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Review

Physiologic root resorption in primary teeth: molecular and histological events

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Abstract: Root resorption is a physiologic event for the primary teeth. It is still unclear whether odontoclasts, the cells which resorb the dental hard tissue, are different from the osteoclasts, the cells that resorb bone. Root resorption seems to be initiated and regulated by the stellate reticulum and the dental follicle of the underlying permanent tooth via the secretion of stimulatory molecules, i.e. cytokines and transcription factors. The primary root resorption process is regulated in a manner similar to bone remodeling, involving the same receptor ligand system known as RANK/RANKL (receptor activator of nuclear factor-kappa B/ RANK Ligand). Primary teeth without a permanent successor eventually exfoliate as well, but our current understanding on the underlying mechanism is slim. The literature is also vague on how resorption of the pulp and periodontal ligament of the primary teeth occurs. Knowledge on the mechanisms involved in the physiologic root resorption process may enable us to delay or even inhibit exfoliation of primary teeth in those cases that the permanent successor teeth are not present and thus preservation of the primary teeth is desirable. (J. Oral Sci. 49, 1-12, 2007)

Keywords: primary tooth; physiologic root resorption; odontoclast.

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Osteoclasts, odontoclasts, and hard tissue resorption

Root resorption is a physiological process in the life span of a primary tooth. The cells responsible for dental tissue resorption are the odontoclasts (1,2). To date, we know little about how the precursors of the odontoclasts appear, what causes their differentiation, what gives them the signal to start resorbing the primary root at a specific area and time, and why they get activated to resorb dental tissue prematurely in some pathologic conditions and not in others.

Osteoclasts and bone resorption

Most available knowledge on hard tissue resorption is based on studies on osteoclastic bone resorption. Actually, there is no adequate scientific evidence to prove that the cells which resorb the dental hard tissues belong to a different cell type to osteoclasts (3). Osteoclasts are multinucleated giant cells the precursors of which arise from a hematopoietic monocyte or macrophage linage (4,5). Their differentiation as well as their function is under the control of factors produced by bone marrow stromal cells or found on the mature osteoblast, a cell that is derived from mesechymal precursors. Two such factors are the RANK (receptor activator of nuclear factor kappa B) ligand (RANKL) that stimulates osteoclast formation and the osteoprotegerin (OPG), a secreted decoy receptor for RANKL, that regulates negatively the osteoclastinogenesis (6-8) (Figs. 1a, 1b). The receptor of RANKL is RANK and is localized on the surface of the osteoclast (9). Physical contact between the osteoblast or stromal cells and the progenitor osteoclast, involving direct interaction between RANKL and RANK, is necessary for osteoclastic formation and activation (10-12) (Fig. 1a).

Another osteoblast/stromal cell product, the macrophage colony-stimulating factor (M-CSF or CSF1) as shown in experiments on the osteopetrotic mouse model, is of paramount importance for osteoclast formation (13-15). M-CSF is a hematopoietic growth factor produced by fibroblasts, endothelial cells, macrophages and monocytes. It is involved in the growth, survival, proliferation and differentiation of hematopoietic (macrophages, osteoclasts, fibroblasts, and endothelial cells) as well as non-hematopoeitic cells (16-19). One of the mechanisms of action of M-CSF is upregulation of RANK in osteoclastic progenitor cells (20) and another involves downregulation of expression of the OPG gene (21) both of which promote osteocastinogenesis. Osteoclast differentiation and activation seems to also be stimulated by cytokines such as tumor necrosis factor-α (TNF-α, inteleukin (IL)-1α, IL-β, IL-6, IL-11 and IL-17 (22). Although some of the above cytokines may act again through modulation of the expression of RANKL or OPG, a separate mechanism that does not depend on the RANK-RANKL system may be also involved. This seems to be true for TNF-α and IL-1α, especially in pathologic bone resorption seen in inflammatory diseases such as rheumatoid arthritis and periodontitis (23,24).

