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Re-Formation: Reactionary or Reparative Dentin

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Abstract

Dentin (s) are complex structures including in the crown, the formation of the mantle dentin mostly atubular, and circumpulpal dentin, crossed along its entire length by 180,000-240,000 tubules per mm². In the root, two superficial layers (the Tomes' granular and the hyaline Hopewell-Smith layers) limit the dentin just beneath the acellular and cellular cementum. Circumpulpal dentin is formed by intertubular and peritubular dentine. The lumens of the tubules are apparently empty or they contain unmineralized collagen fibers and/or odontoblast processes. Circumpulpal dentin includes the primary and secondary dentin, both physiological. Apexogenesis and apexification constitute two crucial events contributing to root formation, and to apical closure. The tertiary dentin is formed in reaction to caries, or wear. Intraluminal mineralization, reactionary and reparative dentins constitute a response to noxious events. Non-collagenous molecules contribute to dentin mineralization or are acting as mineralization inhibitors. Osteopontin is essential for the formation of tertiary dentin after a trauma, whereas tunnels and osteodentin labeling persisted during the formation or re-formation of a dentinal bridge.

Keywords

Dentinogenesis; Mantle Dentin; Circumpulpal Dentin; Intertubular Dentin; Peritubular Dentin; Odontoblasts; Tomes' Granular Layer; Hyaline Hopewell-Smith Layer; Reactionary Dentin; Reparative Dentin; Tertiary Dentin; Osteopontin; Apexogenesis; Apexification

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Global Composition of Dentin

The Global composition is given in Table 1.

Mineral phase	70% in weight	40-45% in vol
Organic matrix	20% in weight	30% in vol
Water	10% in weight	20-25% in vol

Table 1: Global composition of dentin [1].

In the crown, under the enamel layer, the mantle dentin is atubular, and contains glycosaminoglycans, followed by circumpulpal dentin. In the root, beneath cementum, the granular layer of Tomes, #20 micrometer in width, combines with the hyaline zone of Hopewell-Smith. Tubules are thin, bended, with a small diameter. The outer layer includes granules and interglobular spaces. In hypophosphatemic teeth, the outer dentin displays large interglobular spaces, whereas the subjacent circumpulpal dentin looks “normal” [2].

Dentin Structure

The bulk of dentin is formed by circumpulpal dentin. This tubular dentin displays two different parts: intertubular and peritubular dentins. In the circumpulpal dentin, the major portion is formed by intertubular dentin. It is a collagen- rich structure. Tubules crossed along its entire length the circumpulpal dentin layer. Crystallites, located along and between the collagen fibers are 60 nm long, 34 Å thick, and 120-135 Å wide. The number of tubules per mm² is about 24,000 per mm². The diameter of the tubules vary according to the location examined (1-2 mm) (near the pulp chamber 2.85 µm, in the middle 3.70 µm, and near the dentin surface 4.28 µm [3]. Intertubular dentin contains type I collagen (90%) and type I trimer (10%), and calcium-proteolipid-phospholipid- phosphate complex, extracted from dentin only after demineralization. The peritubular dentin does not contain collagen. Rhombohedral crystals have 9-10 nm in height and a = b 25 nm, therefore appearing isodiametric on sections [4].

The different dentin layers include:

Primary dentin 15-20 nm, formed during the early stage of dentin formation, up to completion of the crown.

Secondary dentin is formed during the complete root formation of the teeth, up to completion of the root, the tooth becoming functional. The primary and secondary dentin layers are physiological.

Tertiary dentin is formed by pulpal progenitor cells in reaction to external stimulation (such as cavities, noxious agents, and wear). This dentin results from physio-pathologic reactions. It contains tubules or is atubular. The tertiary dentin is the result from parietal dentin formation to the detriment of the pulp. Adherent to the parietal dentin, or isolated within the dental pulp

either as calcospherites or as diffuse mineralization, the tertiary dentin is formed in reaction to a trauma (caries aggression or pulpal lesion).

