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Cementum: Composition, Formation and Regeneration

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Abstract

Cementum is forming a thin layer over the root. Incremental lines of Salter reflect periodic deposition, separating mixed cementum into successive layers. Cementum plays a role in the anchorage of the teeth and adaptative, reparative and regenerative functions. Entrapped in cementum, cementoblasts become cementocytes located inside lacunae. Type I (90%) and III (5%) collagens constitute the major components of the matrix. In addition, non-collagenous proteins include proteoglycans, bone sialoprotein, osteopontin, fibronectin, osteonectin, α_2 -HS glycoprotein (also named fetuin-A), osteonectin and non-specific alkaline phosphatase (NSAP). It contains also cementum-specific proteins, a number of growth factors (IGF, FGF, PDGF, TGF β , BMPs and EGF), transcription factors, enamel-associated proteins and tuftelin, involved in the initial stages of enamel mineralization. These molecules contribute to cementum formation, structural and molecular repair and may be used for cementum regeneration.

Keywords

Acellular A fibrillar Cementum; Acellular Fibrillar Cementum; Cellular Cementum; Intermediate Cementum; Cementoblasts; Cementocytes; Lacunae; Non-Collagenous Proteins; Collagens; Non-Collagenous Matrix Proteins; Cementum Regeneration

Composition of Cementum

Cementum is a thin tissue serving to attach the roots via collagen fibers, forming the Periodontal Ligament (PDL), inserted in the bony socket. Entrapped cementoblasts become cementocytes, inside lacunae. Acellular extrinsic fiber cementum grows very slowly on the upper middle portions of the root. Cellular cementum compensates abrasion or attrition and contributes to tooth anchorage. Found either alone, as radicular repair tissue or contributing to the cellular mixed cementum, inside grooves or furcation. The ability to be rapidly deposited demonstrates its participation to a reparative tissue [1]. The recent knowledge on cementum composition has been translated to the clinic. Among the various strategies, structural molecules, growth and transcription factors play essential role in cementum regeneration.

Terms	Abbreviation	Organic components	Location	Function
Acellular, afibrillar cementum	AAC	Homogeneous matrix, no cells, no collagen fibrils	At dentino–enamel junction, on enamel	Unknown
Acellular, extrinsic fiber cementum	AEFC	Collagen fibrils as Sharpey's fibers, no cells.	Cervical to middle root	Tooth anchorage
Cellular, intrinsic fiber cementum	CIFC	Intrinsic collagen fibrils and fibers, cementocytes	Apical and interradicular root surfaces, resorption lacunae, fractures	Adaptation, repair
Acellular, intrinsic fiber cementum	AIFC	Intrinsic collagen fibrils and fibers, no cells	Apical and interradicular root surfaces	Adaptation
Cellular, mixed, stratified cementum (AEFC + CIFC/ AIFC)	CMSC	Intrinsic collagen fibrils and fibers, collagen fibrils as Sharpey's fibers, cementocytes	Apical and interradicular root surfaces	Adaptation, root anchorage

Table 1: Classification of cementum.

Cementum is classified into intermediate cementum, acellular and cellular cementum. Cementum is composed of calcified collagenous fibrils (Sharpey's fibers), glycosaminoglycans and Proteoglycans (PGs). Type I collagen accounts for 90% of all collagens that develops into intrafibrillar apatite crystals. Certain non-collagenous proteins regulate mineralization.

Composed primarily of BSP and OPN, they possess cell attachment properties through the arg-gly-asg (RGD) sequence. The major glycosaminoglycans present in human cementum are hyaluronic acid, dermatan sulfate and chondroitin sulfate. Keratan sulfate appears to be also a major components. After digestion with keratinase II and endo-beta-galactosidase, two proteins are produced. Lumican and fibromodulin are localized predominantly in non-mineralized cementum (pre-cementum and peri-cementocyte), suggesting that they play regulatory roles during mineralization. It contains also the large hyaluronan-binding proteoglycan, versican, localized in lacunae housing cementocytes. Decorin is associated with biglycan in the pre-cementum area. Osteoadherin, a KSPG, is associated to the initial phase of cementum formation, requiring an accumulation of proteoglycans. Cementum contains many non-collagenous proteins, including some major phosphoproteins such as osteopontin and bone sialoprotein filling the spaces created during collagen assembly, allowing mineral deposition across the entire collagen meshwork.

Both OPN and BSP in mature teeth display adhesion function to cells and initiate mineralization. OPN regulates cell migration and survival via interactions with integrins and participates to monocyte-macrophage activation and phagocytosis [2]. In cementum, OPN is implicated in bio-mineralization by playing role in matrix mineralization.

