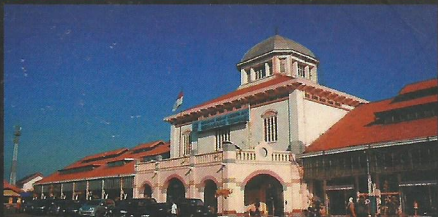
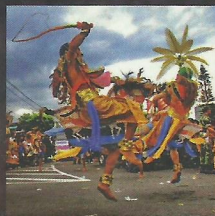
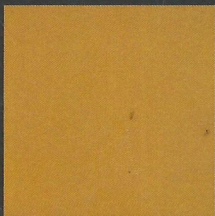
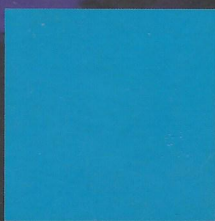




"New Horizons in Indonesian Oral Health Care"

PROCEEDINGS

of The 7th FDI – INDONESIAN DENTAL
ASSOCIATION (IDA) JOINT MEETING




November 12th-13th, 2011
Gumaya Tower Hotel, Semarang - Indonesia



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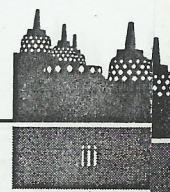
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TABLE OF CONTENT

| NO | TITLE | AUTHOR | PAGE |
|-----|---|---|------|
| 1. | Clinical Requirement For Oral Medicine That Reached By The Students With Competence Based Curriculum (cbc) | Nafi'ah , Setyaningtyas D., Isidora KS., Darmawan IGNP | 1 |
| 2. | The Transtheoretical Model: A Basis For Changing Dental Behaviour To Improve Oral Health | Dini Setyowati | 6 |
| 3. | The Impact Of Tooth Puppet Theater Toward The Mprovement Of Children Dental And Oral Health Knowledge In Tk Hjriyah Ili Palembang | Bertha Aulia, Arizka Suraida | 11 |
| 4. | A Hypothesis In Relationship Between Oral Health And Whole Health On Molecular Level | Adi Prayitno | 15 |
| 5. | Role Of Etyl Para Methoxi Cinamat (kaempferia Galanga L. Extract) On Platelet Agregation In Rats (sprague-dawley Strain) | Pudji Astuti | 20 |
| 6. | Antifungal Test Of Piper Betle Linn Leaf 35% To Candida Albicans | Dewi Puspitasari, Maharani Laillyza Apriasari | 26 |
| 7. | Differences of ability various Kinds Of tea can Cause Tooth Discolorisation | Ratnawati Hendari, Lanny Sunarjo, Irma HY Siregar | 33 |
| 8. | Neem (azadirachta Indica) : One Of Solution To Overcome Allergic Reaction In Oral | I Dewa Ayu Ratna Dewanti | 37 |
| 9. | Topical Application Of 10% Cashew Fruit (<i>anacardium Occidentale</i> L) Extract Decreased Salivary Ph And Volume In Woman With Recurrent Aphthous Stomatitis (ras) | Juni Handajani; Novitasari Eko Werdiningsih; Juwita Raditya Ningsih | 43 |
| 10. | The Influence Of Bleaching Agent On Cigarette Smoke On The Changes Of Thickness Of Epithelial Tongue | Ivan Arie Wahyudi; Indwiani Astuti; Siti Sunarintyas | 48 |
| 11. | Trial Of Simple Natrium Fluoride Patchon Fluoride Stability Based On Storage Time And Types Of Patch Packaging | Diyah Fatmasari | 54 |
| 12. | Comparison Of Effectiveness Of Antibacterial And Antifungal Of Black Cumin Oil On Growth <i>Streptococcus mutans</i> And <i>Candida Albicans</i> (in Vitro) | Depi Praharani | 61 |
| 13. | The Giving One Week Of Probiotic Lactobacillus Reuteri Prodentis Inhibits The Growth Of Colonies On Dental Caries In Streptococcus Mutans Children | Putu Yetty Nugraha | 66 |
| 14. | The Utilization Of Stevia Side From <i>Stevia Rebaudiana</i> As An Alternative Sweetener To Prevent Dental Caries | Avina Anin Nasia; Nisa Yulianti Suprahman; Aan Mi'dad A | 74 |
| 15. | Concentration Of 10 % In The Extract Of Areca Catechu L. May Reduce The Number Of Colonies Of Candida Albicans On The Heat Cured Acrylic Resin | Ni Kadek Sugianitri | 80 |
| 16. | Changes In Vsc Level During 150 Minutes After Tooth Brushing And Tongue Cleaning Using Antiplaque Toothpaste Compared With Placebo | Irnmanda D.H ; Siti Aliyah Pradono | 85 |
| 17. | The Uveitis - Periodontal Disease Connection In Pregnancy: Controversy Between Myth And Reality | Widyawati Sutedjo; Chiquita Prahasanthi; Daniel Haryono Utomo | 91 |
| 18. | Management Of Fibrous Epulis In 3 Years Old Children | Indira Chairulina Dara; Hendrarlin Soenawan | 98 |
| 19. | The Adverse Effects Of Volatile Sulfur Compounds (vscs) In Periodontal Healing | Rikko Hudyono; Ernie Maduratna Setiawatie | 104 |

