

Apexogenesis & Apexification

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Abstract

Apexogenesis and apexification constitute two alternatives possibilities to endodontic therapies. Apexogenesis is a phenomenon implicating a vital pulp. The thin dentin walls of the large canals place the tooth at greater risk for root fracture. Root lengthening is associated with tooth eruption. The treatment objective is to maximize the opportunity for apical development and closure. This is known as apexification that is occurring when the pulp is non-vital, infected or not. Apexification enhanced the continued root dentin formation inside the lumen, linked with apical closure and possibly with radicular dental pulp regeneration. A new treatment option of revascularization has recently been introduced after triple antibiotic therapy. It involves disinfecting the root canal system. After laceration of the periapex with a file until bleeding occurs, it provides a matrix of blood clot into which cells could grow. In parallel, it involves the sealing of the coronal access.

Keywords

Apexogenesis; Apexification; Odontoblasts.

Introduction

Apexogenesis (root elongation) and apexification

Apexogenesis

It takes in consideration the role that stem cells may have in the continued root development. This is related to the biological activity of Hertwig's epithelial root sheath (HERS). Stem cells have the capacity to self-replicate and differentiate into specialized tissue type. The odontoblasts and also at later stage, the pre-odontoblasts (Höhl cells) secrete dentin and are integral to the pulp – dentin complex. Primary dentin is formed until the full length of the root development is reached. This is followed by dentin formation that proceeds as secondary

dentinogenesis and the associated tooth eruption. The outer and inner enamel epithelia constitute the two layers of the Hertwig's sheath. This is a layer of cuboidal cells. They are also named Hertwig's epithelial root sheath (HERS). This epithelial bilayer is derived from the inner and outer enamel epithelia. They fuse below the level of the cervical margin of the crown. These layers are widely accepted as the main region responsible for root formation. The results indicated that some stratum intermedium cells are originated from the inner enamel epithelium, while others are derived from the inner enamel epithelium. The cells of the Hertwig's epithelial root sheath are linked by desmosomes and gap junctions, hemidesmosomes being adherent to the inner and outer basement membranes. Mesenchymal cells of the dental follicle become cementoblasts. Cells from the dental sac cross the dissociated HERS. The outer layer disintegrates. Between the dissociated epithelial outer layer, the cells invade the surface of root dentin (the so-called mantle dentin). In contrast, acellular cementum and cementogenesis take origin from the inner epithelial cells. Bone-like molecular characteristics of cementum, and alkaline-phosphatase are essential enzymes to mediate cementogenesis.

Apexogenesis continues at a slower rate throughout the lifetime of the individual. As the root and pulp develop, the dental papilla located apically to the developing pulp contributes to the root formation. HERS is very sensitive to trauma and once destroyed by trauma or by infection, the normal root development is stopped without further differentiation of odontoblasts.

Table 1: Root formation (apexogenesis)

1- Cells taking origin in the dental pulp papilla differentiate and migrate from the central part toward the lateral margins of the outer dental papilla. Undifferentiated mesenchymal cells of the dental papilla migrate and become differentiated odontoblasts, implicated in dentin formation.
2- Odontoblast contribute to form the dentin of the root, in close association with pulp cell proliferation.
3- From the cervical loop of the enamel organ, epithelial cells of the external and internal enamel epithelium proliferate and form an double layer of cells known as Hertwig's epithelial root sheath (HERS), linked by desmosomes and gap junctions, attached by hemi-desmosomes to the limiting basement membranes.
4- A fenestrated network is formed around the elongating root (moving toward the functioning occlusal plan during tooth eruption).
5- The epithelial root sheaths are known as HERS. They are located around the dental papilla, and along the dental follicle.
6- The inner epithelial sheath initiate dentinogenesis during the root formation. The root sheath progressively enclose the expanding dental papilla.
7- With root elongation, the sheath becomes fenestrated and the remnants constitute the epithelial rests of Malassez.
8- The dentin layer becomes gradually thicker, and the apical part, above the cervical loop, contribute to the lengthening of the tooth.