Upon activation, osteoclasts adhere to the bone matrix and form a unique ruffled border structure which is isolated from the surrounding microenvironment by a clear zone. The ruffled border represents folds of the cell-membrane in which the cytoplasm projects forming finger-like structures. These projections increase the available surface area and thus, the action territory of the osteoclast. The initial step in the bone resorption process is the acidification of the extracellular area under the ruffled border (3). The necessary H^+ ions are produced and delivered to the subosteoclastic space via the H^+-ATPase pump that is present in the ruffled border (25,26). The link of the hydroxyapatite crystals to collagen is cleaved and the crystals are thereby dissolved by the acid. After the solubilization of the hydroxyapatite crystals, the exposed organic matrix is digested by enzymes secreted by either the osteoclasts or other cell types (27). Osteoclast-produced lysosomal enzymes, metalloproteinase-9 (MMP-9), cathepsines, particularly cathepsin K, are considered to be of major importance in bone remodeling (28).

Odontoclasts

Ultrastracturally, odontoclasts possess similar characteristics to those of the osteoclasts (29,30). However, they are generally smaller in size than osteoclasts and once they become multinucleated they have fewer nuclei and form smaller resorption lacunae than the osteoclasts (31). The enzymatic and metabolic properties of odontoclasts are also similar to osteoclasts (32,33). Odontoclasts release hydrolytic enzymes onto the resorption lacunae or the lysosomes for the degradation of collagenous and non-collagenous organic matrices (34,35). They demineralize extracellularly the apatite crystals of the dental hard tissues by means of an H^+-ATPase (34) and subsequently they degrade dentin proteins by the action of cathepsin K and MMP-9 (33,36). Thus, they are able to resorb dentin as well as predentin and at the end of the resorption phase they lose their ruffled borders and become detached from the resorbed surfaces (1).

The control of the odontoclast function has been reported to have similarities but also differences with that of the osteoclasts. In this regard, immunohistochemical studies have shown that the RANK receptor is expressed by odontoclasts and the RANKL by odontoblasts, pulp and periodontal ligament (PDL) fibroblasts, as well as by cementoblasts (37,38). Similar studies have shown M-

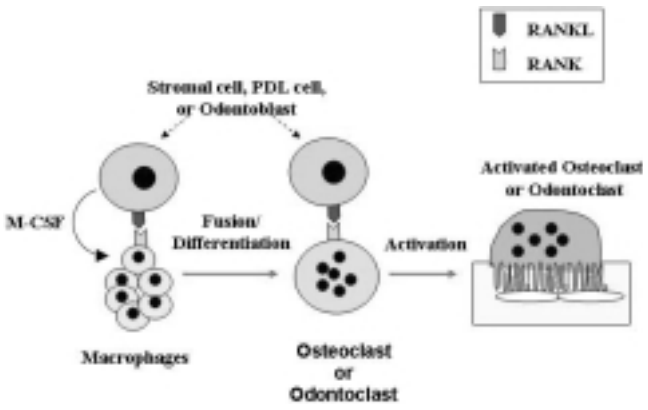

Fig. 1a Schematic representation of RANK/RANKL system interaction for osteoclast and/or odontoclast differentiation and activation.

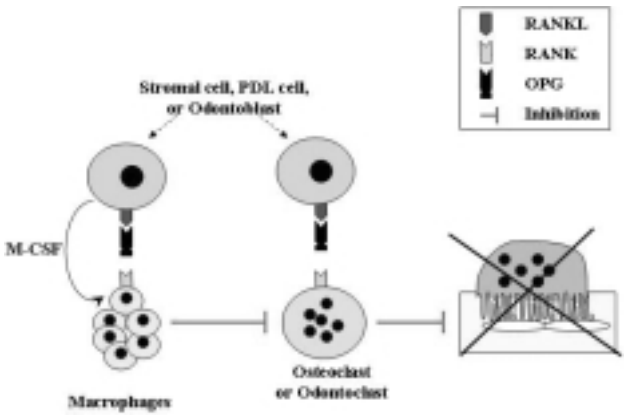

Fig. 1b Schematic representation of OPG-mediated inhibition of osteoclast and/or odontoclast differentiation and activation.

