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The rôle of immunological reactions in apical cyst formation and the fate of epithelial cells after root canal therapy: a theory

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ABSTRACT – Activation of the epithelial cell rests of Malassez by various means, results in proliferation of these cells and formation of apical periodontal cysts. Several theories for the genesis of apical periodontal cysts have been suggested which are not satisfactory. Available evidence indicates that development and destruction of these lesions are mediated by immunological reactions.

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After teeth form in the jaws, some remnants of Hertwig's epithelial root sheath persist in the periodontal ligament. These epithelial remnants known as cell rests of Malassez were first described by MALASSEZ in 1885[23]. Numerous physiological processes and pathologic conditions have been associated with them, including cementogenesis, dentin formation, prevention of ankylosis, cementum and alveolar bone resorption, formation of periodontal pocket, and formation of apical periodontal cysts[1,4,5,17a,19,21,24,25,32a,32b,38,39,56,58]. Epithelial cell rests are present in most dental granulomas and in all periapical cysts. Yet their behavior in these diseases is not yet well understood. This paper reviews the characteristics of epithelial cell rests of Malassez, and present theories concerning their rôle in apical periodontal cyst formation. It also discusses the possibility that immunological reactions help to initiate cavities in the proliferating epithelium of chronic periapical lesions, and their rôle in the destruction of epithelium after root canal therapy.

Characteristics of epithelial rests

In routine histologic examination of the human periodontal ligament, epithelial cell rests can be identified in the cervical, middle, and apical thirds of the ligament[39,55b,58] (Fig. 1). Each cell has a large nucleus and a narrow peripheral rim of cytoplasm. The ultrastructural morphology of these cells and histochemical evidence suggest that they are quiescent[51b,55b]. This evidence includes the high nucleus-cytoplasm ration, low ribonucleic acid content, the presence of glycogen, the absence of neutral lipids,

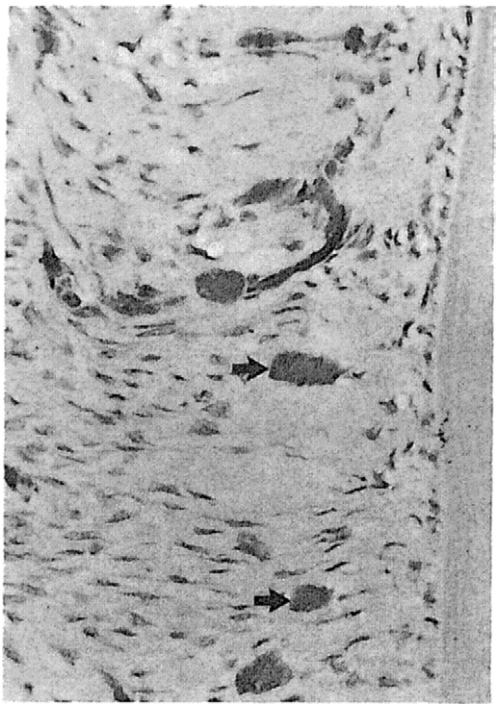

Fig. 1. Photomicrograph of human periodontal ligament containing epithelial cell rests of Malassez (arrows). (H & E, original magnification ×360).

and minimal amounts of rough endoplasmic reticulum.

The epithelial cell rests can have pathologic significance if they are capable of proliferation, and it appears that they are. GRUPE *et al.*[10] found that activated cell rests exhibit significantly increased cytoplasm, little succinic dehydrogenase activity, absence of glycogen, and accumulation of neutral lipid. Electron microscopic examination of the activated cell rests *in vitro* confirmed these characteristics[29].

To determine whether proliferated epithelium in the apical granuloma structurally resembles activated epithelium *in vitro*, TEN CATE[51b] obtained such epithelium from periapical tissues of monkey incisors which were exposed and left open for 16 weeks. Electron microscopy examination revealed that the epithelial cells did indeed resemble activated *in vitro* epithelium. They had extensive cytoplasm with a great deal of rough endoplasmic reticulum, no glycogen, and few lipid droplets.