Formation of the apical zone

A series of dental tissues are formed in the apical zone. They include 1) the apical cell-rich zone, 2) the apical papilla mesenchyme and 3) the radicular dental pulp. Apexogenesis involves both lengthening (associated with eruption of the teeth), and the thickening of the dentin layer, to the detriment of the lumen (pulp space). Apexogenesis result from the contribution of cells issue from the dental papilla. They become after differentiation, odontoblasts involve in the production of dentin, whereas differentiation of cells from the cervical loop contribute to the lengthening of the tooth.

Apexogenesis is a natural physiologic process of root development. The term is used to describe the endodontic procedure of preservation of pulp vitality. It has also been suggested that maturogenesis is a more appropriate term than apexification, because not only the apex but the entire root is allowed to mature [1].

Calcium hydroxide induced the deposition of calcified material. It became the standard treatment protocol for the therapy of non-vital immature tooth. Many other biomaterials have been used to induce apexification, but none has truly replaced calcium hydroxide. Calcium hydroxyde–induced apexification might require 6-24 months for barrier formation. The barrier formed is often porous and not continuous. Further development of the root does not takes place. Intra-canal calcium hydroxide dressing can also make the tooth brittle because of its hygroscopic and has proteolytic properties. The rationale of revascularization is that if a sterile tissue matrix is provided in which new cells can grow, pulp vitality can be re-established. It provide a matrix into which the cells from the periapical tissues could grow and re-establish pulp vascularity, slowly replacing the necrotic tissue.

It is possible that a few vital pulp cells remain alive at the apical end of the root canal. These cells may proliferate into the newly formed matrix and differentiate into odontoblasts. The newly formed odontoblasts can lay down atubular dentin at the apical end, causing apexogenesis, as well as on lateral aspects of dentinal walls of the root canal, reinforcing and strengthening the root.

The other possible mechanisms implicated in apexogenesis are the followings:

- The development of multipotent dental pulp stem cells. They differentiate into odontoblasts and deposit tertiary or atubular dentin.
- Cementum and Sharpey's fibers (of the alveolo-dental ligament) are at the origin of the newly formed tissues.
- Stem cells from the apical papilla or the bone marrow can form bone or dentin *in vivo*.
- The blood clot itself is a reservoir of growth factors. The advantage is that achieving continued root lengthening and strengthening, the result is a reinforcement of lateral dentinal walls with deposition of new dentin/hard tissue.

Complete root development requires a viable pulp containing cells that can differentiate into dentin-producing odontoblasts. The dental pulp is complex with a variety of cells, nerves, and

blood vessels. It is important to keep in mind the required prerequisites, including :

- cells that are capable of differentiating into pulp cells,
- synthesizing a signal that is required for the cell differentiation,
- inside an appropriate scaffold, suitable for guiding regeneration of the tissues [2].

The procedure that induces apexogenesis is undertaken to preserve the remaining vital tissue and allow completion of root formation and apical maturation. Apexification is related to the immature teeth. Apexification is then performed to treat immature teeth with non-vital pulp by inducing a calcified barrier at the open apex [3].

Apexogenesis is a natural physiologic process of root development. However, the term is used more commonly to describe the endodontic procedure of preservation of pulp vitality in a traumatized tooth with pulp involvement, so that the affected tooth could develop its full growth potential.

It was earlier unthinkable that the tissue in the periapical region of a nonvital infected tooth could regenerate.

1. Therefore, a classic treatment option for such teeth was to perform surgical endodontic procedure to seal the wide-open, often blunderbuss apical opening. It is possible that a few vital pulp cells remain at the apical end of the root canal. These cells might proliferate into the newly formed matrix and differentiate into odontoblasts under the organizing influence of cells of Hertwig's epithelial root sheath, which are quite resistant to destruction, even in presence of inflammation processes.
2. Another mechanism may be attributed to the stem cells located in the periodontal ligament, which can proliferate, grow into the apical end and within the root. They may deposit hard tissue both at the apical end and on the lateral root walls.
3. A third possibility could be attributed to the stem cells from the apical papilla or the bone marrow.
4. Instrumentation beyond the confine of the root canal are susceptible to induce bleeding. This may also transplant mesenchymal stem cells from the bone into the canal lumen. These cells have extensive proliferating capacity. The blood clot itself, being a rich source of growth factors, could play an important role in regeneration. These include platelet-derived growth factor, vascular endothelial growth factor (VEGF), platelet-derived epithelial growth factor, and other tissue growth factors which could stimulate differentiation, growth, and maturation of fibroblasts, odontoblasts, and cementoblasts [1].