Reparative or sclerotic dentins are seen after direct capping with growth factors (Epidermal growth factor, basic fibroblast growth factor, insulin-like growth factor II, platelet-derived growth factor-BB, and Transforming Growth Factor- β 1 (TGF β -1). Connexin 43, reelin, and osteoadherin are identified in differentiation-associated genes in odontoblast cells, playing a role in the recruitment of odontoblasts when dentin repair is initiated. The primary cilium of odontoblasts has been described near the Golgi apparatus, close to the centrioles. A cross-talk occurs between odontoblasts and pulp nerve axons [3].

In the root two morphologically distinguishable dentin outer layers are present superficially. They include the granular Tomes' layer and the hyaline Hopewell Smith layer, limiting the periphery of circumdentin. These layers have a dark appearance which is due to the branching and looping back of dentinal tubules. This appearance, specific to root dentin, possibly result from the differences in the rates of formation of coronal and root dentin. Unlike the granular Tomes' layer, this later displays a width up to 20 μ m. The innermost layer of dentin is known as predentin, and it is the initial dentin matrix that is laid down prior to mineralization. It can be distinguished by its pale color when stained with haematoxylin and eosin. The presence of odontoblastic processes allows the mixed secretion of matrix components (collagen and proteoglycans). Predentin is 10-40 μ m in width, depending on its rate of deposition (Fig. 1).

Figure 1: Regeneration and repair process in dentin [5]. a) Reactionary dentin, b) reparative dentin, c) closure of a reparative dentinal bridge. A biodegradable collagen matrix was used as scaffold and small-molecule GSK-3 inhibitors, connected to reparative dentinogenesis acting as Wnt agonists.

The Remaining Dentin Thickness (RDT) plays an important role in tertiary dentin formation [6]. When the thickness of the RDT vary between 2,5-0,5 mm, the number of odontoblasts is reduced by 13,6%. For a RDT between 0.5-001 mm, the number of odontoblasts is decreased by 33.7%. In an exposed pulp cavity, the number of odontoblasts are reduced by 99,0%.

Dentin Composition

Extracellular Components (ECM) are classified into fiber-forming structural molecules (collagens I, III, V), non-fiber-forming structural molecules (including proteoglycans and glycosaminoglycans) and “matricellular proteins” (osteopontin, SPARC, CCN2, tenascin-C and Fibulin-5) that have no structural functions (Fig. 2 and Table 2 and 3).

Figure 2: Schematic representation of the mesenchymal stem cells found in the teeth. DPSCs, dental pulp stem cells; SCAPs, stem cells from the apical papilla; SHEDs, stem cells from human exfoliated deciduous teeth. MSCs derived from bone marrow (BMMSCs) are capable of giving rise to various lineages of cells, such as osteogenic, chondrogenic, adipogenic, myogenic, and neurogenic cells. The dental-tissue-derived stem cells are isolated from specialized tissue with potent capacities to differentiate into odontogenic cells.

Table 2: The successive steps of collagen synthesis: Reprinted from [7].

<u>Collagens:</u> Type I, Type I trimer ■ Type V ■ Type III ■ Type VI, IX, X, XI, XII
<u>Proteoglycans:</u> Decorin (PG II), Biglycan (PG I), Chondroitin, 4- & 6-sulphate containing, Dermatan sulphate, Keratan sulphate, Perlecan (heparan sulphate).
<u>Lipids:</u> Phospholipids (phosphatidylcholine, phosphatidylethanolamine), Cholesterol, Cholesterol ester, Triacylglycerols
<u>Proteolytic enzymes,</u> Enamelysin, Matrix metalloproteinase (MMPs), Tissue inhibitors of matrix metalloproteinases (TIMPs), Gelatinases
<u>Glycoproteins/sialoproteins:</u> Osteonectin, Dentine sialoproteins (DSPs), Dentine phosphoproteins (DPPs), Bone sialoprotein, Osteopontin, Bone acidic glycoprotein 75, Syndecan 2, Alpha-2-HS-glycoprotein (AHSG) Laminin
<u>Serum-derived proteins:</u> Albumin, Fibronectin, Immunoglobulins
<u>Phosphoproteins:</u> Dentine matrix protein 1, 2, Carboxyglutamate A, Osteocalcin, Matrix Gla protein,
<u>Growth factors:</u> Transforming growth factors (TGFs), Chondrogenic-inducing factor, Bone morphogenic proteins (BMPs 2, 4, 7), Fibroblast growth factors (FGFs), Insulin-like growth factors (IGFs), Amelin-1 transient expression