CSF and the negative for osteoclastinogenesis regulator OPG, to be constitutively expressed by odontoblasts, ameloblasts, and dental pulp cells (39,40). As in the case of the osteoclasts, the expression of the RANKL, OPG and M-CSF by theses dental cells seems to be important for the differentiation and activation of locally found preodontoclasts under both physiologic and/or pathologic root resorption conditions. Similarly to osteoclasts, RANKL is also expressed on odontoclasts suggesting an autocrine or paracrine effect of this molecule on these cell types (38), as well as a possible involvement in pseudopodial mobility and resorption lacunae formation in the same manner as in osteoclasts (41).

On the other hand, systemic factors such as parathormone or drugs such as indomethacin affect differently the bone and root resorption processes. Indomethacin, an inhibitor of prostanoid synthesis, inhibits the resorption function of osteoclasts whereas it enhances root resorption by odontoclasts (42,43). Similarly, root as opposed to bone resorption, is not affected by parathormone (PTH) and is not observed in patients suffering from hyperparathyroidism (44,45). Interpretation of such observations however, should be performed with caution. It has been shown that parathormone does not act directly on osteoclast or odontoclast cells. Instead, it causes gaps on the osteoblastic layer which covers the bone and to which osteoclasts are attracted, bind, and start resorption (44). In contrast to osteoblasts, cementoblasts which cover the root surface, do not respond to parathyroid stimulation in the same manner, and this may explain the resistance of the root surface to this hormone (44,46). This explanation is also supported by the observation that a traumatized tooth that becomes ankylosed loses protection of the cementoblastic layer resulting in attachment of the root to the alveolar bone, and PTH administration causes resorption of both bone and root (47).

Besides the osteoblastic layer, the bone surfaces are covered and therefore protected by another layer of unmineralized tissue, the osteoid layer, between the mineralized front and the osteoblasts (3,48). Similarly to the bone, the root is covered by collagen fibers, cementoblasts, and a thin zone of cementoid under the cementoblasts, all of which are believed to protect the root from resorption (44,49). Additionally, cementum being more resistant to resorption than dentin offers another layer of protection which has to be breached before root resorption starts (50,51).

The main difference in bone and tooth biology is that the bone undergoes constant physiologic turn over, whereas teeth only in the case of primary dentition undergo "normal" resorption. Although protection of the root from resorption while the adjacent bone is constantly degrading is a puzzling phenomenon, even more intriguing is the question why the roots of the primary teeth eventually resorb while the roots of the permanent teeth do not. This paper describes the clinical, histological and mainly the known molecular events that occur during the physiologic root resorption process of deciduous teeth in an attempt to summarize the current knowledge on this intriguing biological phenomenon.

Primary root resorption with an existing primary successor tooth

The consistency and symmetry between the left and right side of the mouth regarding the exfoliation timing of the primary teeth and of the emergence of the permanent successors are indeed fascinating, and suggest that shedding of the primary teeth and eruption of the permanent teeth are coupled and may be programmed events.

The pressure of the erupting permanent tooth is believed to play a contributory role in setting off resorption (52), but the presence of a permanent successor is not a prerequisite for this process to occur. Primary teeth without a permanent successor do eventually resorb although their exfoliation timing is later than usual (53,54). The eruption process of the permanent teeth is regulated by factors such as the function of endocrine glands (hypophysis, thymus, thyroid gland), or nutrition (deficiency in Ca and Mg, vitamin A, C and D deficiency) and therefore, these factors have an indirect effect on the resorption course of the primary tooth root (53). Hypothyroidism (55,56), pituitary dwarfism, (57) and chronic malnutrition (58) can delay shedding of primary teeth presumably because they interfere with the eruption process of the permanent teeth.

The root resorption of the primary teeth starts at the site of the root of the deciduous tooth that is closest to the permanent successor (59). In the anterior teeth for example, the completed crown of the permanent successor is found lingual to the apical third of the root of the primary predecessor. The eruptive movement of the permanent tooth has a labial and incisal direction and thus at first, it causes the resorption of the lingual surfaces of the apical third of the primary tooth root. Once the labial surface is also resorbed, the permanent tooth is found underneath the primary tooth root. From then on, resorption proceeds horizontally in an incisal direction, until the primary tooth sheds and the permanent tooth erupts in the oral cavity. In some instances, the permanent mandibular incisors will not move enough labially during their eruption and before their emergence. This causes an incomplete or delayed resorption of the root of the primary predecessor incisors

and may result in eruption of the permanent incisors lingually of the primary incisor which still remain in the mouth (Fig. 2).