Apexification

Pulp necrosis arrest further root development of an immature permanent tooth. To induce the formation of an apical mineralized tissue barrier, the method used specifically is named

apexification because of its high pH, calcium hydroxide not only weakens the root but may also inhibit new tissue formation within the canal. The possibility of vital tissue regeneration in the root canal space with a continuous increase in root thickness and length has been demonstrated for immature teeth.

There are three major components in tissue engineering which are implicated in apexification:

- Cells that are capable of hard tissue formation (differentiated odontoblasts),
- Scaffolds that can support cell growth and differentiation,
- Molecules that provide signalling and intracanal dentin formation.

Dental pulp stem cells are able to differentiate into functional odontoblast-like cells with an active mineralization potential. They may be used in dental tissue engineering via stem cell – based approaches. This is due to an increased alkaline phosphatase activity, dentine sialoprotein expression and to the formation of mineralized nodules. Platelet-rich plasma is a natural reservoir of various growth factors that can be collected, unlike the chemically processed molecules or recombinant proteins that may cause undesired side effects and expose the tissue to unnecessary risks. The use of platelet-rich plasma (PRP) in combination of DPCs may be beneficial for new tissue formation and for apical closure [4].

The protocol for pulp revascularization / revitalization begins with root canal irrigation with minimal instrumentation and then continues with disinfection with an antibiotic mixture. The most commonly reported dressing is a triple antibiotic paste (TAP), which consists of ciprofloxacin, metronidazole, and minocycline. It is presumed that the blood clot serves as a scaffold in which stem cells from the apical papilla (SCAP) populate the clot. In addition, growth factors released from platelets and the dentinal walls serve as a promoter for stem cell division and differentiation processes.

Immunohistochemistry and gene profile analysis have identified perivascular cells by using markers, such as alkaline phosphatase and α -smooth muscle actin, in differing proportions on STRO-1 positive cells. BMPs appear to be the key regulators of apexification.

The cell line are grown and expanded before being implanted into the root canal, resulting in protracted clinical treatment times. The implanted cells then need to reliably adhere to the disinfected root canal walls. Lastly, the implanted tissue lacks a crucial vascular supply, and it is technically difficult to replant the three-dimensional regenerated pulp without damaging the cells. When an open root apex exists, a similar scaffold design adjacent to a vascular supply may assist apexification by thickening and closing the apical portion of the root with hard tissue.

No published reports are involving the use of genetically manipulated cells for apexogenesis or apexification procedures. Novel genes and finding appropriate vectors are mandatory to control cell-specific safe delivery. The phenotype repopulating the open root apex has still to

be selected by environmental factors [5].

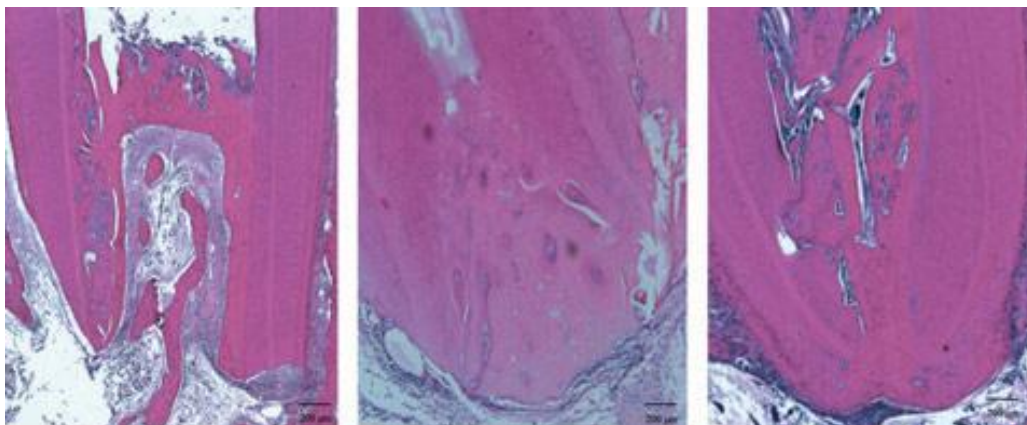
The apical part of the root includes three compartments: an apical cell-rich zone (where apical stem cells are mostly located and constitute a reservoir of undifferentiated pulp cells progenitors SCAP cells [6]. Cells are located in the apical papilla mesenchyme, and in the radicular dental pulp.

