

What Ages First: Pulp or Dentin?



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Abstract

Dental pulps stem cells have regeneration potentials. Young pulp cells convert when they mature into cell-producing dentin. In the pulp, the targeted cells are specifically pulpoblasts, fibroblasts, immune and inflammatory cells. In the coronal part of the teeth, capillaries irrigate 100-150 μ m round or oval domains, allowing the cleaning of continuous zones. In the root, an uninterrupted fish net-like arrangement is located at the periphery of the dental pulp. Thrombus leads to degenerative processes, or to pulp degradation. Pulp necrosis, apoptosis, or nemosis guide pulp impairment. They may influence pulp renewal. Stem cells include Dental Pulp Stem Cells (DPSCs), Exfoliated Deciduous Teeth Stem Cells (SHEDs), Platelet Derived Growth Factors (PDLSCs), Dental Follicle Precursors (DFSCs) and Apical Papilla Stem Cells (SCAPs). An ascending layer of cells issued from the apical papilla mesenchyme contributes to pulp regeneration. Initially, apical cell-rich zones are undifferentiated, and cell sliding involves the transfer from the apical part of the root to the crown, moving from the sub-odontoblastic layer to the radicular dental pulp. Linked by intercellular junctional complexes, pulp cells are interconnected by gap- and tight- junctions. They are transported toward the crown, tightly associated by intercellular junctions. In addition, lateral sliding occurs between the mesial cavities and the central pulp. Later, translocation takes place between the central pulp and the distal horn. This is obvious after an injection with Bio (a Glycogen Synthase Kinase-3 specific inhibitor implicated in regenerative medicine). After a single injection, labeled cells become scarce and in the apical papilla mesenchyme, cells slide laterally from the mesial to the distal pulp horn, where they become undetectable. As pulp cells become older, VEGF promotes blood vessel formation. The activation of the ERK pathway leads to the expression of osteogenesis-related genes, such as Cbfa1, Col I, ALP, and OCN, responsible for dentin formation and mineralization of extracellular matrix components (Tables 1 & 2). TNF- α , Notch, p38 MAPK, TGF- β , Msx1, Msx2, and JNK signaling pathways are implicated in osteogenic differentiation. Dental pulp cells, young and/or old odontoblasts/osteoblasts contribute to bone and dental tissues regeneration. Adipose tissue is another source of mesenchyme stem cells. Young pulp cells become older, producing a dentin layer that contribute efficiently to geriatric odontology.

Table 1: Molecules implicated in dentin formation.

Χολλαγενος: Στυχτυραλ φιβερος (90%)	Τυπι (~90%) αδτυπι Τρι μερ (11%); Τυπι ΙΙΙ αδ γενος (1-3%)
Non-collagenous proteins (10%)	Dentin sialoprophosphoprotein (DSPP) cleaved into:
a) Phosphorylated	a) Dentin sialoprotein (DSP),
b) Small integrin-binding ligand N-linked glycoproteins (SIBLINGs)	b) Dentin Glycoprotein (DGP),
	c) Dentin Phosphoprotein (DPP)
	Dentin matrix protein 1 (DMP1)
	Bone sialoprotein (BSP)
	Osteopontin (OPN)
	Matrix Extracellular Phosphorylated Glycoprotein (MEPE)
Non-Phosphorylated ECM	a) Osteonectin, adiponectin
	b) Osteocalcin
	c) Serum-derived proteins (a2HS glycoprotein, albumin)
Proteoglycans	Decorin, biglycan, glycosaminoglycans:
	a) heparan sulfate proteoglycan,
	b) dermatan sulfate proteoglycan,
	c) chondroitin sulfate proteoglycan
ECM	Fibromodulin, osteoadherin

Enzymes	<ul style="list-style-type: none"> a) Acid & alkaline phosphatases b) Matrix metalloproteinases (MMPs): MMP-2, MMP-9, stromelysin (MMP-3). c) Tissue inhibitors of metalloproteinases (TIMPs). d) Disintegrin and metalloproteinase (ADAMs). e) Disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS).
Growth factors	TGF β , $\Phi\Gamma\Phi\sigma$, IGF 1 & 2, $\subseteq\Gamma\Phi$, BMPs
Phospholipids	Extracellular, intracellular & membrane associated phospholipids
STEM cells	<ul style="list-style-type: none"> Dental pulp stem cells (DPSCs) Platelet derived growth factor (PDLSCs) Dental follicle precursors (DFSCs) Apical papilla stem cells (SCAPs)

Table 2: Pulp molecules.