The etiologic factor(s) necessary to activate epithelial cell rests are undetermined. GRUPE *et al.*[10] have tentatively suggested that a system with low O_2 and high CO_2 tension can be an initiating factor in epithelial proliferation.

The apical periodontal cyst

The apical periodontal cyst, which is the most common of oral cysts, is a sequela of the periapical granuloma originating from an inflammatory response to the content of the root canal system. The proliferation of epithelium within the periapical granuloma is believed to be necessary for apical periodontal cyst formation. Microscopically, the apical periodontal cyst consists of a pathologic cavity usually lined by a relatively thick, stratified squamous epithelium. The connective tissue immediately adjacent to the epithelium is invariably infiltrated by lymphocytes, plasma cells, and polymorphonuclear (PMN) leukocytes. The lumen of the cyst contains a fluid which stains pale pink with hematoxilin eosin stains.

The pathogenesis of the apical periodontal cyst is not fully understood, and no completely satisfactory theories have been suggested. The two prevailing theories are the breakdown theory and abscess cavity theory.

The "breakdown" theory

The "breakdown" theory postulates that after the epithelial cell rests are provoked into cell multiplication, a mass or ball of cells is produced which derives its nutrition from the sorrounding connective tissue. Supposedly, continuous growth of the cell ball removes central cells from their nutrition; consequently, the innermost cells undergo liquefactive degeneration, and a microscopic cyst is formed[11,16,44,48,51b]. There are some problems with

this theory. There is no evidence that lack of blood supply accounts for the death of central cells in an apical periodontal cyst[43]. In fact, the vessels of microcirculation permeate every tissue of the body, and cells are never more than 127 μ from a vessel[60]. Moreover, the proliferating epithelium of periapical granulomas is usually invaginated by the surrounding connective tissue[11] (Fig. 2).

The "abscess cavity" theory

According to another school of thought, a cyst is formed when an abscess cavity is formed in connective tissue[25,50]. It is thought that these epithelial cells, like other epithelial cells, proliferate and line the pre-existant cavity, because of their inherent tendency to cover exposed connective tissue surfaces. Some of the difficulties with this theory are: (1) TOLLER and others[7,17b,53a,54] have observed a comparatively high rate of discontinuities in the linings of apical periodontal and dentigerous cysts; (2) the epithelial cell rests of Malassez appear to differ from the epithelial cells in other parts of the body, according to studies by THOMPSON and others[22,34,52]. These investigators buried autogenous dermis grafts subcutaneously and examined the cyst formation. Microcysts were recognized after only a few days and then they gradually disappeared and no clinically significant cyst developed.

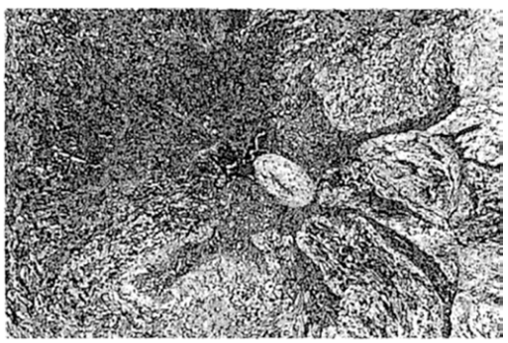

Fig. 2. Photomicrograph of a human periapical biopsy showing invagination of proliferating epithelium by the connective tissue. (H & E, original magnification ×90).

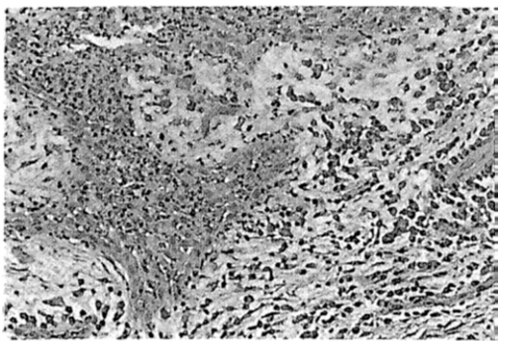

Fig. 3. Photomicrograph of a human periapical cyst. The epithelium is infiltrated by numerous PMN leukocytes. The infiltrate of surrounding connective tissue is mainly monocytic cell in nature. (H & E, original magnification ×360).