Other cementum matrix components include osteonectin, producing cellular extrinsic and intrinsic fibers, osteocalcin, laminins and growth factors, including BMP-2 to - 4 and IGF-I.

Cementum contains sialoprotein modulating the adhesion of pre-cementoblasts. OPN is a phosphorylated acidic glycoprotein that play a role in the differentiation to cementoblasts. Osteoblast markers are unchanged. Blood circulation is a source of OPN [3]. Following its transportation via serum, OPN is located in the direct cell environment. Alpha₂-HS glycoprotein, known as fetuin-A, belong to the class of plasma-binding proteins.

Both OPN and γ carboxyglutamic acid proteins regulate mineralization. They are negative regulators. Based on these observations, low concentrations growth in vitro. Osteonectin also acts as a negative regulator by preventing, rather than promoting matrix mineralization. Inorganic pyrophosphate (PPi) is an inhibitor of HAp mineral precipitation whereas Alp1/TNAP promote mineralization [4].

Bone Morphogenetic Proteins (BMPs)

BMPs and BMP antagonists form a family within the TGF- β superfamily. They regulate bone repair [5]. Urist reported that BMPs induce cartilage and bone formation when implanted intramuscularly in a rodent model [6]. BMPs are synthesized in a precursor form. Structural and chemical differences may be responsible for variations of their biologic potential and

binding characteristics. More than 20 BMP-related proteins have been identified. Bone and cartilage are produced through an epithelial-mesenchymal interaction.

The BMPs are classified into three subfamilies. Both BMP-2 and BMP-4 have 80% amino acid sequence homology. The second group, consisting of BMP-5, -6 and -7, displays 78% amino acid sequence homology whereas the third group is composed solely of BMP-3. BMPs induce the production of runt-related transcription factor. Sonic hedgehog (Shh) is another growth-factor-like protein which binds to a specific cell-surface receptor, suggesting that Shh is an upstream regulator of BMP production.

BMP receptors bind to two distinct BMP receptors subfamilies: a short extracellular domain, a single membrane-spanning domain and an intracellular domain with an active serine/threonine region. The type II receptor is the primary binding site of the ligand and after activation, phosphorylation of type I receptor occurs. Its association with various specific receptors is regulated by Smad proteins. They link the ligand receptors signals to the transcription control. Delivery systems that have mechanical and surgical properties are appropriate for the controlled release of BMPs and identification of the optimal condition for periodontal regeneration [5].

Organic (natural or synthetic)	Inorganic (natural or synthetic)
Organic polymers-allogenic / xenogenic collagen (absorbable collagen sponge), fibrin, poly-a- hydroxyl acids, hyaluronan, methylmethacrylate.	Autogenous bone, Hydroxyapatite, calcium phosphates, calcium sulfates, β tricalcium phosphate, and bioglass technologies.

Table 2: Carrier systems for the delivery of BMPs.

Organic (natural or synthetic): Organic polymers-allogenic / xenogenic collagen (absorbable collagen sponge), fibrin, poly-a- hydroxyl acids, hyaluronan, methylmethacrylate.

Inorganic (natural or synthetic): Autogenous bone, Hydroxyapatite, calcium phosphates, calcium sulfates, β tricalcium phosphate and bioglass technologies.

Cementum-Specific Proteins

Molecules that are express exclusively in cementum are reviewed now. The Cementum-Derived Growth Factor (CGF) is a 14-kDa protein. The second specific molecule is named Cementum Attachment Protein (CAP). Antibodies to CAP positively labelled cementum and no other tissue.

Cementum Derived Attachment Protein (CGF) and cementum derived growth factor: Blood circulation is a source of Osteopontin (OPN), component of acellular extrinsic fiber cementum [3]. The molecule specific to cementum is taking origin from the Cementum-Derived Growth Factor (CGF), promoting their differentiation into cementoblasts, including cytosolic Ca^{2+} .

Another protein named Cementum Attachment Protein (CAP) is a 55-kDa collagenous protein, whereas the PTPLA/ cementum attachment protein codes for a 15-kDa protein that has no collagen sequences. The cementum attachment protein seems to be strongly associated with collagen chains in the cementum matrix.

Cementum protein-1 is a single-copy as a 26 nascent protein. The human cementum protein-1 gene maps to chromosome 16 (16p13.3). It is a nuclear protein. The precise role of attached carbohydrates is unknown; however, glycosylation may affect the function of cementum protein-1 during the mineralization process because their anionic surface can bind a large number of Ca^{2+} ions and regulate hydroxyapatite crystal growth. Cementum protein-1 play a role at the early stages of mineralization during the formation of octa-calcium phosphate. In small crystals, the mineral phase is transformed into hydroxyapatite by hydrolysis and can only be detected in large crystals because of its slow kinetics of transformation.