Component		
Collagens	a) Collagens	<ul style="list-style-type: none"> Type I (56%) Type III (41%) Type V (2%) Type VI (0.5%): thin fibrils – 100 nm periodicity Fibrillin-containing microfibrils, Type IV basement membrane (around blood vessels and capillaries)
Non-collagenous proteins	<ul style="list-style-type: none"> a) Small integrin-binding ligand N-linked glycoproteins (SIBLINGS). b) Phosphorylated ECM proteins 	<ul style="list-style-type: none"> a) Bone sialoprotein (BSP) b) Osteopontin (OPN), MEPE. c) Dentin sialo phosphoprotein (DSPP): cleaved into DSP, DPP, DGP, d) DMP1
	a) Non-phosphorylated ECM proteins	<ul style="list-style-type: none"> a) Fibronectin b) Osteonectin (secreted protein acidic and rich in cysteine- SPARC) c) Osteocalcin d) Tenascin
	a) Glycosaminoglycans, proteoglycans (small leucine-rich proteoglycans SLRPs)	<ul style="list-style-type: none"> a) Versican, b) Chondroitin sulfate -4, c) Chondroitin sulfate -6, d) Dermatan sulfate (DS) (implicated in collagen fibrillogenesis) e) Keratan sulfate (fibromodulin and lumican- implicated in collagen fibrillogenesis) f) Hyaluronic acid
Cellular and pericellular pulp molecules	<ul style="list-style-type: none"> a) Growth factors b) Receptors of growth factors 	<ul style="list-style-type: none"> a) BMPs b) TGF β c) $A\chi\tau\iota\omega\iota\nu$ d) Smad 1, Smad 7
	a) Protein taking origin from the plasma	a) Fibronectin

	a) Enzymes	a) MMPs (collagenase-2, -9, MMP-8, MMP-13), stromelysin-3, b) Collagenase inhibitors (TIMPs), c) Alkaline and acid phosphatases (nonspecific alkaline phosphatase: TNAP), d) Disintegrin and metalloproteinase 28 (ADAM28), e) PMN elastase, f) Cysteine cathepsin G, Dipeptidyl peptidase II, Catalytic lysosomal and ECM enzymes: g) Matrilin-2, matrilin-4, CD-4, interleukin-1 β
STEM cells	a) Lipids, phospholipids	Membrane and ECM phospholipids
	a) Dental pulp stem cells, Stem cells present during crown formation, b) Periodontal ligament stem cells, c) Apical papilla stem cells, d) Stem cells present in deciduous tooth, e) Exfoliated deciduous teeth stem cells, f) Dental follicle stem cells	a) DPSCs b) PDLSCs c) SCAP d) SHED

Keywords: Pulp; Dentin; Stem Cells; A Mini-Review.

Abbreviations: DPSCs: Dental Pulp Stem Cells; SHEDs: Exfoliated Deciduous Teeth Stem Cells; PDLSCs: Platelet Derived Growth Factors; DFSCs: Dental Follicle Precursors; SCAPs: Apical Papilla Stem Cells; ASCs: Adipose-Derived Stromal/Stem Cells; OPN: Osteopontin; OCL: Osteoclast; ECM: Extracellular Matrix Components; ALP: Alkaline Phosphatases

Introduction

Deep carious lesions lead to irreversible pulp damage. Stem cells located in dental pulps replicate and retain potentials for regeneration [1-12]. They are implicated in the repair of defective cell types, carious lesions and genetic therapies. After

the formation of a thin outer mantle dentin, a thick circumpulpal dentin is created, including the primary and secondary dentins [orthodontin (tubular dentin) and osteodentin, which are developed long after the pulp formation]. Reparative (or tertiary) dentin is formed after a pulp horn exposure (Figure 1).

Formation of reparative dentine

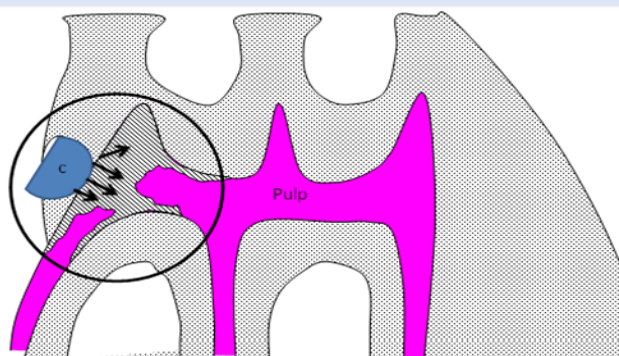


Figure 1: Schematic representation of a tooth molar, showing the formation of reparative dentine. The preparation of a cavity (C) induces the formation of reparative dentine in the mesial part of the dental pulp (arrows).