In the primary molar area, the developing permanent teeth are also found initially lingually to their predecessors. As growth proceeds, the developing tooth moves under the divergent roots of the primary tooth. The position and the size of the follicle affect the pattern of the root resorption with 36% of the primary teeth showing uneven resorption on one or more roots at any given time (60). The roots of the primary lower second molar are highly curved and divergent and the interroot distance is often larger than the size of the follicle of its successor. Depending on the position of the follicle of the successor, unequal influences may be applied to the roots. This can explain the uneven root resorption observed in more than one third of all lower second molars at any given time after its initiation (Fig. 3). This is also seen in the upper primary molars where the root that lags behind in resorption is the highly divergent palatal root. In 56% of the primary maxillary second molars, the palatal root of the primary upper second molars demonstrates reduced resoption compared to its other roots. The incidence of eneven root resorption is lower for the primary first molars and this is probably due to the smaller difference between its interroot distance and the size of the crown of its successor (60).

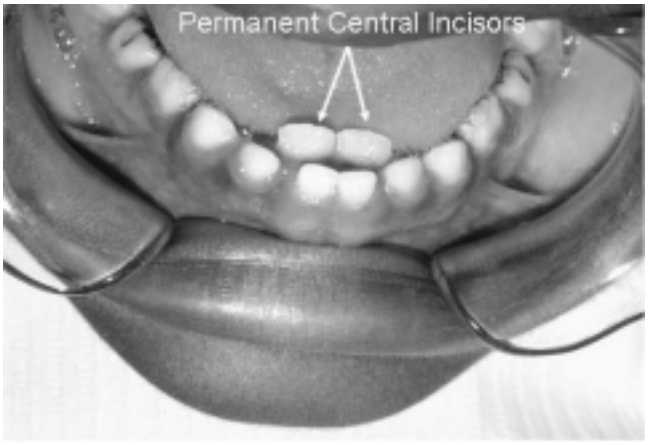

Fig. 2 Eruption of permanent mandibular central incisors lingually of their primary predecessors (Courtesy Dr. Robert J Musselman, LSU School of Dentistry, New Orleans).

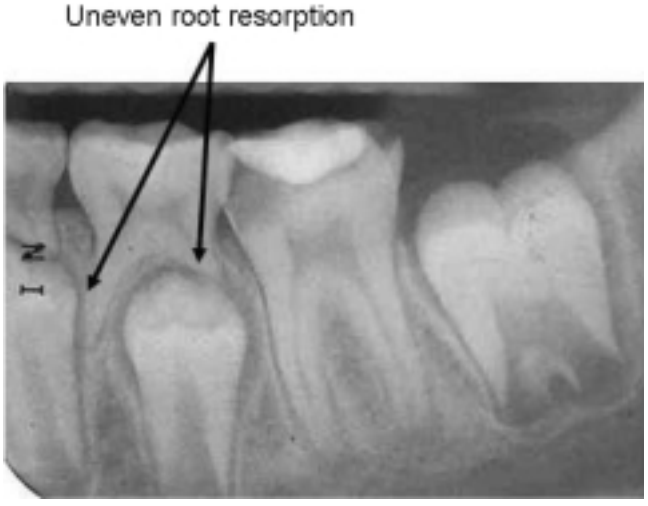

Fig. 3 Uneven resorption of the root of the primary mandibular left second molar.