Table 3: Composition of the dentin extracellular matrix (Essentials of Oral histology and embryology (Mosby) [8].

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Dentin Matrix Protein -1: (DMP-1 induce cytodifferentiation of dental pulp stem cells into odontoblasts [9]. During tooth development, the dentin secreted prior to the completion of the root formation is defined as the primary dentin and comprise the bulk of the circumpulpal dentin. This dentin is formed at a rate of 4 μm per day. Secondary dentin is the dentin bordering the pulp. Non-collagenous proteins include several glycoprotein and the SIBLING proteins [10].

Sialophosphoprotein (DSPP) acts as signal in dentinogenesis and dentin regeneration. This molecule is processed proteolytically by MMP-20 and MMP-2 into Dentin Sialoprotein (DSP) at the N-terminus, Dentin Glycoprotein (DGP) is a proteoglycan located in the middle of the molecule and Dentin Phosphoprotein (DPP), located at the C-terminus [11]. DPP bind to Integrins V3 and activate the intracellular signaling via MAPK and FAK-Erk pathways. Ser-Asp/Asp-Ser repeat regions of the DPP bind to calcium-phosphate deposition and promote hydroxyapatite crystal growth and mineralization via CaMKII cascades. Furthermore, the middle domain and COOH-terminal region of the DSP bind to cellular membrane receptors, integrin $\beta 6$ and occludin, inducing cell differentiation [12].

Cellular (neutrophils, monocytes / macrophages, mast cells and stem cells) and molecular components of the wounded tissue are involved in this cascade of processes. Macrophages contribute to the removal of apoptotic bodies. Inflammation includes different forms of cell death (apoptosis, necrosis, nemosis, and autophagy). Mediators of repair and inflammation encompass growth factors (TGF- β , TGF- α , FGF, PDGF, EGF, 2-2- DSPP) in adult's teeth.

DSPP in adult's teeth: During early development Sonic Hedgehog (SHH), Fibroblast Growth Factor (FGF), Transforming Growth Factor, Bone Morphogenetic Protein (TGF/BMP), WNT, Notch, parathyroid hormone-related protein (PTHrP)/ PTHrP receptor (PPR) (PTHrP/PPR) signaling, and Hippo-YAP/TAZ pathway are recurrently involved in the regulation of tooth development, of mineralization and tooth eruption [13].

Apexification implies for necrotic teeth the induction of apical closure. The calcium hydroxide or Mineral Trioxide Aggregate (MTA) give rise to high success rate.

Dspp heterozygous mice was characterized by excessive attrition of the enamel at the occlusal surfaces, thicker floor dentin of the pulp chamber, decreased pulp volume, and compromised mineralization of the dentin. The teeth in patients with DD-I have a normal clinical appearance; however, radiologically, the roots are pointy and short or even no roots. DSPP is cleaved proteolytically into dentin sialoprotein (DSP) regulating the initiation of dentin mineralization, whereas dentin phosphoprotein DPP is involved in the maturation of mineralized dentin [14,15].