In the pulp, the targeted cells are specifically pulpoblasts, fibroblasts, immune and inflammatory cells. Different groups of cells are concerned by pulp regeneration. They include odontoblast-like cells, a whole collection of immune cells, central and peripheral nerves, ending at close vicinity of odontoblast cell

bodies. Odontoblasts involve the Raschkow's sub-odontoblastic network. Vascular and lymphatic vessels recolonize and irrigate the wounded pulp tissue [13,14]. Altogether, these cells play a role in pulp physiology, including functionality within the central pulp (Figure 2).

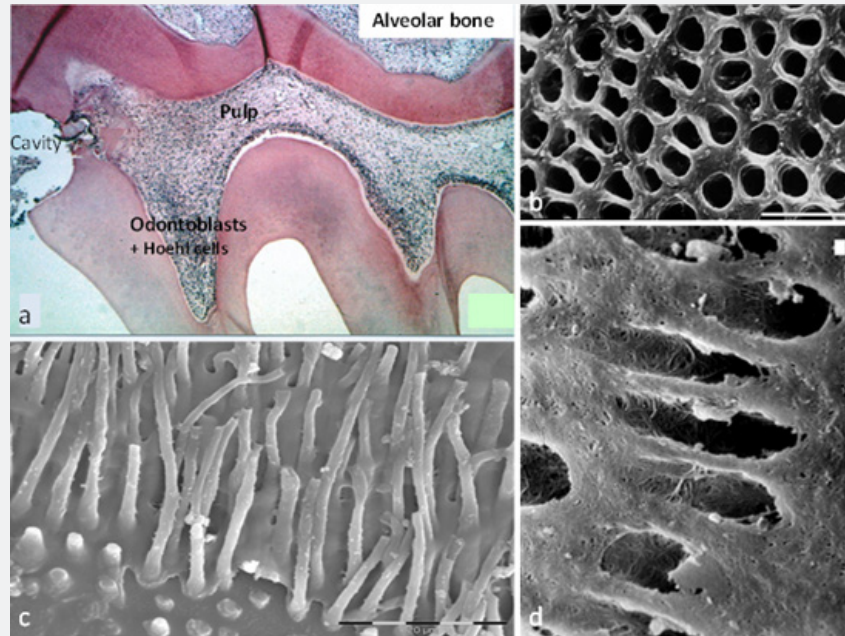


Figure 2: The maxillary molar is implanted into alveolar bone. Hoehl cells and odontoblasts are located at the periphery of the pulp. A drilled cavity has been prepared. **a)** Vertical section of the coronal pulp, **b)** Intertubular network between tubules enlarged after acid etching, **c)** Resin replica-Longitudinal section of dentin tubules, **d)** Replica of longitudinal section after citric acid etching. Collagen fibers are seen in the lumen of tubules.

