be slower compared to calcium hydroxide (Accorinte et al., 2008). In an ideal clinical case, exposed pulp should be closed by the complete bridge of good quality dentin in a short period. The process of dentinogenesis involves complex interactions among various factors, both inside and outside the cells. If extracellular stimulation can

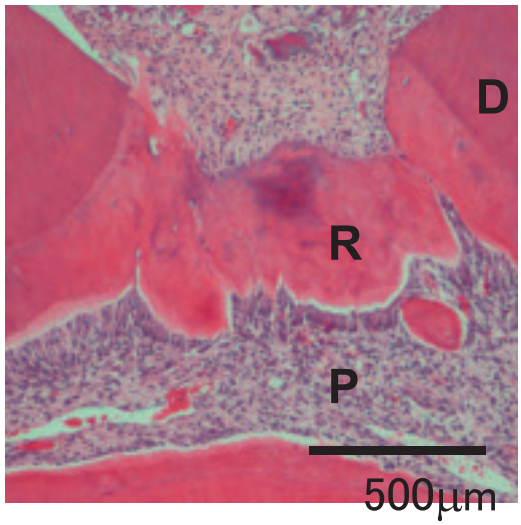

Figure 3 : Reparative dentin formation by dentin phosphophoryn-collagen composite at 3-week in rat R : reparative dentin, D : dentin, P : pulp

be directed to direct pulp capping agents, it will be pivotal for differentiation of exposed pulp cells into odontoblasts and thus initiate dentin formation. In order to get the desired result, the stimulant molecule should possess mineralizing potential. In recent years, studies are being conducted with specific focus on the potential of bioactive agents such as dentin extracellular matrix molecules, for example, bone morphogenic proteins BMP-2 ; BMP-4 ; and BMP-7 (osteogenic protein-1 : OP-1), dentin matrix protein-1 (DMP-1), matrix extracellular phospho-glycoprotein (MEPE), bone sialoprotein (BSP), and so forth enamel matrix derivative, stem cells (Saito et al., 2004, Iohara et al., 2004, Six et al., 2002, Gericke et al., 2010, Six et al., 2007). The dentin extracellular matrix molecules are promising materials because of their involvement in dentinogenesis during the development of teeth (Ravindran et al., 2013). Therefore, they can bring out the potential of stem cells or progenitor cells located within the pulp to the maximum, to proliferate and differentiate into odontoblast-like cells and consequently produce the extracellular matrix, which will eventually undergo mineralization. From the studies discussed in the review, it is evident that DPP can be considered as a novel direct pulp capping agent. However, many aspects of this protein and its microstructure have yet to be studied before it can be applied for clinical use. Studies experimenting with the RGD domain of DPP found that RGD promotes rapid cell attachment (Tang and Saito, 2016) and initial cell attachment is established as an effective indicator for matrix mineralization (Harbes and Healy, 2005). Hence, if RGD peptides can be included in pulp capping materials, this can preferentially recruit odontoblasts and induce faster wound healing in exposed pulp tissue.