| | | | |
|-----|--|---|-----|
| 20. | Ranula Marsupialisation In pediatric Patient | Ekasari W | 111 |
| 21. | Golden Proportion As One Of Esthetic Components And Its Application In Orthodontics | Luciana; Nia A. Ismaniaty | 117 |
| 22. | Eruption Hematoma In Children | Sri Ratna Laksmiastuti , Arianne Dwimega | 125 |
| 23. | Management Of Mucous Membrane Pemphigoid | Dyah Juniar Hymawatty | 130 |
| 24. | Management Of Dentigerous Cyst In A Young Boy A Case Report | Rahmi Syaflida; Abdul Latif | 133 |
| 25. | The Precision Attachment Of Custom Made Mouthguard Better Than Boil And Bite | Ria Koesoemawati | 137 |
| 26. | A Camouflage Treatment Of Class Ii Division 2 Malocclusion With 3 Premolars Extraction | Ervina R Winoto | 144 |
| 27. | The Effect Of Polyvinyl Alcohol On Local Calcite Hydroxyapatite-gelatin Biocomposite As Bone Graft Applications | Isti Rahayu Suryani; Adhi Anindyajati; Alva Edy Tontowi; Widowati Siswomihardjo | 149 |
| 28. | Holistic Dental And Oral Treatment In Children With Complete Atrioventricular Septum Defect (cavsd) | Sella; Sarworini B Budiardjo | 155 |
| 29. | The Role Of P.gingivalis And Oxidative Stress In Periodontitis Induced Myocardial Infarction | Hardini Dyah Astuti; Ernie Maduratna Setiawatie; Rikko Hudyono | 162 |
| 30. | Biostimulation Of Low Intensity Laser Therapy (lilt) In Orthodontic Treatment | Ida Bagus Narmada | 167 |
| 31. | Healing Of Periapical Lesions In Non Vital Tooth #36 Post Root Canal Treatment, Children 9 Years Old | Andria Diarti ; Sarworini B.Budiardjo | 176 |
| 32. | Correction Of Scissors-bite Dental On Second Molar Using Modified Nance Holding Arch (nha) | Irena winata; Retno Windayati | 181 |
| 33. | The Effect Of Premolar Extraction In Orthodontic Treatment On Temporo Mandibular Joints And Masticatory Muscles | Grahita Aditya ; Miesje Karmiati Purwanegara | 188 |
| 34. | Deep Bite Correction Methods | Sigit Handoko Utomo ; Benny M. Soegiharto | 193 |
| 35. | Drug Interaction Of Analgesics In Clinical Dentistry | Didi Nugroho Santosa | 198 |
| 36. | Bone Remodelling For Reimplantation And Transplantation Of The Teeth Anterior On The Great Bone Lose After Trauma | Heru Maksmara | 203 |
| 37. | Indirect Mechanisms Of Periodontitis-induced Atherosclerosis | Emmaria Siregar , Poernomo Agoes Wibisono , Rikko Hudyono | 209 |
| 38. | Management Of Hemangioma On The Tongue By Hot Saline Injection | Eky Nasuri, Corputty Johan Edwin | 216 |
| 39. | Apex Resection And Retrograde Filling After Enucleation Of Radicular Cyst | Teuku Ahmad Arbi; Abdul Latif | 219 |
| 40. | Superficial Ranula Managed By Marsupialization Surgical Technique | Arfan Badeges; Evy Eida Vitria | 223 |
| 41. | Hypertension And Periodontitis Fact Or Myth | Ega Lucida CH K, Poernomo Agus Wibisono; Rikko Hudyono | 229 |
| 42. | Coronal Leakage In Temporary Post Core Crown Cemented With Eugenol And No Eugenol Contain Temporary Cements Eugenol Contain Temporary Cements | Albertus Fredi S., Farisza Gita, Roselani W.Odang | 233 |