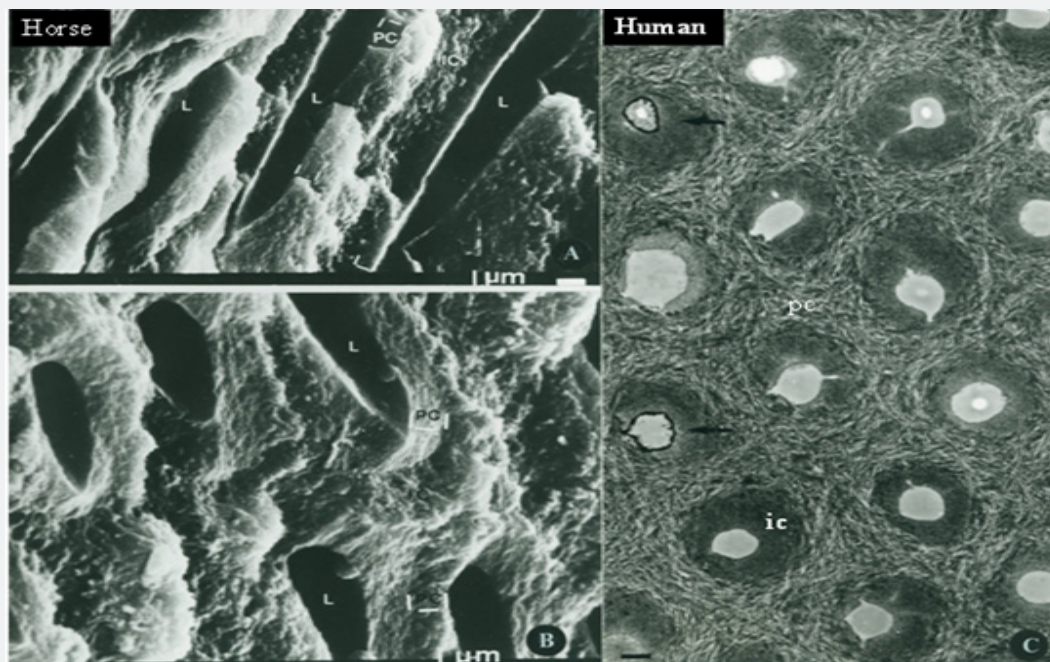


Figure 3: Sections of longitudinally **a)** and transversally **b)** cut tubules from a horse molar. L are lumens of tubules. IC: intertubular dentin. PC are peritubular dentin. In **c)** Human dentin evidenced a network of pericanalicular dentin (pc) and intratubular dentin (ic). Peritubular dentin forms a stable network

In the coronal part of the teeth, capillaries irrigate 100-150 μ m broad domains, round or oval areas, allowing the cleaning of continuous adjacent zones [15,16]. Along the periphery of the pulp, capillaries allow peripheral vascularization and this distribution favours pulp regeneration. In the middle of the pulp, arterioles and venules are in continuity and contribute to stimulate pulp regeneration. In the root part, a fish net-like arrangement is continuous at the periphery of the dental pulp. Thrombus leads to degenerative processes, and ultimately to pulp degradation. Pulp necrosis, apoptosis, or nemosis leads either to the totality of pulp degradation, or specifically allows pulp renewal [17,18] (Figure 3).

In contrast, the formation of dentin implicates a series of molecules (Table 2). Mineralizing molecules are including adiponectin, type I collagen, alkaline phosphatase, DMP-1, α 1-dentin sialoprotein, dentin sialoprotein and dentin sialophosphoprotein, MEPE, dentin matrix metalloprotease MMP-3, MMP-9, PGs (decorine, biglycan, osteoadherin, fibromodulin) and osteopontin [19-22]. To conclude with the construction of dental tissues, first a dental pulp is formed, and later a dentin layer is deposited along the initial layer of mantle dentin (orthodentin and osteodentin). At the periphery of the pulp, odontoblasts polarize and differentiate (Figure 4).

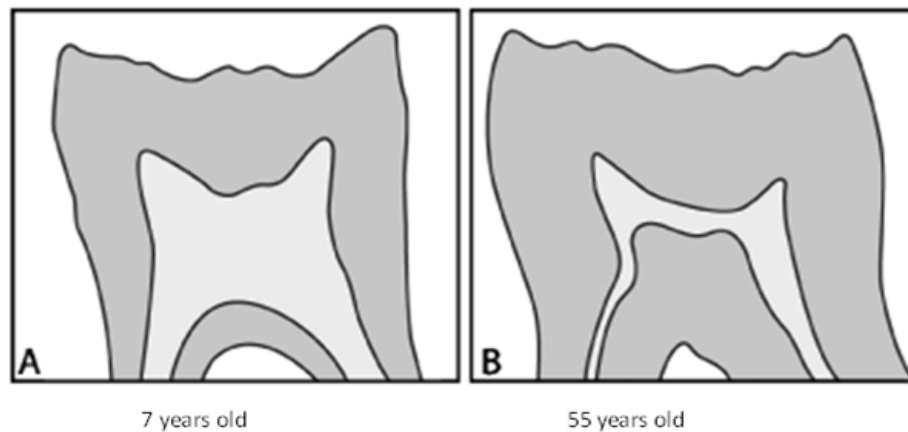


Figure 4: A: Coronal part of a young molar (7years old) compared with B: old crown of a molar (55 years old).

The prevalence of caries is rather high (about 85% in the 65-74 year-old patient) and significant in the aging population. In younger patients, the 35-45 year-old group of patients, the carious prevalence is limited to 80.2%. Pulp inflammation is

lower in young patients and higher in the older patient group. In this clinical context, a significant impact is related to the aging pulp.

