Immunopathology of Apical Periodontitis and Refractory Cases

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Abstract
Apical periodontitis is a relatively frequently encountered disease in clinical dentistry; however, its pathogenesis and etiology are not easily elucidated. Therefore, it is not always cured, even when carefully following the highest standards of treatment and intractable apical periodontitis may occur. In addition, in long-term root canal treatment of difficult cases with infectable tissue, there may be misunderstandings between the dentist and patient. While acute pain is an indispensable symptom in detecting lesions and disease, sustained chronic pain can decrease an individual’s quality of life with various negative outcomes, including decreased motivation to work. Therefore, endodontic treatments and pain control measures for a diseased tooth in intractable apical periodontitis must be developed. This review outlines the progression from the onset of the lesion and examines the immunology of apical periodontitis based on studies of model animals, indicating that interleukin-1β is a key factor in elucidating the disease state and is expected to lead to the development of an effective treatment for refractory cases.

Keywords: Apical periodontitis; Bone resorption; IL-1β; RANKL

Introduction
In clinical dentistry, apical periodontitis caused by bacterial infection of apical foramen is a frequently encountered disease. Acute inflammation can develop into chronic inflammation due to the attenuation of inflammatory stimuli via the root canal. In apical periodontitis, tissue destruction is caused by both the bacterial infection and the immune response, as a biological defense reaction to remove the pathogenic substances. Once the causative agent is removed by the immune response, restoration of the immune response is activated and tissue repair and healing can occur. Among various immune responses, cytokines such as interleukin (IL)-1 and tumor necrosis factor (TNF) have been shown to involve in acute apical periodontitis and bone destruction. This review describes the mechanism of apical periodontitis development, and the involvement of cytokine in exacerbating apical periodontitis based on immune response and bone destruction.

Mechanism of Apical Periodontitis Development
Apical periodontitis occurs due to bacterial infection of the apical foramen, which causes acute inflammation of the apical periodontal tissue. Neutrophil and macrophage infiltration is observed in periapical lesions during the acute phase. Acute inflammation can develop into chronic inflammation due to the attenuation of inflammatory stimuli via the root canal (Figure 1). Acute serous apical periodontitis can occur after operations to treat apical periodontitis (e.g. pulpectomies and root canal treatments). In successful root canal treatments with aesthetic decoration and stimulus removal, inflammation disappears and the healing process begins. However, bacterial infections can occur on the outside of the apical foramen and lesions can progress to acute purulent apical periodontitis (Figure 2). Acute suppurative apical periodontitis can develop following the progression of suppurative pulpitis, gangrenous pulpitis, and dental pulp gangrene; this generally occurs via bacterial proliferation in the root canal. In addition, acute purulent apical periodontitis can occur after the activation of osteoclastic bone resorption and spread within the alveolar bone marrow as acute alveolitis and to the jawbone marrow. Although rare, this can develop into osteomyelitis of the jaw, which can lead to sepsis.

In many cases, the abscess destroys the relatively thin bone cortex on the buccal or lingual side. Abscesses form under the periosteum, causing the inflammation to expand further into the surrounding soft tissue, which can result in the formation of a fistula and a shift from acute apical periodontitis to chronic apical periodontitis.

In contrast, when the bacterial infection in the root canal weakens,
the lesion shifts from the active phase to the repair phase. Granulation tissue grows in the abscess, gradually absorbing the abscess and shifting into granulomatous inflammation. At this stage, it is considered to be a periapical granuloma and many macrophages and lymphocytes can be observed in the lesion (Figure 3). In chronic periapical abscesses or periapical granulomas, epithelial rests of Malassez often proliferate within the lesions (Figure 4) and can occur as cysts [1].

In apical periodontitis, tissue destruction is caused by both the bacterial infection and the immune response, as a biological defense reaction to remove the pathogenic substances. If the causative agent is removed by the immune reaction, restoration of the immune response is activated and tissue repair and healing can occur (Figure 5).

Since it is difficult to directly sample lesions to study apical periodontitis in humans, animal models are often used. Figure 6 shows a time course of the inflammatory response in apical periodontal tissue based on a histological investigation in rats with experimentally induced apical periodontitis. An acute inflammatory reaction was observed in the lesions, composed mainly of neutrophils. The reaction peaked on day 14, after which a chronic inflammatory reaction was observed in the lesions, composed mainly of lymphocytes and plasma cells. Bone resorption increased biphasically on days 2 and 14. The first
Cytokines play a significant role in both acute and chronic inflammatory processes. They are signaling molecules that mediate and regulate the immune response, hematopoiesis, and many other cellular processes via cytokine networks. Cytokines can be produced by various immune cells and act as regulatory signals to control immune responses and the destruction of tissue.

### Cytokine Involvement in the Immune Response during Acute Apical Periodontitis

Various cytokines are involved in the immune response during acute apical periodontitis. IL-1β is a cytokine that is involved in the activation of osteoclasts and macrophages expressing IL-1β in the vicinity of bone, resulting in bone resorption.