| | | | |
|-----|--|---|-----|
| 43. | Fissure Sealant Interface Microleakage Using One Step Adhesives | Sandy Christiono | 239 |
| 44. | Post-core-crown As Restoration Of Fractured Tooth After Endodontic Treatment | Nansi Meilatia, Daru Indrawati | 244 |
| 45. | Central Diastema Closure With Composite Resin | Novita Amelia, Gatot Sutrisno | 250 |
| 46. | Emergency Treatment Of Periodontal Abscess | Fira Rafini; Robert Lessang | 256 |
| 47. | Pathomechanism Of Atherothrombotic Disease Caused By <i>Streptococcus Mutans</i> (an <i>In Vitro</i> Study) | Purwanto; I Dewa Ayu Susilawati | 262 |
| 48. | Crp And Il-1b Gene Polymorphisms And Crp In Bloodin Periodontal Disease | Auerkari El, Suhartono AW, Djamal NZ, Verisqa F, Yunaini Suryandari DA Kusdhany LS Masulili SLC | 268 |
| 49. | Maternal Health Behavior Of Early Childhood Caries In 3 Years-old Children | Febrina Tri Wardhani, Sarworini B. Budiardjo Retno Widayati | 275 |
| 50. | The Role Of Prostaglandin In Orthodontic Tooth Movement | Retno Widayati | 280 |
| 51. | Recurrent Aphthous Stomatitis With Some Food Allergy As Predisposing Factor | Maharani Laillyza Apriasari | 287 |
| 52. | Orthodontic Camouflage Treatment Of Class Iii Open Bite Malocclusion | Olivia Pribadi; Krisnawati | 292 |
| 53. | Antibacterial Effect Of <i>Mahkota Dewa</i> (<i>phaleria Macrocarpa</i> (scheff) Boerl.) Extract In <i>Enterococcus Faecalis</i> Growth As Alternative Of Root Canal Irrigation | Siti Rusdiana Puspa Dewi; Rini Bikarindrasari; Hafiz Hadiwijaya | 298 |
| 54. | Children Toothpaste Composition And Decrease Of Bacterial Count In Saliva | Sri Ratna Laksmiastuti; Yunita Setya Putri | 304 |
| 55. | A Study Of The Salivary Flow Rate And The Number Of Calcium Ion In Saliva | Tecky Indriana | 309 |
| 56. | The Increased Of Glycosaminoglycan And Hydroxyproline Content In Rat Cartilage Mandibles After Insulin Like Growth Factor- α Induction | IGA Wahyu Ardani | 315 |
| 57. | Biostimulation Of Low Intensity Laser Therapy (lilt) In Orthodontic Treatment | Ida Bagus Narmada | 321 |
| 58. | AMELOBLASTOMA OF THE JAWS: CLINICOPATHOLOGICAL, RADIOGRAPHIC, AND DEMOGRAPHIC CHARACTERISTICS AT THE ORAL SURGERY CLINIC OF CIPTOMANGUNKUSUMO HOSPITAL | Wenny Yulvie; Benny S Latief | 328 |
| 59. | Adiposed Derived Mesenchymal Stem Cell Conditioned Media: Promising Therapy For Tooth Regeneration | Dewi A Margono, Indah Yulianto, Siti Mardewi SA, Boy BM Bachtiar, Yuda Fibrianto, Yuyun Rindiastuti | 333 |
| 60. | Fish Thorn Prospect As Component Of Dental Pulp Capping Which Can Quicken Dentine Regeneration | I Dewa Ayu Ratna Dewanti; Erawati Wulandari | 338 |
| 61. | Hemangioma Of The Tongue | Istien Wardani, Dyah Ayu R, Ayu Listya | 343 |
| 62. | Molecular Mechanisms Of Radicular Cyst Formation | Shanty Chairani | 347 |
| 63. | Relieving Idiopathic Dental Pain Without Drugs: Is It Possible? | Haryono Utomo, M. Rulianto | 353 |
| 64. | The Effect Of Antibiotic Paste On Largeperiapical Lesions After Single-visit Endodontic Treatment | Maria Tanumihardja | 361 |