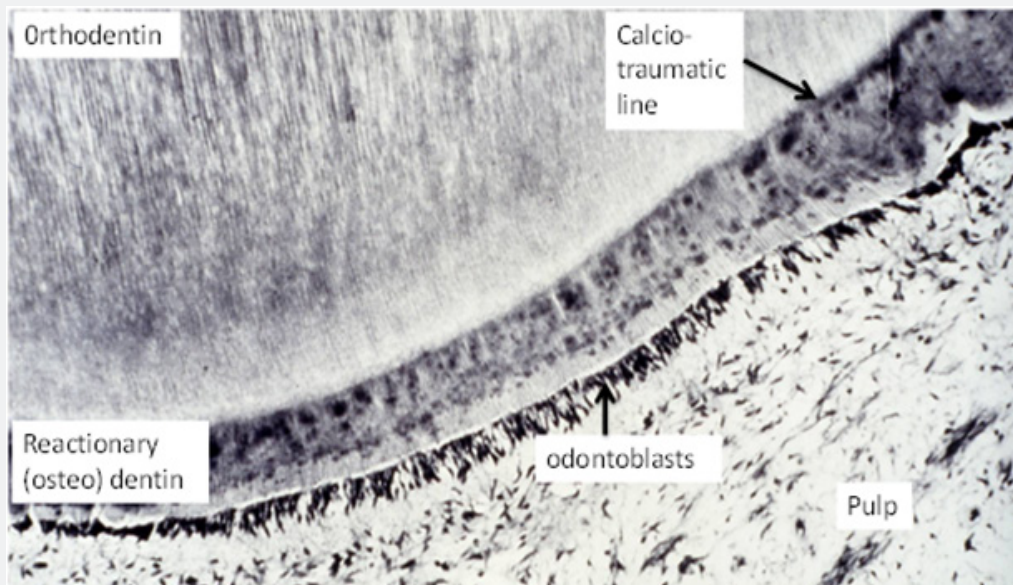


Figure 5: Tubular orthodentin is disconnected from reactionary dentin (granular structure) by a calciotraumatic line (arrow). The periphery of the pulp (P) contains odontoblasts (O), and cell-free and cell-rich zones.

Bio 14d: Reactionary dentin filling the isthmus between the mesial and central pulp chamber

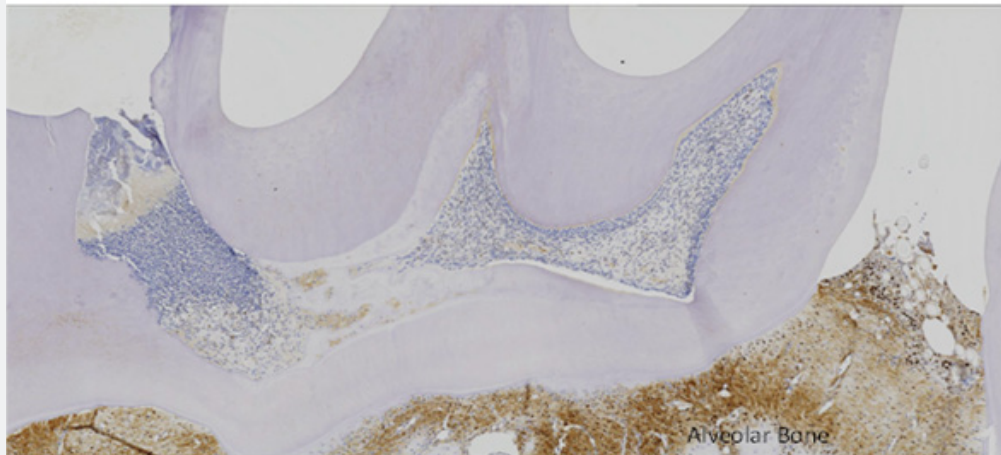


Figure 6: Reactionary dentin fills the isthmus between the mesial and central parts of the pulp.

Pulp stem cells constitute a heterogeneous population. In dental tissues, stem cells include 1) dental pulp stem cells (DPSCs), 2) exfoliated deciduous teeth stem cells (SHEDs), 3) platelet derived growth factor (PDLSCs), 4) dental follicle precursors stem cells (DFSCs) and 5) apical papilla stem cells (SCAPs). Adipose-Derived Stromal/Stem Cells (ASCs) play crucial role in the treatment of craniomaxillofacial defects [23]. ASCs are committed toward an osteogenic phenotype. Angiogenesis and osteogenesis support bone regeneration. Plasma membrane-derived vesicles are important mediators

in cell-to-cell communication. Growth factors, cytokines, RNAs and microRNA perform biological activities on target cells. They activate regenerative or reparative processes [18]. Bioengineering teeth may be obtained from cultured tooth bud cells [24,25] (Figures 5 & 6).