The goals of apexogenesis are the followings:

- Allowing a continued development of root length for a more favorable crown-to-root ratio.
- Allowing the remaining odontoblasts to lay down dentin, producing a thicker root and decreasing the risks of root fracture.
- Promoting root end closure, creating a natural apical constriction for root canal filling.
- Generating a dentinal bridge at the site of the pulpotomy. It suggests that the pulp has maintained its vitality.

II- Apexification

Figure 1 : Different apical closure types in group dental pulp cells + platelet rich plasma. Some bone-like tissue form a bridge and merge with cementum-like tissue to close the apex. Reprinted from [4,7].



Apexification is a method of inducing a calcified apical barrier or continued apical development of an incompletely formed root in which the pulp is necrotic [8]. The developing consensus approach to accomplish apexification is to instrument root canals, to remove the necrotic tissue, and to place MTA in the root canal apex, with the remainder of the canal obturated with gutta-percha.

In the absence of a vital pulp, dentin deposition is arrested. When an immature tooth is affected by caries or trauma, the pulp requires proper management according to the degree of inflammation and keeping some vitality.

Artificial apical barriers are formed after implantation of a variety of materials. Apexification was demonstrated in a complete layer of cementum when using MTA as a root-end filling inducing apical hard tissue formation in immature roots.

An alternative treatment of the immature permanent tooth is apexification procedures. The

classic apexification method involves long term application of Ca(OH)_2 . A more recent method of apexification involves the use of MTA as an apical barrier followed by placing either a root filling or obturating material. However, it is important to note that apexification by either Ca(OH)_2 or MTA completely prevents any further root development in terms of increased radiographic measures of either root length or width. The immature tooth treated by apexification procedures demonstrates healing of apical periodontitis, but does not achieve the goals of continued root development or restoration of functional pulp tissue [9].

Apexification is defined as ‘a method to induce a calcified barrier in a root with an open apex or the continued apical development of an incomplete root in teeth with necrotic pulp’.

Success rates for calcium hydroxide apexification are high. Apexification is a method of inducing apical closure through the formation of mineralized tissue in the apical pulp region of a non-vital tooth with an incompletely formed root. It is composed of osteocementum, osteodentin or bone, or by some combination of the three [10].

Table 2: Apexification or apical closure induction [10].

1-	Ca(OH)_2 induces apical closure. The pH is favorable. It associates the calcium ions release, the hydroxyl ion and the antibacteria effects.
2-	Laceration of the periapex with a file is useful until bleeding occurs.
3-	The blood clot itself is a rich source of growth factors, that could play an important role in regeneration. These factors include platelet-derived growth factor, vascular endothelial growth factor (VEGF), platelet-derived epithelial growth factor. These tissue growth factors may stimulate differentiation, growth, and maturation of fibroblasts, odontoblasts, and cementoblasts.
4-	Some remnants of the root sheath (including the dental sac around the apex) remain intact and form cementoblasts.
5-	Remnants of the dental pulp encompass stem cells from the apical papilla or the bone marrow. Instrumentation beyond the confines of the root canal induce bleeding and can also transplant mesenchymal stem cells from the bone into the canal lumen.
6-	Stimulation of undifferentiated mesenchymal cells initiate cementogenesis at the apex.
7-	Tricalcium phosphate acts as a matrix for the invasion of blastic cells, allows cellular proliferation and differentiation. It favors deposition of hard tissues. Resorbable ceramic is replaced by bone.
8-	Stem cells located in the periodontal ligament, can proliferate, grow into the apical end and within the root canal. The deposition of hard tissue occurs both at the apical end and on the lateral root walls.