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MOLECULAR MECHANISMS OF RADICULAR CYST FORMATION

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ABSTRACT

Radicular cysts are the most common cystic lesions affecting the jaws. They are most commonly found at the apices of teeth with necrotic pulps or defective root canal filling. It presupposes that physical, chemical or bacteria injury resulting in death of pulp followed by stimulation of epithelial cell rests of Malassez, which normally can be found in periodontal ligament. But it still unclear how are the epithelial cell rests stimulated to proliferate and how does the bone destruction occurs throughout cyst growth. The purpose of this study is to give a short overview of the molecular mechanisms of radicular cyst formation. It was reported that the inflamed cells in periapical of necrotic teeth can induce the production of proinflammatory cytokines and growth factors, which those factors mediate proliferation of epithelial cell rests. As the cysts develop, the surrounding bone will get resorbed. The expression of receptor activator NF κ B-ligand (RANKL) and matrix metalloproteinases (MMP) were found in cyst cavity, which suggest the significance of these molecules in mediate bone resorption in inflammatory periapical lesions. Radicular cysts are most likely induced by the initiation of an inflammatory focus of necrotic teeth which trigger proliferation of epithelial and bone resorption.

Key words: radicular cyst, epithelial cell rests, inflammatory stimulation, bone resorption

INTRODUCTION

A cyst is a pathologic cavity which is lined by epithelium.¹ Radicular cysts are most frequently seen in all kinds of all jaw cysts: They are referred to as odontogenic cysts, because they are lined by nonkeratinized stratified squamous epithelium, which is derived from odontogenic epithelium.^{1,2} Radicular cysts are usually found at the apices of necrotic teeth or defective root canal filling.³ However they may also be found on the lateral aspects of the roots in relation to lateral accessory root canals.

Physical, chemical or bacteria stimuli can influence tooth and make it become necrotic. The death of dental pulp is followed by inflammatory reactions around the apical area.^{2,3,4} Until now, a large number of cells, cytokines, and enzymes involved in these reactions have been described; however, the molecular mechanism underlying the pathogenesis of radicular cysts are not fully understood. The aim of this study is to give a short overview of the molecular mechanisms on how radicular cysts can be formed and developed.

Epithelial proliferation

The radicular cysts arise from the proliferation of the epithelial remnants of Malassez in response to stimulation of chronic inflammatory processes in the apical region of the necrotic teeth.^{1,4} The main factor in the pathogenesis of the radicular cysts is bacterial endotoxin, which can be found in high amounts in the necrotic tooth. Endotoxin has mitogenic effect on epithelial cells.³ They were reported to stimulate keratinocyte proliferation directly and indirectly by the stimulation of cytokines synthesis. The expression of cytokines and chemokines has been shown to be enhanced by bacterial endotoxins.^{4,5}