ASCs derived from pulp donors showed a high expression of osteogenic markers. This is the case for Osteopontin (OPN), Osteocalcin (OCL), and BMP-2. A high mineral content is found in the pulp and dentin of old patients [1,9,21,26] (Figure 7).

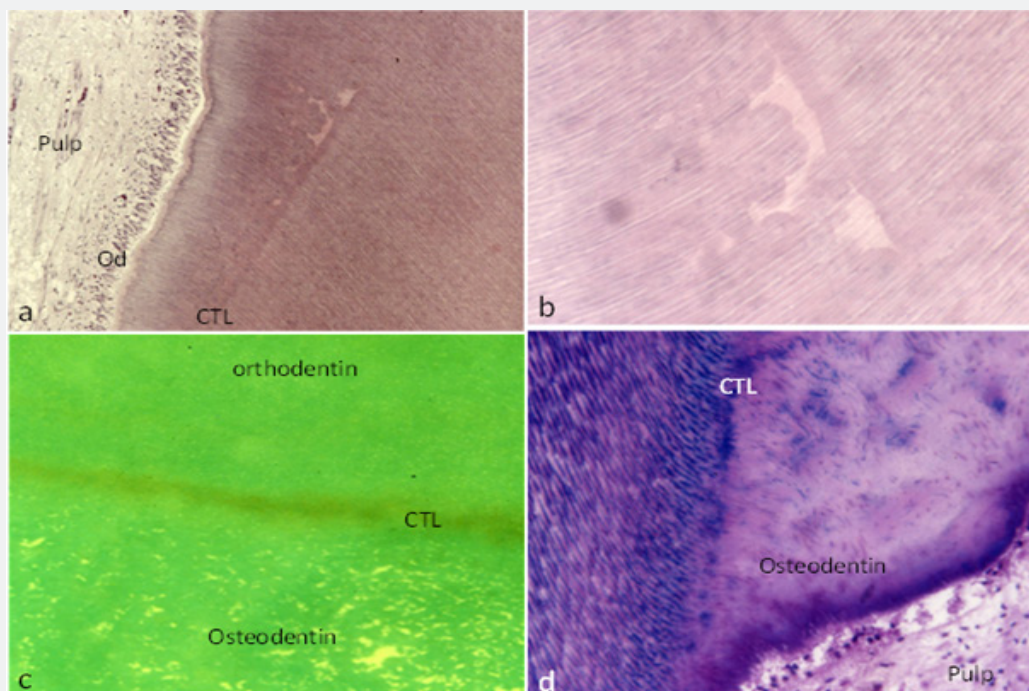


Figure 7: In a and b a calciotraumatic line (CTL) separates the granular osteodentin from the tubular orthodentin. Odontoblasts are located at the periphery of the pulp. In c and d orthodentin is separated from osteodentin by a dense calciotraumatic line (CTL).

Pulp regeneration implies a cascade of cells, sliding from the apex toward the upper part of the crown. In the apical part, undifferentiated cells contribute to colonize the root. The ascending cells move beneath the odontoblast layer, and form a continuous layer that will further colonize the sub-odontoblastic

layer. They proliferate, multiply and concentrate in the apical cell-rich zone. In the root, cell sliding starts near the apical part. The ascending layers of cells contribute to pulp regeneration [24,25] (Figure 8).