Dentin ECM includes molecules that are also found in bone, such as the proteoglycans, Osteonectin (ON), Osteopontin (OPN), Osteocalcin (OCN), Bone Sialoprotein (BSP), and Dentin matrix protein 1 (Dmp1). In addition to ECM molecules, the presence in tooth matrix

have been reported as: 1) growth factors; 2) serum-derived proteins; 3) lipids; and 4) degradative enzymes such as proteinases.

Dentin Matrix Protein -1 (DMP-) 1 induces cytodifferentiation of dental pulp stem cells into odontoblasts [9]. During tooth development, the dentin secreted prior to the completion of the root formation is defined as the primary dentin and comprises the bulk of the circumpulpal dentin.

Matrix Extracellular Phosphoglycoprotein (MEPE) regulates bone and dentin mineralization by binding to hydroxyapatite via ASARM domain located at the C-terminus.

Osteocalcin (OCN) or bone gamma-carboxyglutamic acid-containing (gla) protein belongs to the SIBLING family that shares many common features, such as containing an RGD sequence, a cell-attachment site, and an acidic serine- and aspartate-rich motif (ASARM). OCN contributes as a mineralization inhibitor to the dentin extracellular matrix.

Bone Morphogenetic Proteins (BMP-2 and -4 [16] are members of a family of 8 BMPs. BMP-1 and -7 and osteogenic protein (OP-2) have so far been cloned and expressed.

Resolvin E1 (RvE1), a major dietary omega-3 polyunsaturated fatty-acid metabolite, is effective in resolving in activating wound healing [17].

Apigenin, a natural product belonging to the flavone class, affects various cell physiology, including cell signaling, inflammation, proliferation cycle, migration, and protease production.. The exposed pulp treated with apigenin treatment showed sound dentin-bridge formation. The in-vitro model ensured the cell toxicity, viability and osteogenic differentiation with apigenin treatment, while the in-vivo model showed the modulating role of apigenin in inflammation control and dentin regeneration with sound dentin-bridge formation. Overall, apigenin treatment would modulate the inflammation by regulating cytokines and TGF- β and BMP signaling, which eventually would facilitate dentin-bridge formation.

Enzymes and Human Odontoblasts

Metalloproteinases (MMP-2, MMP-9, stromelysin (MMP-3), MT-MMP, TIMP- 1 <<<3), enamelysins (MMP-20), Tissue-Nonspecific Alkaline Phosphatase (TNAP), and serum albumin-derived proteins (α HS2-glycoprotein, albumin) are suggested to function in ECM degradation and re-internalization.

Collagenase I, collagenase I/Hyaluronidase and hyaluronidase. Immunostaining of Dentin Sialoprotein (DSP), aquaporin-4 (AQP4), MMP 20 are crucial in these processes [18].

Reelin; periostin, growth factors including transforming growth factor- β (TGF- β 1-3), Bone Morphogenetic Proteins (BMPs), insulin-like growth factor-1 and 2 (IGF-1 and -2), Fibroblast

Growth Factor-2 (FGF-2), FGF-23, adrenomedullin, and several angiogenic growth factors, such as Platelet-Derived Growth Factor (PDGF) and Vascular Endothelial Growth Factor (VEGF) [15]. Sclerostin inhibits the BMP6 and BMP7 but not BMP2 and BMP4 activity. Six different BMPs are co-expressed temporally and spatially. Ten BMP members are cloned for the pulp and dentin regeneration. Ten BMP members [Bmp2, Bmp4, Bmp6, Bmp7, Bmp8, Growth/differentiation factor (Gdf)1, Gdf5, Gdf6, Gdf7, Gdf11 and Glial Cell Line-Derived Neuro-Trophic Factor (GDNF)] implicated in bone and dentin regeneration [19].

TISSUE NONSPECIFIC ALKALINE PHOSPHATASE (TNSALP) plays critical roles in the mineralization of skeletal tissue. Matrix Gla Protein (MGP) is a potent inhibitor of Runt-related transcription factor 2 (RUNX2)/Core binding factor 1 (Cbfa 1) is a transcription factor critical for bone and dental mineralization. PHEX (phosphate regulating endopeptidase homolog X-linked) is also a crucial molecule.