Among the components of the erupting permanent tooth, the dental follicle and the stellate reticulum seem to play important roles in the resorption of the deciduous root (61,62). Since the 1930's Kronfeld (63) suggested that the dental follicle is responsible for the resorption of the root of the primary tooth. Although never proven, it was believed and it is still assumed that it is the pressure of the erupting permanent tooth that causes the differentiation and activation of the odontoclasts. However, elegant studies performed by Marks and Cahill (64) showed that the dental follicle of the permanent tooth rather than the tooth itself controls the tooth eruption process. In these animal experiments, the developing tooth crown was removed and inert substitutes of teeth, such as silicone and metal replicas, were placed in the dental follicles. The tooth substitutes erupted successfully in the mouth indicating that the dental follicle regulates and coordinates the resorption events of the overlying bone and presumably of the roots of the primary predecessor tooth. Uneventful resorption of the overlying bone and resorption of the deciduous root occurred even when the erupting movement of the tooth was inhibited by transmembane wires (65). In contrast, removal of the dental follicle from erupting teeth prevented their eruption (64). Hence, the development of the eruption pathway, which involves bone resorption and resorption of the primary tooth root, seems to be a genetically programmed event that does not depend on the pressure from the erupting tooth.

At a critical time in the eruption process, cells from the stellate reticulum of the developing tooth secrete parathyroid hormone (PTH)-related protein (PTHrP). PTHrP is a developmental regulatory molecule which is required for tooth eruption (66). Secreted PTHrP then binds in a paracrine function to the neighbor PTHrP receptors expressed by cells in the dental follicle (67-69). Interleukin-1α is also secreted by the stellate epithelium and in a similar manner binds to the IL-1α receptors found on the dental follicle (70). The stimulated dental follicle cells in turn, secrete monocyte recruiting factors such as colony-stimulating factor-1, monocyte chemotactic protein-1 or

vascular endothelial growth factor (70,71). Under the influence of these factors, monocytes are recruited from the rich vasculature adjacent to the dental follicle into its coronal region (52,72). In the favorable environment of the dental follicle, these monocytes fuse and subsequently differentiate into hard tissue-resorbing cells, i.e., osteoclasts or odontoclasts once they come in contact with RANKL-expressing cells (Fig. 4). The question of course is whether there are available RANKL-expressing cells around to drive the differentiation of the monocytes to active osteoclasts and/or odontoclasts. Osteoblasts, for example, are practically absent from the alveolar bone overlying the crown of the developing tooth. Actually, 60% of this bone surface has been shown to be covered by osteoclasts (73). However, the dental follicle cells and the bone stromal cells adjacent to the dental follicle express RANKL (74,75). Interestingly, PTHrP has been found to increase the RANKL and to downregulate the OPG expression levels on the dental follicle cells (68). This indicates that the dental follicle cells can replace the osteoblasts in this tooth microenvironment and coordinate the differentiation and activation of monocytes to osteoclasts and/or odontoclasts. Furthermore, PTHrP has been shown to increase the RANKL and decrease the OPG expression by the PDL cells (76). The similar action of PTHrP on the dental follicle and PDL cells is not a surprise since the PDL is a derivative of the dental follicle. In fact, under non-resorbing conditions, PDL cells from deciduous teeth or permanent teeth, were found to express OPG and not RANKL (77-79). This preferential expression inhibits osteoclast formation and thus protects the root from resorption. On the contrary, human PDL cells around the roots of resorbing decidous teeth express enhanced levels of RANKL and decreased levels of OPG thereby supporting the ongoing root-degrading activity (80).

Recently, cementoblasts were reported to express RANKL and OPG and the levels of their expression to be modulated by PTHrP (81). Interestingly, under non-resorbing conditions cementoblasts seem to secrete large amounts of OPG and this may be one mechanism by which cementum is protected more than bone from resorption (82). PTHrP-treatment of cementoblasts resulted in reduction in OPG levels and this suggests that in the dental follicle environment, the critical OPG to RANK ratio is skewed in such a way that it supports instead of inhibiting osteoclastinogenesis (82). Sahara (52) observed an intimate cell-cell relationship between cementoblasts and preodontoclasts in rabbit teeth that were at the initial (78) stages of the root. This close relationship apparently triggers the cytodifferentiation of the preodontoclasts which leads to their attachment to the root surface, fusion to each other, and ultimately to formation of functionally active odontoclasts.