Other cementum molecules: Cementum protein-23 seems to be also cementum specific. It is localized to the cementoïd matrix and cementoblasts [7]. Sclerostin was detected only in cellular cementum. It points to regenerative processes and to similarity between cellular cementum and bone. Fibroblast Growth Factor 23 regulates phosphate homeostasis. Mutation in humans causes autosomal dominant hypophosphatemic rickets. Matrix Extracellular Phosphoglycoprotein and the Small Integrin-Binding Ligand N-linked Glycoprotein (SIBLINGs) family: Genes in this family include BSP, OPN, DMP-1, DSPP (DSP and DPP) and MEPE. The DSPP transcript is processed and results in three proteins, namely DSP, DGP and DPP. Other matrix components include osteonectin and laminins. Several GF are sequestered in the cementum. These molecules are TGF- β and insulin-like growth factor-I. Tissue Non-Specific Alkaline Phosphatase (TNAP): Defective formation of acellular cementum is observed in mice lacking the TNAP gene. It was deposited as a thin and irregularly defective layer. The cellular cementum was unaffected [8].

Enamel-associated protein in cementum: Amelogenins increase the expression of osteoprotegerin. They accumulate in cement lines and in the spaces among the mineralized collagen fibrils [9]. In addition, ameloblastin (also known under the name of amelin and sheathlin), is present in enamel matrix derivative, as well as tuftelin, involved in the initial stages of enamel mineralization. All together associated, they may contribute to cementum regeneration.

Growth Factors	
IGF-1:	proliferation, differentiation, matrix synthesis
FGF:	proliferation, differentiation, matrix synthesis, angiogenesis
PDGF:	proliferation, differentiation, matrix synthesis
TGF- β :	matrix synthesis, angiogenesis, chemotaxis
BMPs:	matrix synthesis, differentiation, bone formation
EGF:	proliferation, differentiation
CGF:	^a proliferation, ^b differentiation
Matrix Components	
Collagens	
BSP	
OPN	
Fibronectin	
Osteonectin	
Cementum- attachment protein: (cell adhesion, differentiation; regulated proliferation, mineralization, survival and angiogenesis). A: Cementum- derived growth factor, isoform of IGF-1. B: Mineralized tissue- forming cells respond better than fibroblasts to these proteins.	

Table 3: Molecules identified in cementum and their activity.

Cementum Formation

HERS (Hertwig's Epithelial Root Sheath) is formed by cuboidal cells of the inner epithelium and the flattened cells of the outer epithelium. Then, the HERS becomes discontinuous, a phenomenon leading to the formation of intermediate cementum, followed by the formation of acellular cementum [10].

The “classical” hypothesis proposes that cementoblasts are cell lineages produced by the dental follicle. An alternative hypothesis considers an epithelial contribution to cementogenesis. Cementoblasts are derived from epithelial-mesenchymal interconversion of HERS cells [11]. Evidence for an epithelial origin of acellular cementum lies in the demonstration that these cells can produce proteins characteristic of epithelial cells [12-14]. Enamel Matrix Proteins (EMPs) (e.g., amelogenin, ameloblastin and enamelin) and other proteins influence cell migration, attachment and matrix secretion. In addition, enamel matrix derivative and tuftelin may also be identified in cementum.

Phenotypic difference between cementum-forming cells and bone-forming cells

Cementocytes embedded in the cementum-like matrix were immunopositive whereas were immunonegative. These results indicate that cementoblasts are phenotypically distinct from bone cells [9].

Acellular vs Cellular Cementum

First, forms on the root mid-portion. The development of acellular cementum seems to be associated with the secretion of enamel-related proteins. Cellular cementum appears to be induced by exposure of the inner layer of the epithelial root sheath into the mesenchymal cells in the dental follicle.

The “alternative” epithelial hypothesis considers a potential epithelial-mesenchymal transformation of the Outer Enamel Epithelium (OEE) cells to a secretory cell-like morphology. It was concluded to a mixed origin for cementum-forming cells, suggesting that a population of cementoblasts was derived from the HERS and passively incorporated within the cementum matrix. An immortalized murine HERS cell line expressed ameloblastin but not amelogenin or enamelin. HERS induces BSP and OCN expression. Acellular cementum is dependent on precise regulatory influence of PPI. Apical cellular cementum implicates regulation by PPI. When PPI was lessened, the cementum of the cervical root grew rapidly. Engulfed cells become cementocytes. This is the major differences between acellular vs. cellular cementum types.