During periapical inflammation, the host cells in periapical tissue, such as fibroblasts, granulocytes, macrophages and lymphocytes, will release a number of inflammatory mediators, proinflammatory cytokines, and growth factors through innate and adaptive immune responses. Inflammatory mediators and proinflammatory cytokines produced by host cells that can be identified in radicular cysts are prostaglandins (PGs), interleukin-1 (IL-1), IL-3, IL-4, IL-6, interferon (IFN), tumor necrosis factor-alpha (TNF- α), and transforming growth factor-alpha (TGF- α).^{2,3,9} It is suggested that those molecules may modulate the biochemical activity of the epidermal growth factor (EGF) receptors or upregulate the EGF receptor genes expression by influencing the transcription factors.² Therefore, it will enhance ligand-receptor binding affinity and stimulate proliferation of epithelial cell rests. Proinflammatory cytokines indirectly may also stimulate the proliferation and growth of the epithelial cell rests by inducing expression of keratinocyte growth factor (KGF) in the stromal fibroblasts.²

Chemokines and their receptor molecules can also be identified in radicular cysts.^{3,5,8,10} Silva et al,¹⁰ reported increasing expression of chemokine receptors: CCR1, CCR2, CCR3, CCR5, and CXCR3 in radicular cysts. Compared to granulomas, cysts expressed the number of chemokines (RANTES, IP-10, and MCP-1) and chemokine receptors (CCR3, CCR5, CXCR1, and CXCR3) higher than granuloma.^{3,5,10} Thus, it suggested that chemokines play a critical role in the development of granuloma to be cyst.¹⁰

The epithelial cell rests of Malassez are quiescent or stable cells, which are generally standby in the G0 phase of the cell cycle.² For these cells, to divide and proliferate, they have enter the cell cycle and undergo synthesis of RNAs and proteins (G1 phase) and synthesis of DNA and chromosome replication (S phase) as well as mitosis (M phase). Appropriate extracellular signals (mitogens) are required to stimulate cells in the G0 phase to enter the G1 phase of the cell cycle.

Several studies have evaluated the expression of cell proliferation markers in the epithelial lining of cystic lesions, such as PCNA and Ki-67.¹¹⁻¹⁴ The proliferative capacity of cells, represented by mitosis, can be identified by the Ki-67 antigen, which is expressed in all active phases of the cell cycle, except in G0.¹³ PCNA is a nuclear nonhistone protein necessary for DNA synthesis, which is elevated during the G1/S phase of the cell cycle. Quiescent and senescent cells have a very low level of PCNA mRNA.¹¹ The expression of PCNA and Ki-67 have been identified in the epithelial lining of radicular cysts.¹¹⁻¹⁴ Those evidences prove that there are proliferative activity in radicular cyst formation.

One of extracellular signals that can stimulate quiescent cells to enter cell cycle is growth factor.² Growth factors are multifunctional, because they are involved in cell growth, cell differentiation, cell activation, secretion and chemotaxis. Binding of growth factors to their specific receptor proteins on the surface of cell membrane activates a series of intracellular target enzymes, protein kinases, which influence transcription and cell cycle control.^{2,3} Several growth factors, such as EFG and KGF released by stromal fibroblast, TGF- α released by macrophages and lymphocytes, and insulin like growth factor (IGF) released by stromal fibroblasts have been identified in radicular cysts.^{2,8} These growth factors will induce epithelial cell rests to divide and proliferate, then it might develop into an apical cysts.

A schematic illustration of the mechanism of epithelial rest cells proliferation by pro-inflammatory cytokines and growth factors produced by host cells around periapical tissue of non-vital teeth is shown in figure 1.

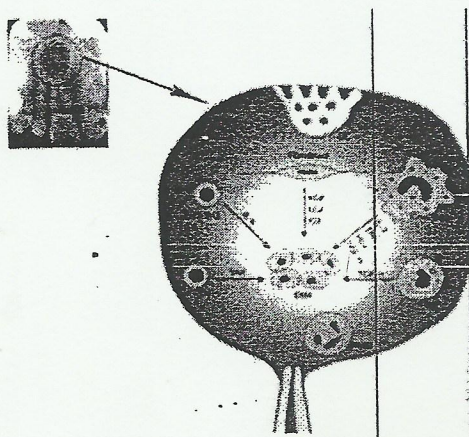


Figure 1.