PTH and PTHrP bind to the same receptor, the PTHrPr expressed among other cells by osteoblasts and cementoblast. Why cementoblast respond differently than osteoblasts when exposed to PTH, as described earlier in this paper, but similarly when exposed to PTHrP is not clear but may be related to yet unknown features that are unique to cementoblasts in comparison to osteoblasts (83). To complicate things more, PTHrP seems to function as a cytokine with spatiotemporal control which means that it can exert both anabolic and catabolic effect, that is bone deposition as well as resorption based on its local concentration and duration of action (84). Whether this applies to dental tissue is unknown. Root resorption of the primary tooth occurs at the same time that dental hard tissues are deposited on the developing permanent successor. It will be interesting to investigate whether PTHrP is also involved in stimulating cementoblast function and if this is the case to explore the implicated fine control mechanisms.

While the primary roots are actively resorbed, the pulpal tissue remains in normal condition and, at least initially, it does not seem to participate in the resorption process. Odontoclasts are not usually found inside the pulp until root resorption is close to completion and not before the resorption level has reached approximately 1 mm below the cementoenamel junction (85-87). During this phase, chronic inflammatory cells, i.e. T and B lymphocytes, infiltrate the coronal pulp and the odontoblasts begin to degenerate (86,87). Bacterial incursion through the gingivo-dental junction seems also to occur at this advanced stage

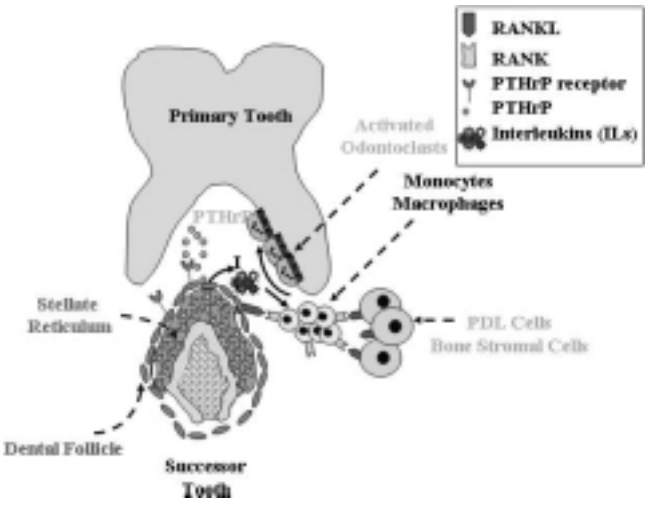

Fig. 4 Schematic representation of molecular and cellular events taking place at the initiation of the primary root resorption process.

of root resorption and may account for the accumulation of the inflammatory cells into the pulp (88). Following the degeneration of odontoblasts, odontoclast cells start resorbing the exposed dentin and the predentin from the inner surface (86). This resorption activity is first found at the pulpal floor of the crown but it then spreads along the pulpal walls towards the pulpal horns (86,89). In the resorbing environment and under the influence of locally produced cytokines, T cells can be activated and express RANKL. The activated T cells can then induce differentiation and activation of the preodontoclast cells (90,91). Alternatively, odontoblasts and pulp fibroblasts which have been shown to express the RANKL (40,92) can interact with the RANK receptor of the recruited mononuclear cells leading to the formation of active odontoclasts. The internal coronal resorption is not confined only to dentin. After the removal of dentin, odontoclasts remove large areas of enamel (93,94). In fact, in some instances the internal coronal resorption is so advanced that the crown of the primary tooth becomes so thin and fragile, like a shell that breaks and exfoliates in pieces (Fig. 5).

The gingival epithelium and the dento-gingival junction also participate in the resorption process of the primary teeth (95). As root resorption advances, the gingival epithelium and the dento-gingival junction migrate apically due to the inflammation at the dento-gingival junction (96). The migrating epithelium actually moves under the crown of the resorbing tooth isolating and therefore, protecting the developing permanent tooth germ from the inflammation in the remaining pulp tissue.