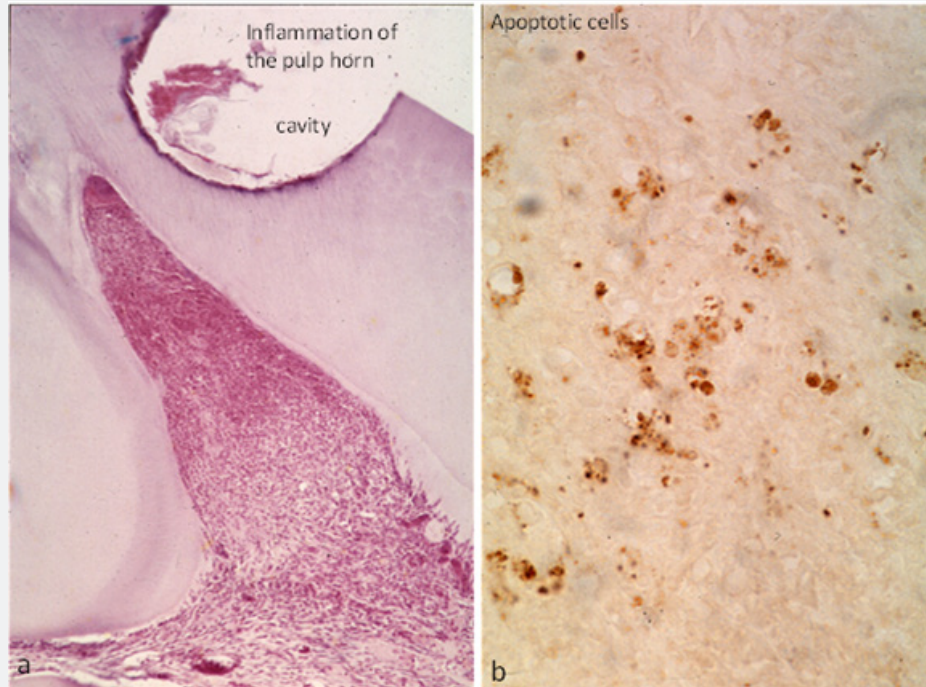


Figure 8: In a the drilling of a cavity (cavity) in the mesial part of the crown induce inflammation of the pulp horn. In b apoptotic cells fills the lowest part of the pulp horn.

Initially, pulp cells are undifferentiated, and move from the sub-odontoblastic layer to the collar of the tooth. Presumably,

cell sliding involves an ascending transfer from the apical part of the root toward the crown [27,28].

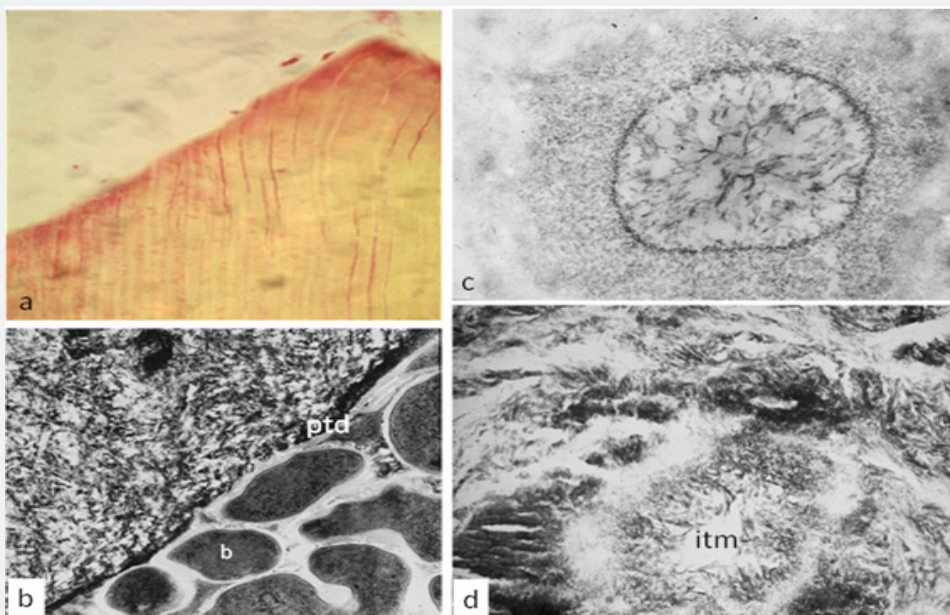


Figure 9: a) Carious decay. Tubules contain bacteria (Brown & Brenn staining). b) Bacteria are present in the lumen of the tubule. Remnants of peritubular dentin (ptd) constitute the limits of circumpulpal dentin. c) Intratubular dentin fills the lumen of the tubule. Peritubular dentin and intertubular dentin are parts of the carious dentin. In d) Intratubular mineralization (itm) occludes the lumen of the tubule

Connected by intercellular junctional complexes, namely desmosome-like junctions, pulp cells are linked by gap- and tight-junctions and they move simultaneously. They are transported along an ascending way, tightly connected by intercellular junctions. They move from the central part of the root to the periphery of the crown where they fan out [29-32] (Figure 9).

In addition, lateral sliding is occurring between mesial cavities prepared after drilling, and the central pulp horn. Afterward, translocation occurs between the central horn and the distal pulp. This is noticeable mostly for rats injected with Bio (a Glycogen Synthase Kinase-3 specific inhibitor implicated in regenerative medicine [32]). After a single injection, labeled cells become scarce in the mesial part of the pulp and they are grouped in the central pulp area. Bio-labeled cells located beneath the odontoblast layer are less numerous in the distal

pulp. It comes out that cells slide laterally from the mesial pulp to the distal pulp horn whereas sliding becomes undetectable in the distal part of the pulp.