A schematic illustration of the mechanism of epithelial rest cells proliferation²

Cyst development and expansion

Once formed, the cyst will experience a slow enlargement. Cystic expansion is influenced by a number of factors, like mural growth, hydrostatic enlargement, and bone resorbing factor.³ Most radicular cysts grow slowly and seldom reach large sizes. The radicular cysts can expand like a balloon, which suggested that the internal pressure is a major factor in the development of cysts. Expansion of cysts is associated with the hydrostatic pressure within the cyst, which is higher than capillary blood pressure. In order to balance the osmotic pressure, fluids from outside enters the lumen. These process makes cyst gradually enlarged.^{1,2,3}

The risen osmotic pressure inside cyst is resulted from the numbers of high molecular weight proteins in cyst fluid, which coming from inflammatory exudates.^{2,3} Other factor that contribute in increasing the osmotic pressure of cyst fluid are mast cells.¹⁵ The number of mast cells were found higher in subepithelial zone of radicular cysts. Mast cells may contribute to cyst enlargement in three ways 1) by direct release of heparin into the luminal fluid, 2) by release of hydrolytic enzymes which could degrade capsular extracellular matrix components, thereby facilitating their passage into the fluid, and 3) by the action of histamine on vascular permeability, thus leading the transudation of serum proteins.¹⁵

Increasing vascular permeability can also be induced by growth factor. Leonardi et al,¹⁶ reported that vascular endothelial growth factor (VEGF) was expressed in the radicular cysts. A number of cell types, including keratinocytes, macrophages, fibroblasts, and lymphocytes are involved in VEGF secretion. VEGF has bioactivity to increase vascular permeability, resulting in accumulation of inflammatory cells and cyst fluid.¹⁶ Hepatocyte growth factor (HGF) can also be found in radicular cysts. HGF might play a role in cyst expansion through inducing lining epithelial cell proliferation and its invasion into capsular connective tissue.⁸

Mechanism of bone resorption in radicular cyst

The most prominent destructive event connected with radicular cyst is the resorption of alveolar bone. The effector cells of this process are osteoclasts. Activated osteoclast will resorb the mineralized matrix and degrade organic components of bone.

The receptor activator of NF κ B-ligand (RANKL) and osteoprotegerin (OPG) can be identified in radicular cysts.^{17,18} Menezes et al.¹⁷ have identified the expression of both molecules in radicular cysts, with the number of RANKL was higher than OPG (the ratio of RANKL / OPG: 1.40 ± 0.04). Both RANKL and OPG are involved in osteoclasts signaling. RANKL is a molecule (ligand) required to stimulate differentiation of osteoclast precursor cells into mature osteoclasts by binding to its receptor, RANK expressed on the surface of osteoclast precursor cells. As a result, mature osteoclast become activated resulting in bone resorption.^{4,19} Whereas OPG is a molecule that acts as a decoy receptor, inhibits RANKL-RANK interaction and thus bone resorption.^{4,19} Identification of RANKL and OPG in radicular cysts demonstrated that both molecules are contributing to osteoclast formation and bone resorption.

Inflammatory cytokines produced by host cells such as IL-1, TNF- α , and PGs can mediate bone resorption.^{2,4,7} Other interleukins that have been implicated in alveolar bone loss are IL-6, IL-3 IL-11, IL-17, and IL-18. Those interleukins were reported to be expressed in radicular cyst.^{2,4,6,8} They can stimulate proliferation of osteoclasts and induce the released of PGs by host cells.² PGs are also a potent inductor for bone resorption by osteoclasts.

Other cytokines that play a role in the process of bone resorption was granulocyte-macrophage colony stimulating factor (GM-CSF) which has been identified in radicular cysts fluid.⁵ GM-CSF together with IL-3 can stimulate the release of macrophage colony stimulating factor (M-CSF) which will then stimulate the differentiation of hematopoiesis stem cell into osteoclast.