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Lipids

Goldberg and Septier showed that the blood-serum-labeled [³H] choline was detected as early as 30 min before any labeling was seen in odontoblasts and predentin [20]. Hence, the blood-serum-labeled phospholipids pass between odontoblasts and predentin and diffuse in dentin prior to any cellular uptake and phospholipid synthesis. Deletion of the gene encoding sphingomyelin phosphodiesterase 3 (Smpd3) leads to a syndrome of severe dentinogenesis imperfecta [21].

Markers such as biglycan, DMP-1, FGF23, Fibronectin, MEPE/OF45, osteopontin, osteopontin, podoplanin, sclerostin, SPARC, are expressed by osteocytes and/or by odontocytes. Zeb 1 promote differentiation of odontoblasts in a stage-dependent manner [22].

Tertiary Dentin: Pulp Capping and Tunnel Defects In Dentin Bridges

In addition to primary and secondary dentins, which are both physiologic, reactionary and reparative dentin (fibrodentin) were identified (physio-pathologic dentin) and sometimes the three terms are used interchangeably. Tertiary dentin is created in response to a stimulus (tooth decay or wear) [23].

Epidermal growth factor, basic fibroblast growth factor, insulin-like growth factor II, platelet-derived growth factor-BB, and transforming growth factor- β 1 (TGF- β 1) absorbed onto a sterile collagen membrane were used separately as pulpal medicaments. Calcium hydroxide, MTA, BSP and a few other capping agents were efficient in the formation of tertiary dentin. Copine7

(CPNE7) used after indirect pulp capping using protein CPNE7 leads to tertiary dentin formation [24].

Calcium hydroxide ($\text{Ca}(\text{OH})_2$) has been used as a pulp-capping agent for decades and it is the most popular material for vital pulp therapy. MTA is a bioactive material with a high sealing ability, superior antibacterial properties and excellent biocompatibility. iRoot BP plus is a convenient, recently applied as a pulp-capping agent. iRoot BP has not been widely used in vital pulp therapy and the supporting evidence for its use is relatively less than that for the use of MTA and $\text{Ca}(\text{OH})_2$. Previous research has indicated that iRoot BP exhibited good biocompatibility with pulp tissue and induced proliferation and reparative dentin bridge formation in dental pulp cells, suggesting that iRoot BP may be used as a pulp-capping agent [25].

Platelet-Rich Fibrin (PRF), which belongs to the second generation of platelet concentrate products, has favorable properties, including osteogenic ability, simple preparation and no added biological agents. PRF was demonstrated to promote cell proliferation and osteogenic differentiation in Human Dental Pulp Cells (HDPCs). Midkine promote odontoblast-like differentiation and tertiary dentin formation [26].

Pulp Capping with $\text{Ca}(\text{OH})_2$

About 89% of all dentin bridges contain tunnel defects [27]. Osteopontin (OPN) was not detected in the physiological and reactionary dentine, while it was strongly immunoreactive in the matrix that surrounded the entrapped cells of reparative dentin [28]. Monoclonal antibody directed against fibronectin receptor stained the cellular components. Both reactionary dentin and reparative dentin are considered as different types of tertiary dentin [29-31].

Conclusion

Reactionary and reparative dentin(s) constitute physiopathologic tertiary dentin (re-formed) in response to tooth decay or wear. Osteopontin is expressed within defective dentinal bridges together with tunnels closing only partially the pulp exposure. By immunocytochemistry, osteodentin is detectable in the reparative dentin bridge. Pulp capping, apexogenesis and apexification are the main events occurring in this layer, and used in dentin therapies to close and heal pulp exposure.

Conflict of Interest

The author declares no conflict of interest.

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