The physiologic resorption of primary teeth is not a continuous process and periods of active resorption are followed by intermittent periods of rest but also by periods of repair (97). During the repair periods, cementoblasts and/or osteoblasts found at the resorption front form calcific structures in limited areas of the root. Such cementum or bone deposition are most prominent in the delayed-shedding stage (87) and may account for partial reattachment of the tooth and explain why children feel their exfoliated teeth going through periods of looseness and fixation. However, the resorption process progresses faster than the repair and the primary teeth eventually shed (59). In addition to the external part of the root, calcific structures, dentin, or fibrous connective tissue (86) are also deposited in the pulp side during the root resorption process indicating similarities of this tooth resorption-repair cycle of events to the bone-remodeling sequence.

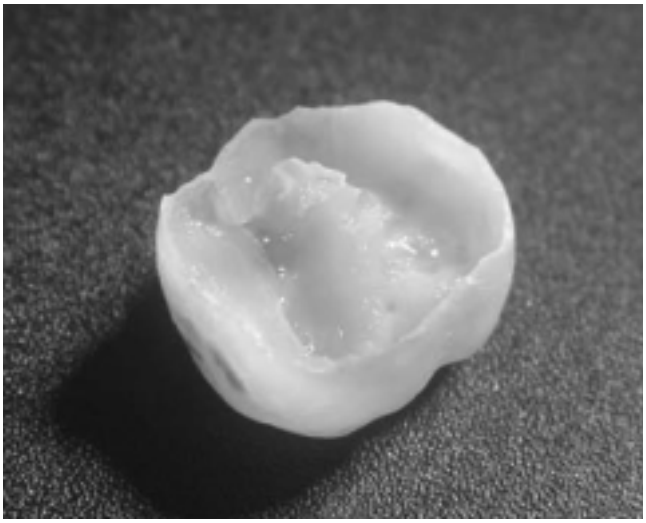

Fig. 5 Internal coronal resorption in an exfoliated primary tooth.

Primary root resorption without a permanent successor

All the events described above are initiated and coordinated by the dental follicle of the permanent tooth germ. However, even the roots of primary teeth that do not have a permanent successor eventually resorb. How this happens, and why it happens faster in some cases and much later in others is largely unknown.

Ordinarily, the root as mentioned earlier is protected from resorption by the presence of a narrow PDL cell layer which is mainly composed of collagen fibers, fibroblasts and cementoblasts (98). Degradation of PDL precedes root resorption and specifically removal of the collagen fibers of the PDL is considered a main step in the initiation of this process (99). Collagen digestion is mediated by matrix degrading enzymes such as the matrix metalloprotenases (MMPs) and their extracellular inhibitors, the tissue inhibitors of metalloproteinases (TIMPs) (100,101). MMPs and TIMPs are produced by osteoblasts (102), PDL cells (103,104) as well as by odontoclasts and osteoclasts (35) and seem to play an important role in normal and pathologic bone and connective tissue turn over, as well as in physiologic root resorption process.

Interestingly, differences have been reported between the PDL of the primary and permanent teeth and may explain, at least in part, the increased susceptibility to resorption seen of the roots of the primary compared to the permanent teeth. Indeed, PDL cells from primary teeth have been shown to produce more collagenase (MMP-9) than PDL cells from permanent teeth and to respond to pro-inflammatory cytokines, such as IL-1 and TNF-α by enhancing the expression of matrix metalloproteinases but not that of the tissue inhibitors of metalloproteinase (104). Since root resorption results when the balance between factors that stimulate (e.g., collagenase, matrix

metalloproteinases) and factors that inhibit (e.g., tissue inhibitors of Metalloproteinase) the resorptive process is skewed towards resorption, the previous findings may explain why disturbances of the PDL, i.e., dental trauma, causes root resorption more frequently in primary than in permanent teeth.

As the face grows and the muscles of the mastication enlarge, the forces that are applied on the deciduous teeth become heavier than the primary tooth periodontal ligament can withstand (59, 105). These constant and overwhelming forces ultimately weaken the primary tooth PDL and/or cause PDL necrosis, which in turn induces local production of cytokines. Under the influence of the locally produced cytokines, macrophages and monocytes are recruited. Furthermore, IL-β, prostaglandin E2 and TNF-α, or hormones such as dexamethasone, and 1,25 (OH)2D3) induced by the weakened PDL stimulate expression of RANKL by the PDL fibroblasts which can then trigger differentiation and activation of the recruited monocytes and macrophages to active odontoclasts (37,106). Once the PDL layer is damaged, the root protection is lost, and resorption starts.