Available evidence indicates that the development of cavities in proliferating epithelium and the final destruction of these cells are mediated by immunological reactions. This evidence includes the presence of PMN leukocytes, lymphocytes, and plasma cells in proliferating epithelium of periapical lesions, presence of immunoglobulins in cyst fluid, and discontinuity in the epithelial linings of most apical cysts.

Presence of immunocompetent cells

Histopathological examination of tissues from apical periodontitis and apical periodontal cysts often reveals the presence of PMN leukocytes in the epithelial strands of the lesions (Fig. 3). This is not accidental. HILL[11] showed that slight proliferation of the epithelial cells in dental granulomas is accompanied by an increase in number of PMN leukocytes in or surrounding the epithelium. As epithelial islands of greater sizes were found, the concentration of PMN leukocytes infiltrated became greater within the epithelium than in the surrounding tissues. JAMES & COUNSELL[14] observe that PMN leukocytes are usually found

in chronic periapical lesions in considerable numbers between the epithelial cells, even when the adjacent connective tissue shows no sign of acute inflammation. The strands of proliferated epithelial cells encircle the inflammatory cells, according to STONES[49] or, put another way, the proliferating epithelial bands are infiltrated by inflammatory cells. In a histological examination of 200 developing and established cysts, SHEAR[45a] found that the proliferating epithelium was frequently associated with an infiltration of PMN leukocytes. He suggests that the stimulus which invoked the inflammation might be within the epithelium. In another study, SHEAR[45b] examined the influence of the inflammatory process on periapical cysts. He found that there was a greater incidence of PMN leukocyte infiltration of the epithelial linings than of the connective tissue walls, and that inflammation of the epithelial linings was a necessary element in spongiosis, degeneration, and eventual ulceration of the epithelium.

In addition to PMN leukocyte infiltration of the epithelium, other immunocompetent cells such as plasma cells and lymphocytes can also be seen in proliferating epithelium of apical periodontal cysts (Fig. 4).

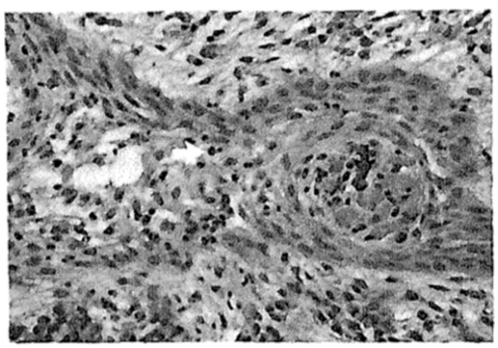

Fig. 4. Photomicrograph of a human periapical granuloma. The proliferating epithelium is infiltrated both by PMN leukocytes (white arrow) and mononuclear cells such as plasma cells and lymphocytes (black arrow). Disintegration of the central part of the epithelium can be seen on the left side of the photomicrograph. (H & E, original magnification ×360).

In an examination of clinically uninfected cysts, TOLLER & HOLBOROW[53b] showed the presence of lymphocytes and plasma cells in a subepithelial layer of these lesions. In many of the sections examined, plasma cells were also seen within the epithelial cell layers.

This histologic examination showed that apparently, the proliferating epithelium is initially infiltrated mostly by PMN leukocytes, and in the later stages of disease, these cells diminish in number, and lymphocytes and plasma cells become the predominant inflammatory cells.

Presence of immunoglobulins in cyst fluids

TOLLER & HOLBOROW[53b] demonstrated the presence of IgG, IgM and IgA classes of immunoglobulins within the cyst walls. Immunofluorescent staining of cyst walls showed that IgA plasma cells were prepondererant, although IgG and IgM cells were also present. In some cases these plasma cells were seen penetrating the epithelial lining of the cyst and entering the cyst cavity.

Electrophoretic analysis of odontogenic cyst fluids has revealed that the level of gamma globulins is often higher in cyst cavities than in the patient's own serum[53c]. Most of the fluid samples showing raised levels of gamma globulins were from cysts whose walls harbored high plasma cell and lymphocyte populations. MORSE *et al.*[27b] investigated the presence of immunoglobulin-producing cells in periapical lesions and found that serum antibodies were produced in these lesions. They suggested that periapical cysts were more active in the production of antibodies than were periapical granulomas.