Apexification may be induced by Ca(OH)_2 or MTA. Revascularization of necrotic pulp has been considered possible after traumatic injury to an immature tooth. A unique set of circumstances exist that favor revascularization. The potential for revascularization appears to directly depends on the race between bacterial infection of the necrotic pulp, and revascularization of the canal space using the ischemic pulp as a matrix [11]. Revascularization involves desinfection the root canal, providing a blood clot into which cells could grow and seal the coronal access. The canals were sampled before and after irrigation with 1.25% NaOCL and after dressing with a triple antibiotic paste, consisting of metronidazole, ciprofloxacin, and minocycline. The access cavity was sealed with a glass ionomer cement (GIC). An increased tooth length was observed. Revascularization

procedures may be conducted on immature non-vital, infected permanent teeth [1]. An endodontic regeneration study on non-human primates by cleaning and shaping root canals. Then laceration of the periapical tissues cause bleeding into the root canals. If vital and not irreversibly inflamed, maintenance of vitality will allow natural continued root development. Maintenance of pulp vitality by using apexogenesis allow continued root development along the entire root length. Depending on the extent of inflammation, pulp capping, shallow or conventional pulpotomy may be indicated. Traditionally, the approach has been to use calcium hydroxide (CH) to induce apexification after disinfection of the root canals.

Metronidazole is a nitroimidazole compound that exhibits a broad spectrum of activity against protozoa and anaerobic bacteria. It has been used both systemically and topically in the treatment of periodontal disease. Metronidazole readily permeates bacterial cell membranes. It binds to the DNA, disrupting its helical structure, and leads to rapid cell death. Completion of endodontic therapy was typically delayed until completion of root-end closure through apexification. Tetracyclines, which include doxycycline and minocycline. Tetracyclines are effective against most spirochetes, and many anaerobic and facultative bacteria. The tetracyclines gain access to bacterial cells. They act by inhibiting protein synthesis on the surfaces of ribosomes. Minocycline is a semi-synthetic derivative of tetracycline.

It is available in many topical forms ranging from gel mixtures to sustained release microspheres. Ciprofloxacin, a synthetic fluoroquinolone, has a bactericidal mode of action. Ciprofloxacin has very potent activity against gram-negative pathogens but displays limited activity against gram-positive bacteria. Most anaerobic bacteria are resistant to ciprofloxacin. Side effects of ciprofloxacin have been reported. It was found that the drug is clinically safe when applied in low doses. When applied as an intra-canal medicament in low doses, adverse systemic side effects should be minimized.

Materials used for the repair of furcal perforations.

Hydroxylapatite-based material and calcium sulfate were used to repair furcal perforations. The success rate was found to be 67% for calcium sulfate, 62% for HAP and 59% for glass ionomers [12]. Experimental calcium phosphate cement (TCP) and MTA were used as repair materials for furcation perforation. MTA exhibited significantly better results than TCP. MTA is a suitable material to close the communication between the pulp chamber and the underlying periodontal tissues [13].

Glass ionomer cement (Chelon Silver) was compared with amalgam [14]. The coronal orifices of the root canals were sealed with amalgam and varnish. No significant difference was found between the mean leakage of the intact pulp chamber floors of the two groups. It is concluded that Chelon Silver was an adequate sealer for furcation perforations. MTA is an alternative root canal obturation material for the treatment of stripping perforation in a C-shaped root canal and for the repair of pulp floor perforation.

MTA materials appear not only to demonstrate sustainable biocompatible behavior but also exhibits acceptable *in vivo* biologic performance when used for root-end fillings, perforation repairs, pulp-capping and pulpotomy, and apexification treatment [15]. It may be concluded that MTA is the most suitable material, more than amalgam for perforation repair, especially when it is used immediately after perforation.

Conclusion

In addition to direct or indirect capping stimulating reparative dentin formation, apexogenesis is the most usual tool for the treatment of endodontic lesions, namely when the pulp is still alive. Apexification constitute the most viable endodontic method for a dental pulp either necrotic, infected or not. After disinfection using a triple-antibiotic therapy, the radicular pulp may regenerate, become functional and restore most of its activities.

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