The conclusions that arise from these experimental approaches are 1) that cells slide in an ascending way from the apex toward the crown, 2) afterward, lateral sliding occurs between the mesial horn and the central/distal pulp. This evolution takes place mostly in the coronal pulp, leading to the terminal differentiation of odontoblasts. In addition, terminal differentiation was strongly linked to the strategic mesenchymal stem cells that are implicated in dentinogenesis, and angiogenesis. Pulp cells are implicated in the implantation of bioactive molecules located in the root, within the dental pulp (Figure 10).

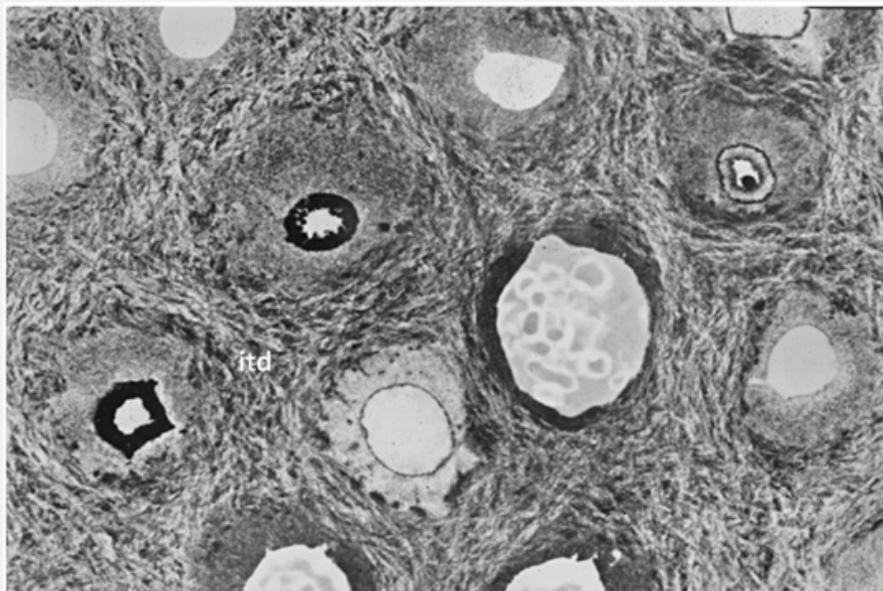


Figure 10: Tubular orthodentin is disconnected from reactionary dentin (granular structure) by a calciotraumatic line (arrow). The periphery of the pulp (P) contains odontoblasts (O), and cell-free and cell-rich zones.

Pulp cells are implicated in geriatric odontology. Angiogenesis shows vascular endothelial growth factor, as well as platelet-derived growth factor, and hepatocyte growth factor. IGF-1, VEGF-D and interleukine-8 improve the recruitment of undifferentiated and/or hematopoietic stem cells associated to different tooth compartments [31]. Combined with biomaterials, such as β -tricalcium phosphate, bioactive glass and platelet-rich plasma, the dental pulp or bone tissue display potential in pulp regeneration. Pulp renewal is also dependent of adipose-derived stromal /stem cells (ASCs).

As cells become older, VEGF promotes new blood vessel formation, and they are also able to recruit hematopoietic stem cells. The activation of the ERK pathway in ASCs leads to the expression of osteogenesis-related genes, such as Cbfa1, Col I, ALP, and OCN, which appears to be responsible for pulp

mineralization of Extracellular Matrix Components (ECM) [21,23,26,29,30,31].

As a conclusion, TNF- α may enhance the osteogenic differentiation of ASCs by increasing specific gene expression, such as osteopontin (OPN), runx-related transcription factor 2 (RUNX-2), and Alkaline Phosphatases (ALP) (Tables 1 & 2) [11]. Molecular investigations clearly confirmed that ERK, TNF- α , Notch, p38 MAPK, TGF- β , Msx1, Msx2, and JNK signaling pathways are strongly implicated in the odontogenic/osteogenic differentiation of ASCs [31-36].

Conclusion

Altogether, young and old dental pulp cells, young and old odontoblasts and osteoblasts contribute to bone and dental tissues differentiation/regeneration. Adipose tissue is an active

source of mesenchyme stem cells. Noticeably, aging tissues contribute efficiently to geriatric odontology.

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