Reference

1. Accorinte ML, Loguercio AD, Reis A, Carneiro E, Grande RH, Murata SS, Holland R. Response of human dental pulp capped with MTA and calcium hydroxide powder. Oper Dent 33(5) : 488-495, 2008.
2. Andelin WE, Shabahang S, Wright K, Torabinejad M. Identification of hard tissue after experimental pulp capping using dentin sialoprotein (DSP) as a marker. J Endod 29(10) ; 646–650, 2003.
3. Ba-Hattab R, Al-Jamie M, Aldreib H, Alessa L, Alonazi M. Calcium hydroxide in endodontics : An overview. Open J Stomatol 6 : 274-289, 2016.
4. Balint E, Lapointe D, Drissi H, Van Der Meijden C, Young DW et al. Phenotype discovery by gene expression profiling : Mapping of biological processes linked to BMP -2-mediated osteoblast differentiation. J Cell Biochem 89 (2) : 401-426, 2003.
5. Bansal R, Bansal M, Matta MS, Walia S, Kaur B, Sharma N. Evaluation of Marginal Adaptation of MTA, Biodentine, and MTA Plus as Root-End Filling Materials—An SEM Study. Dent J Adv Studies 7(01) : 006-011, 2019.
6. Bortoluzzi EA, Broon NJ, Bramante CM, Garcia RB, de Moraes IG, Bernardineli N. Sealing ability of MTA and radiopaque Portland cement with or without calcium chloride for root-end filling. J Endod 32(9) : 897-900, 2006.
7. Butler WT, Ritchie HH, Bronckers AL. Extracellular matrix proteins of dentine. InCiba Foundation Symposium 107-117. John Wiley & Sons Ltd, 1997.
8. D'Souza SE, Ginsberg MH, Plow EF. Arginyl-glycyl-aspartic acid (RGD) : a cell adhesion motif. Trends in Biol Sci 16 : 246-250, 1991.
9. Fisher LW, Fedarko NS. Six genes expressed in bones and teeth encode the current members of the SIBLING family of proteins. Connective tissue research 44(1) : 33-40, 2003.
10. Frantz C, Stewart KM, Weaver VM. The extracellular matrix at a glance. J Cell Sci 123(24) : 4195-4200, 2010.
11. Freeman K, Ludington Jr JR, Svec TA, Pinero GJ, Hoover J. Continuously infused calcium hydroxide : its influence on hard tissue repair. J Endod 20(6) : 272-275, 1994.
12. George A, Bannon L, Sabsay B, Dillon JW, Malone J, Veis A et al. The carboxyl- terminal domain of phosphophoryn contains unique extended triplet amino acid repeat sequences forming ordered carboxyl-phosphate interaction ridges that may be essential in the biomineralization process. J Biol Chem 271(51) : 32869–32873, 1996.
13. George A, Hao J. Role of phosphophoryn in dentin mineralization. Cells Tissues Organs 181(3-4) : 232-240, 2005.
14. Gericke A, Qin C, Sun Y, Redfern R, Redfern D, Fujimoto Y, Taleb H, Butler WT, Boskey AL. Different forms of DMP-1 play distinct roles in mineralization. J Dent Res 89(4) : 355-359, 2010.
15. 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 48(2) : 221-227, 2013.
16. Harbers GM, Healy KE. The effect of ligand type and density on osteoblast adhesion, proliferation, and matrix mineralization. J Biomed Mater Res A. 75(4) : 855-869, 2005.
17. He G, Ramachandran A, Dahl T, George S, Schultz D, Cookson D, Veis A, George A. Phosphorylation of phosphophoryn is crucial for its function as a mediator of biomineralization. J Biol Chem 280(39) : 33109-33114, 2005.
18. Iohara K, Nakashima M, Ito M, Ishikawa M, Nakasima A, Akamine A. Dentin regeneration by dental pulp stem cell therapy with recombinant human bone morphogenetic protein-2. J Dent Res 83(8) : 590-595, 2004.
19. Kim JW, Nam SH, Jang KT, Lee SH, Kim CC, Hahn SH et al. A novel splice acceptor mutation in the DSPP gene causing dentinogenesis imperfecta type II. Human Genetics 115(3) : 248-254, 2004.
20. Kim JW, Simmer JP. Hereditary dentin defects. J Dent Res 86(5) : 392–399, 2007.
21. Koike T, Polan MA, Izumikawa M, Saito T. Induction of reparative dentin formation on exposed dental pulp by dentin phosphophoryn/collagen composite. Biomed Res Int, 2014.
22. Linde A. Dentin matrix proteins : composition and possible functions in calcification. The Anatomical Record 224(2) : 154-166, 1989.
23. Mejare I. Endodontics in primary teeth. Textbook of Endodontology by G Bergenholtz, P Horsted-Bindslev, and C Reit, Eds., 102–119, 2003.
24. Narayanan K, Srinivas R, Ramachandran A, Hao J, Quinn B, George A. Differentiation of embryonic mesenchymal cells to odontoblast-like cells by overexpression of dentin matrix protein 1. Proc Natl Acad Sci USA, 98(8) : 4516-4521, 2001.
25. Polan MA, Handa K, Saito T. Dentin phosphophoryn promotes odontoblast differentiation *in vitro* and induction of mineralized tissue-like matrix *in vivo*. J Oral Tissue Eng 11(3) : 201-212, 2014.
26. Ravindran S, Gao Q, Kotecha M, Magin RL, Karol S, Bedran-Russo A, George A. Biomimetic extracellular matrix-incorporated scaffold induces osteogenic gene expression in human marrow stromal cells. Tissue Eng Part A 18(3-4) : 295-309, 2011.
27. Ravindran S, Snee PT, Ramachandran A, George A. Acidic domain in dentin phosphophoryn facilitates cellular uptake implications in targeted protein delivery. J Biol Chem 288(22) : 16098-16109, 2013(1).
28. Ravindran S, Zhang Y, Huang CC, George A. Odontogenic induction of dental stem cells by extracellular matrix-inspired three-dimensional scaffold. Tissue Eng Part A 20(1-2) : 92-102, 2013(2).
29. Ruoslahti E, Pierschbacher MD. New perspectives in cell adhesion : RGD and integrins. Sci 238(4826) : 491-497, 1987.
30. Saito T, Ogawa M, Hata Y, Bessho K. Acceleration effect of human recombinant bone morphogenetic protein-2 on differentiation of human pulp cells into odontoblasts. J Endod 30(4) : 205-208, 2004.
31. Saito T, Yamauchi M, Abiko Y, Matsuda K, Crenshaw MA. *In vitro* apatite induction by phosphophoryn immobilized on modified collagen fibrils. J Bone Miner Res 15 (8) : 1615-1619, 2000.
32. Saito T, Yamauchi M, Crenshaw MA. Apatite induction by insoluble dentin collagen. J Bone Miner Res 13 (2) : 265-270, 1998.
33. Sfeir C, Lee D, Li J, Zhang X, Boskey AL, Kumta PN. Expression of phosphophoryn is sufficient for the induction of matrix mineralization by mammalian cells. J Biol Chem 286(23) : 20228-20238, 2011.
34. Six N, Lasfargues JJ, Goldberg M. Differential repair responses in the coronal and radicular areas of the exposed rat molar pulp induced by recombinant human bone morphogenetic protein-7 (osteogenic protein 1). Arc Oral Biol 47(3) : 177-187, 2002.
35. Six N, Septier D, Chaussain-Miller C, Blacher R, Den-Besten P, Goldberg M. Dentonin, a MEPE fragment, initiates pulp-healing response to injury. J Dent Res 86(8) : 780-785, 2007.
36. Sreenath T, Thyagarajan T, Hall B, Longenecker G, D'Souza R, Hong S, Wright JT, MacDougall M, Sauk J, Kulkarni AB. Dentin sialophosphoprotein knockout mouse teeth display widened predentin zone and develop defective dentin mineralization similar to human dentinogenesis imperfecta type III. J Biol chem, 278(27) : 24874-24880, 2003.
37. Suzuki S, Sreenath T, Haruyama N, Honeycutt C, Terse A, Cho A et al. Dentin sialoprotein and dentin phosphoprotein have distinct roles in dentin mineralization. Matrix Biol 28(4) : 221-229, 2009.