Other molecule that contributing in bone resorption is matrix metallo proteinase (MMP). MMP is a protease enzyme that can degrade extracellular matrix, including collagen, fibronectin, laminin, and proteoglycans. The expression of Matrix Metallo Proteinase (MMP) can be found in radicular cyst. Walhgren et al,²⁰ reported that MMP 2, MMP 8 and MMP 9 are expressed in radicular cysts. Cytokines released by inflammatory cells will stimulate the epithelial cells, fibroblasts, macrophages, neutrophils and endothelial cells to produce MMP. Endotoxin from bacteria can also stimulate the production of MMP by host cells. This proteolytic enzyme has contribution in degrading bone matrix and basement membrane during the process of cyst expansion.

DISCUSSION

The pathogenesis of radicular cyst involves the activation of epithelial cell rests of Malassez after physical, chemical, or bacterial injury. Three phases of cystic formation has been described : initiation, cyst formation, and cyst enlargement. It is established that the radicular cysts are a result of inflammatory process in the periapical tissues.²⁴ Humoral and cellular immune responses play a role in the pathogenesis of these lesions.

Constant irritation from necrotic pulps will result in an inflammatory response within the periapical area. There are upregulated the expression of proinflammatory cytokines (IL-1, IL-6, IL-8, and TNF- α), inflammatory mediators (PGs), chemokines, and growth factors (EGF, KGF, TGF- α , FGF, HGF) in radicular cysts, released by surrounding host cells.^{2,3,5,6,8} The high levels of those molecules is most probably due to ongoing stimulation of the lesion by bacterial toxins released from the infected root canal. All of those molecules synergistically stimulate cell rests of Malassez to enter cell cycle and begin to proliferate.³

As cyst grows, there are increasing vascular permeability induced by mast cell and formation of inflammation exudates originating from the lytic product of the dying cell in the cyst lumen.⁴ Therefore, the osmotic pressure of the cyst fluid will increase, To equalize the osmotic pressure, fluid enters the lumen, resulting in expansion of the cyst.

The growth of radicular cysts will be accompanied by local bone destruction, resulted from activated osteoclasts. Proinflammatory cytokines, interleukins, prostaglandins, and TNF- α are known to stimulate bone resorption through the upregulation of RANKL.¹⁷ The actions of RANKL include promotion of osteoclast differentiation, stimulation of osteoclast activation, survival, and adherence to bone surface.^{17,18} Therefore, the number of activated osteoclast increase, thus increasing bone destruction. Increasing proteinase (MMP-2, MMP-3, MMP-8, MMP-9, and MMP-13) released by host cells also contribute in degrading extracellular matrix of bone.²⁰



Schematic illustration of molecular mechanism of radicular cyst formation is shown in figure 2.