Discontinuities in epithelial lining

A final piece of evidence suggesting that cavity formation in the epithelium of periapical

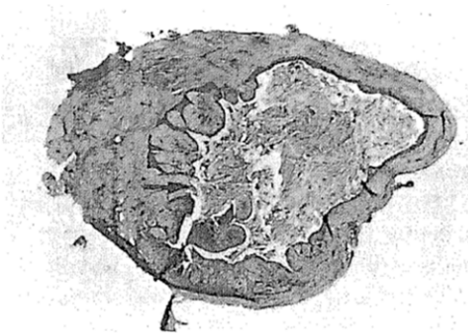

Fig. 5. Photomicrograph of a human periapical cyst showing a central cavity surrounded by epithelium and a connective tissue capsule. Many areas of discontinuity can be seen in the epithelium which encircles the central cavity (black arrows). (H & E, original magnification × 18).

lesions is mediated by immunological reactions is the discontinuity of the epithelial lining of most cysts (Fig. 5). TOLLER[53a] found that 1/3 of uninfected apical and residual cysts showed discontinuities of the epithelial linings.

The rate of epithelial discontinuity was increased to 75% when he studied 33 cysts with keratinizing epithelial walls. This discontinuity of the cyst walls can result from destructive actions of immunological reactions, if proliferating epithelium has antigenic properties.

Antigenic reaction

(1) There are 4 different ways that activated epithelial cell rests can acquire antigenic properties. Pointing out one way, ODLAND & ROSS[30], GIBBONS[6], and others[36a,36b,46] have recognized the capacity of migrating epithelial cells in man, mammals, and amphibians to phagocytose and digest debris and particles in the path of their migration. The proliferating epithelial cell rests can ingest the antigenic materials which continuously egress from a diseased root canal system into the periapical tissues. The ingested antigenic material(s) and carrier (epithelial cell) can be recognized as an antigenic unit and can thus elicit immunologic reactions.

(2) Antigenicity could also occur through an antigenic cross reactivity between the infective and non-infective root canal antigens on the one hand and the proliferating epithelial cell rests on the other. Thus the epithelial cells stimulate antibody production and cell-mediated immune responses. This phenomenon has been suggested as a possible mechanism for recurrent aphthous ulceration and Behcet's syndrome[19a-d].

(3) According to a third scenario, immunological responses within the proliferating epithelium can be directed against the metabolic products of proliferating epithelial cells during an inflammatory response and not necessarily against cells themselves. WESTALL[59] has suggested that undeaminated host proteins released through a disease state can invoke an autoimmune response. In other words, if the body has not encountered released metabolites in that form, the material might be recognized as non-self.

(4) Finally, apical cysts are derived from cell rests which have completed their normal tooth-forming function early in life. The aging process can cause a random accumulation of somatic genetic changes in cells[3]. As this phenomenon occurs in epithelial cell rests, a slight histo-incompatibility may elicit immunological reactions (auto-immunity). Whatever might be the mechanism of epithelial cell antigenecity, the resulting immunological reactions may destroy the proliferating epithelial cells and thus facilitate the formation of an apical periodontal cyst.

Cytotoxicity

Cytotoxicity through immunological reactions is either mediated by antibodies and complement or by the T or K lymphocytes[40].

In cytotoxic reactions mediated by antibodies and the complement, antibodies react directly with antigens tightly bound to cells. The antigens may be natural components of the cell, or they may be antigens that have become intimately associated with the tissue cells. This

reaction is complement-dependent. When two adjacent IgG molecules or one IgM molecule becomes bound to a corresponding antigen (in this case the epithelial cell), the complement components become activated. Activation of the complement system results in the formation of small holes in the cell membrane.

In T cell cytotoxicity reactions, the sensitized T lymphocytes interact with the target cells. This reaction does not require the presence of humoral antibody or complement. Close contact between T lymphocytes and the target cells is required for cell lysis to occur. In addition to direct contact which causes cell death, T lymphocytes can be activated by some antigens and can produce substances called lymphokines. One of the lymphokines, an enzyme known as lymphotoxin, is released by activated lymphocytes. *In vitro* cytotoxicity studies have shown that lymphotoxin is a soluble toxic factor which can destroy both aggressor and target cells[8,42].