38. Tang J, Saito T. Effect of dentine phosphophoryn-derived RGD peptides on odontoblast-like cells. Int Endod J 49(7) : 670-683, 2016.
39. Tawil PZ, Duggan DJ, Galicia JC. MTA : a clinical review. Compend Contin Educ Dent (Jamesburg, NJ : 1995) 36(4) : 247, 2015.
40. Wei X, Ling J, Wu L, Liu L, Xiao Y. Expression of mineralization markers in dental pulp cells. J Endod 33 (6) : 703-708, 2007.
41. Yasuda Y, Izumikawa M, Okamoto K, Tsukuba T, Saito T. Dentin phosphophoryn promotes cellular migration of human dental pulp cells. J Endod 34(5) : 575-578, 2008.
42. Yoshiko Y, Wang H, Minamizaki T, Ijuin C, Yamamoto R, Suemune S et al. Mineralized tissue cells are a principal source of FGF23. Bone 40(6) : 1565-1573, 2007.

Dr. Tubayesha HASSAN

2015 : Bachelor of Dental Surgery, Sapporo Dental College, Dhaka, Bangladesh
2018 : Post graduate student, Division of Clinical Cariology and Endodontology, Department of Oral Rehabilitation, School of Dentistry, Health Sciences University of Hokkaido, Japan