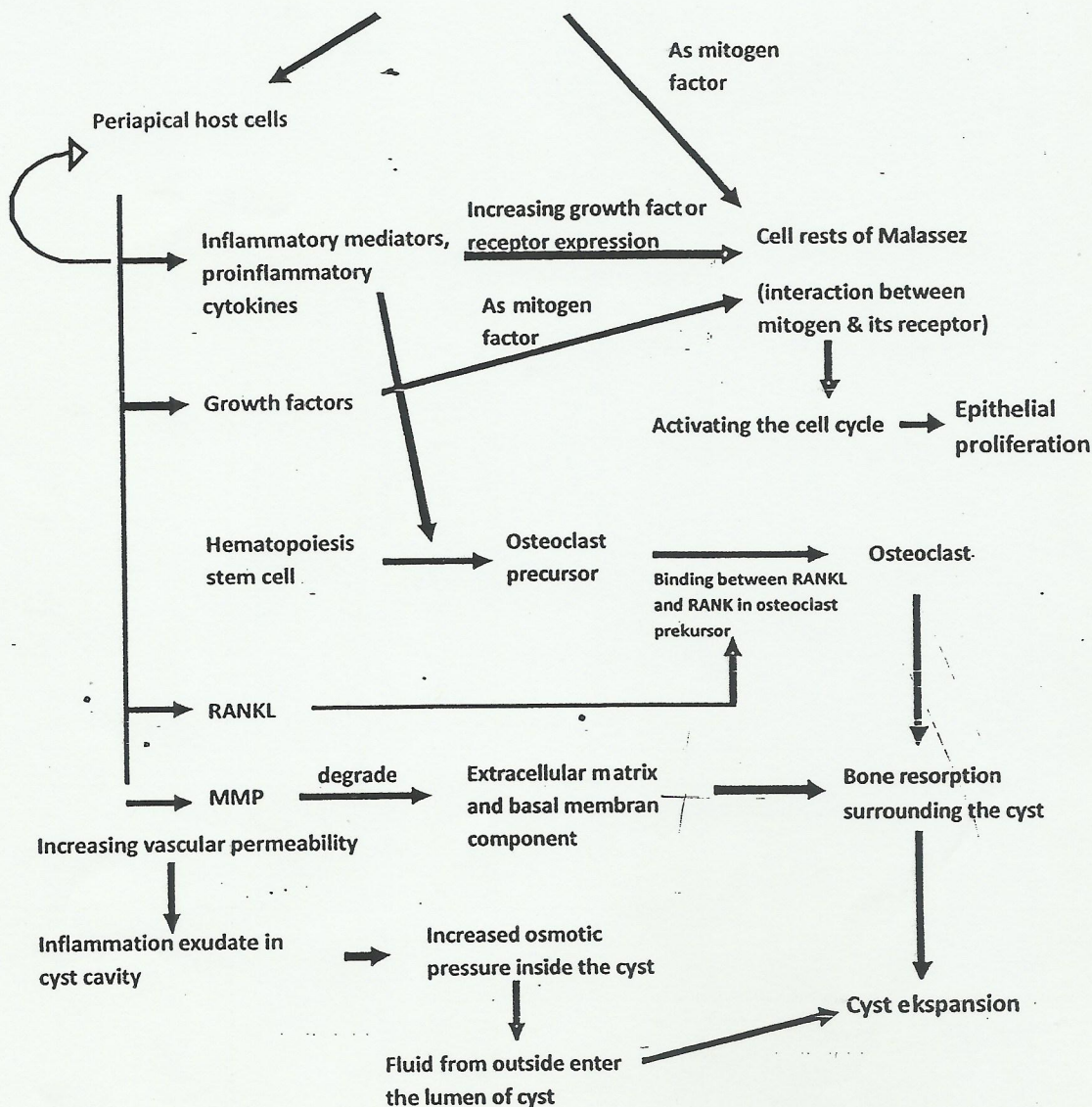


Figure 2.
Schematic illustration of molecular mechanism of cyst formation

Understanding the molecular mechanism behind the pathogenesis of radicular cysts will provide the basis for the development of treatments for these lesions. Having eliminated successfully the initiating root canal infection by proper root canal treatment may prevail over tissue destructive events. The lesion may heal completely by remineralization and the inflammatory characters will disappear. However, radicular cysts sometimes continuously expand after root canal therapy and eventually have to be removed by surgical procedure. This phenomenon suggests that processes other than those induced by infection contribute to the growth of these cysts. Hayashi et al.⁸ has identified factors for angiogenesis, such as Ang, HGF, and IL-8, growth factors for epithelial cells (HGF), and bone resorbing factor (IL-6), which their releases were not induced by inflammatory stimuli. Those findings could possibly explain the persistent growth of radicular cysts after root canal treatment.

The resorption of alveolar bone by osteoclasts is the most dominant destructive event from radicular cyst. The fact that RANKL is required for osteoclast development suggests that agents which inhibit its activity may be therapeutic. Alternatively, soluble OPG, which inhibits osteoclast formation by blocking RANKL-RANK interaction, also has the potential to be developed for future therapeutic use for this lesion.

CONCLUSIONS

Radicular cysts are most likely induced by the initiation of an inflammatory stimulation of necrotic teeth. Humoral and cellular immune responses will get activated, thus trigger proliferation of epithelial cell rests of Malassez and stimulate bone resorption process.

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