Structure of Cementum

Classification of acellular and cellular cementum: (Table 1 and Fig. 1 and 3).

Figure 1: Lack of acellular cementum on *Alpi*^{-/-} molar root surfaces.

Figure 2: The cervical enamel-cementum junction in humans: acellular, cellular and mixed cementum.

Figure 3: Incremental lines of Salter in mixed cellular cementum.

- The Acellular Afibrillar Cementum (AAC). According to Bosshardt, serum proteins such as osteopontin or α_2 -HS glycoprotein, also named fetuin-A, are at the origin of the AAC [1,3].
- Acellular Extrinsic Fiber Cementum (AEFC) contains intrinsic fibers of the cementum proper [4,15]. AEFC covers the coronal half of the cervical root and do not contains cementocytes. The diameter of the extrinsic collagen fibers is about 3 to 6 μm . OPN in acellular cementum takes origin in the direct environment transportation via serum [3]. AEFC is usually confined to the coronal half of the root implanted into dentin.
- Cellular Intrinsic Fiber Cementum (CIFIC) covers the dentin. The CIFIC has mainly a repair function. The cementum contains extrinsic Sharpey's fibers and intrinsic fibers of the cementum proper. This cementum is forming lamellae, corresponding to a twisted plywood model. It is called mixed stratified cementum, about 150-200 μm thick [16,17].
- The Cementum called Mixed Stratified Cementum (CMSC) is confined furcation and it participate mainly in the repair of roots.
- Intermediate cementum was investigated by many authors and identified as a part of the mantle dentin. Other authors believe that this intermediate cementum is an enaemloïd-like tissue produced by the epithelial root sheath. This hypothesis refers to an epithelial origin. The root sheath participates in the formation of intermediate cementum but not of the proper dental cementum [18]. It indicates that the matrix is formed by the epithelial root sheath of Hertwig. This noncollagenous matrix was possibly of the same nature as enamel matrix proteins [1,19].

Regenerative Therapy

Fibroblasts recreating the original periodontal attachment have been recognized since a long time. Guided Tissue Regeneration (GTR) has been applied with variable success to regenerate periodontal defects [20,21].

Clinical therapies implicate root planning and surgical treatments. Two important elements cellular and molecular events occur during the early stage of cementum regeneration. Two strategies are involved: the use of scaffolds and bioactive molecules controlling drug delivery. The predictability and quality of the regenerated cementum should closely contribute to the attachment function. Two strategies have been used:

1. The mucogingival flap and planning root surfaces
2. Placing barrier membranes under gingiva. GTR prevent the ingrowth of epithelial cells and provide space to regenerate PDL and alveolar bone

Cementum wound healing and regeneration are involving three interdependent phases [22].

1. Blood haemorrhage
2. Neutrophils
3. Monocytes cleaning of the wound

Macrophages secrete many mediators that regulate the activities of cells implicated in healing. Re-epithelialisation, due to the migration and proliferation of epithelial cells, occurs together with angiogenesis and the synthesis of collagens. “Granulation tissue” replaced the clot. New blood vessels are degraded and dies from apoptosis. Heparin-binding EGF are angiogenic. TGF- β , $\alpha_5 \beta_1$ and $\alpha_v \beta_6$ integrins, vitronectin receptors $\alpha_v \beta_5$ are expressed and type I collagen receptor $\alpha_2 \beta_1$ occurs and also sprouting capillaries.

In adult, cell-ECM interactions. Failure to regenerate is due to the absence of stem cells. However, many adult tissues undergo self-renewal [23].

In cementum, a variety of non-collagenous proteins has opened a new research area of great therapeutic potential. The application of cementum-derived growth and/or attachment factors result in accelerated wound healing rather than regeneration [1]. The activation of the Wnt signaling pathway induces *in-vivo* cementum regeneration and *in-vitro* cementogenic differentiation [24]. Positive for collagenase-I, integrin β_1 , fibronectin and ALP and current researches showed that the following novel approaches promoted the repair and regeneration of cementum: These methods represent the new therapeutic approaches for treating periodontitis and induce periodontal regeneration [25].

Conclusion

Cementum is a tissue that attach the tooth to the alveolar bone via collagen fibers. Cementum, together with ligament and the socket bone, constitute the links of the root to its environment. Cementum contains specific molecules shared with the supporting/anchoring tissues. These molecules are implicated in the control of cementogenesis and provide new methods to induce periodontal regeneration.

Conflict of Interest

The author declares no conflict of interest.

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