In addition to T cell cytotoxicity, PERLMANN[35] has shown the presence of an antibody-dependent cell-mediated cytotoxicity. This reaction is carried out by cells other than T cell lymphocytes. These killer cells are known as K cells. K cells have Fc receptor sites for immunoglobulins but are immunoglobulin-negative cells themselves. K cell cytotoxicity requires IgG immunoglobulin and does not need complement components. In K cell cytotoxicity, close contact is required between the K cells and the target cells.

Other mechanisms leading to target cell death have also been detected[5]. Antibodies to surface antigens can induce cytotoxicity of lymphoid cells leading to destruction of the antigenic target cells. This is a non-phagocytic reaction which does not require complement. Therefore, if the stimulating antigen is a surface component of another cell, sensitized lymphocytes can attack the cell by direct binding and can selectively destroy the target cell.

According to another mechanism, the lymphocytes may become cytotoxic to target cells bearing histocompatibility antigen against which the T cells have been previously sensitized.

Since all the necessary elements (e.g. complement, PMN's, plasma cells, immunoglobulins, and lymphocytes) which are required for cytolytic, antigen-antibody complex, and cell mediated reactions have been found within and around the proliferating epithelium in periapical granulomas and apical periodontal cysts, it is conceivable that activated epithelial cell rests of Malassez are destroyed by immunological reactions. These reactions attract immunocompetent cells into the proliferating epithelium and consequently destroy them.

Fate of epithelium after root canal therapy

Treating an apical periodontal cyst with nonsurgical endodontic therapy is still controversial, especially since radiographic, cytologic, and immunoelectrophoresis examinations of periapical lesions have been unreliable for differentiating between apical periodontal cysts and periapical granulomas[4,12,27a,27c]. Investigators generally report that more than 20% of their patients have apical periodontal cysts[1,2,18a,18b,20,28,33,37,41,47a,47b,57].

Endodontists commonly claim that nonsurgical endodontic therapy is successful in more than 90% of cases[9,13]. If more than 20% of periapical lesions are cysts, it seems logical that many cysts heal without surgical methods, and there is no need for the clinician to differentiate between apical cysts and periapical granulomas. If immunologic reactions do participate in the destruction of the proliferating epithelial cells in periapical granulomas and apical periodontal cysts, the high success rate claimed by endodontists should be naturally expected. If periapical lesions are inflammatory responses to the antigenic content of the root canal system, and the epithelial proliferation is a response to these irritating materials, then when the source of the irritation is removed, the

immune system gradually destroys and removes the proliferated epithelial cells. Therefore, if antigens are removed, the epithelium gradually resolves. OEHLERS[31] studied 168 residual lesions which were deliberately left *in situ* after the extraction of the related teeth. He found that more than 90% of these lesions, including cysts, were eliminated by the body once the causative agents were removed. If the irritation continues, the immunological responses may not keep up with the old and newly formed proliferating epithelium. In contrast, if immunological responses were fast and severe enough to deal with proliferating epithelium in periapical lesions, little or no epithelium would be present.

In a histologic examination of periapical residual cysts, MOLYNEUX[26] found that when inflammation was intense, the epithelium was dificient or absent. He also noted that the median age of patients with inflammatory cysts was 33 years, while the age of patients with non-inflammatory cysts averaged 63 years. As an individual age, it is generally believed that overall efficiency of the immune system is weakened. This phenomenon, together with individual susceptibility to dental cyst formation, may explain why only some lesions of chronic apical periodontitis become apical cysts when epithelium is present in most of these lesions.

Conclusion

Much evidence has accumulated which supports the view that a key element in the development and demise of apical cysts is the immune responses. Investigations are needed to delineate the antigenic properties of proliferating epithelial cell rests as well as the possible antigens which may give such lively qualities to these otherwise quiescent cells. This new view of apical cysts may not fundamentally change the way these conditions are treated, but it should allow the practicing dentist to proceed with more understanding and precision and therefore with more confidence.

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