Another etiology of mechanical trauma and thus initiation of the above cascade of events in the susceptible primary tooth-PDL, is abnormal occlusion conditions occurring during the mixed dentition phase, i.e., permanent teeth in one arch occluding with primary teeth in the other arch (53). When deciduous teeth were protected from such occlusion forces, in experimental animals, the root resorption of the protected teeth was significantly delayed (53). In these series of experiments, maxillary cuspids and incisors were deprived from their permanent successors and a splint-bridge extended from the left to the right primary cuspid was placed to protect the maxillary incisors from occlusion forces. Interestingly, histologic examination of the protected roots revealed thick layers of bone-like tissue repairing already started resorption defects. This indicates that in the alternating resorption-repair phases in the root resorption process, the splint-bridge enhanced the repair resulting in significant extension of the life span of the primary teeth.

The susceptibility of the PDL that surrounds the primary tooth compared to that of the permanent tooth may also offer an explanation for the selective resorption of the root of only the primary cuspid, and not of the neighbor permanent teeth, during eruption of the maxillary permanent cuspid. Simple contact of just the follicle of the developing permanent tooth with the root of its deciduous predecessor tooth is associated with physiologic primary root resorption (107). On the contrary, for pathologic root resorption of the adjacent permanent tooth roots, physical contact between the crown of an unerupted permanent tooth itself with these roots is required (107). In this end, two extracellularly matrix proteins associated with odontoclast adhesion and activation, osteopontin and bone sialoprotein, were found to be more heavily expressed in the PDL which surrounds resorbing primary teeth compared to that found in the permanent teeth (108). This spatial expression may promote selective binding of odontoclasts to and subsequently resorption of deciduous roots. Bone sialoprotein and osteopontin play important roles in the development and repair of cementum (109). Although it is not biologically impossible for these noncollagenous extracellular proteins to be involved in anabolic and catabolic processes the factors that direct their actions are unknown. Besides the susceptibility of primary tooth PDL to resorption, osteoclastic activity on bovine deciduous dentine was found to be greater than that on permanent dentine, indicating chemical differences in their composition and partly explaining the susceptibility of the deciduous tooth root to resorption compared to the permanent roots (110).

Clinically, we have no accurate predictors for the survival of the primary teeth without a successor (111,112). In some cases they are maintained well into adulthood whereas, in other cases they exfoliate much faster. It has been observed however, that if a primary molar remains in the dental arch with no significant root resorption up to 20 years of age it has then a favorable prognosis for long-term survival (113). A reliable prediction would be beneficial for orthodontic treatment planning of non-crowded individuals for whom extraction of primary teeth and closing of spaces may not be advisable. Understanding what controls and regulates the root resoption process may allow us one day to manipulate biology and thereby keep the primary dentition for as long as it is needed.

Besides the hard tissue resorption, exfoliation of the primary tooth involves removal of soft tissues such as the pulp and the periodontal ligament. There is not much information in the literature regarding the clearance of these tissues. Macrophages seems to be involved in the digestion of degenerated cells, whereas fibroblasts have been reported to remove the periodontal ligament (30). Ten Cate and Anderson (114) on the other hand, suggested that the collagen is broken down extracellularly by means of a collagenase the action of which is regulated by a collagenase inhibitor. They observed abruptness in the periodontal ligament loss and apoptotic (programmed) death of the PDL cells (114) and concluded that shedding of the primary teeth is a programmed event.

In conclusion, the molecular events of physiologic root resorption of the primary teeth show similarities with the

bone remodeling process. Now, we understand more than before on the operating mechanisms but we are far from having a complete picture. Besides the RANKL and OPG, other molecules such the transcription factors c-fos and NFkB are involved in osteoclast and possibly in odontoclast formation (70). As in many instances in biology, multiple factors with overlapping functions possibly participate in the orchestration of the events that ultimately guarantee resoprtion of primary tooth and eruption of the permanent successor. Delineating the series of events will certainly contribute to our understanding of both the physiologic and pathologic root resorption processes.

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