 Although formocresol is a powerful disinfectant, it can cause tissue damage. Apical periodontitis induced by pharmacological factors exhibits severe inflammation, and clinical symptoms are more persistent than those caused by mechanical stimulation. The effects of formocresol applied directly to the open apex are thought to be related to severe destruction of periapical lesions, resulting in markedly higher infiltration by inflammatory cells. This induces IL-1β overproduction by macrophages, exacerbating the periapical lesion and leading to apical periodontitis. A recent report suggested that IL-1β has a central role in tissue destruction in apical periodontitis.

### Factors Exacerbating Apical Periodontitis

A number of recent reports have suggested the involvement of biofilms formed by various bacteria on the apical foramen inside and outside the apex in prolonged inflammation. It has been suggested that pulp deactivators, including arsenite and paraformaldehyde, as well as intracanal disinfectants, including phenol and formocresol, induce fairly strong irritation. When these irritants are used incorrectly, they leak into the periapical tissue and cause severe inflammation, leading to the activation of osteoclasts and macrophages expressing IL-1β in the vicinity of bone, resulting in bone resorption.

### Cytokine Table

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Cytokine-producing cell</th>
<th>Target cell</th>
<th>Main function</th>
<th>Effects on bone</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1α/IL-1β</td>
<td>monocyte, dendritic cell, B cell, fibroblast, epithelial cell, endothelial cell, macrophage</td>
<td>thymus lymphocytes, T cell, B cell, neutrophil, tissue cell, osteoblast</td>
<td>immune regulation, inflammation</td>
<td>Bone destruction</td>
</tr>
<tr>
<td>IL-6</td>
<td>macrophage, T cell, monocyte, fibroblast, B cell</td>
<td>T cell, B cell, thymus lymphocytes, tissue cell, osteoblast</td>
<td>cell differentiation, protein synthesis of acute phase</td>
<td>Bone destruction</td>
</tr>
<tr>
<td>IL-8</td>
<td>macrophage</td>
<td>neutrophils, basophils</td>
<td>chemotactic factor</td>
<td></td>
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<tr>
<td>IL-10</td>
<td>T cell</td>
<td>Th1 cell</td>
<td>inhibition of cytokine synthesis</td>
<td></td>
</tr>
<tr>
<td>IL-17</td>
<td>T cell</td>
<td>T cell, macrophage, fibroblast, endothelial cell</td>
<td>inflammation, neutrophil migration</td>
<td>Bone destruction</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>T cell, NK cell</td>
<td>lymphocytes, monocytes, tissue cells</td>
<td>immune regulation, B cell differentiation, MHC I expression</td>
<td></td>
</tr>
<tr>
<td>TNF-α</td>
<td>macrophage, lymphocyte, mast cell</td>
<td>macrophage, granulocyte, endothelial cell</td>
<td>inflammation, fibrosis</td>
<td>Bone destruction</td>
</tr>
</tbody>
</table>

| Figure 7: Model for the bone destruction mechanism and proinflammatory cytokines in the periapical lesion. |
The Role of Macrophages

Macrophages produce both bone resorption cytokines and osteoblast growth factors such as transforming growth factor (TGF)-β [12]. TGF-β primarily inhibits T cell proliferation and blocks the effects of pro-inflammatory cytokines. It has been suggested that macrophages are not only related to enhancing tissue destruction in apical periodontitis, but also to the suppression of tissue destruction and the activation of healing mechanisms [13].

Intractable Disease Control

Anti-cytokine therapies that attempt to reduce inflammatory cytokine activity by controlling their production have attracted attention for their potential in treating intractable diseases [14]. Recent animal and human studies have shown that blocking IL-1 activity may be therapeutically beneficial. For example, IL-1RA or soluble type IL-1R treatment reduces the severity of endotoxin-induced sepsis and impedes the progression of arthritis in experimental models [15]. Additionally, IL-1β-converting enzyme inhibitor blocks the progression of type II collagen-induced arthritis in mice [16]. In an attempt to find an effective novel cure for periapical lesions that have difficulty in subsiding due to severe inflammation, healing mechanisms could be activated by suppressing IL-1β production and secretion using a combination of antibacterial agents and IL-1β inhibitors. However, the mechanisms underlying the pathogenesis and progression of periapical lesions remain unclear; additional research is necessary to define the roles of immunological elements such as inflammatory cytokines like IL-1β in order to develop more effective treatments for refractory periapical lesions.

Conclusion

IL-1β is closely involved in the repression of intractable apical periodontitis and the bone destruction mechanism of inflammation regulation. Investigating a variety of inflammatory regulators, including inflammatory and anti-inflammatory cytokines that are likely involved in tissue destruction in apical periodontitis, will be necessary to develop novel endodontic treatments for intractable apical periodontitis. This is a key factor in elucidating the disease state and is expected to lead to the development of an effective treatment for refractory cases.

References


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