Review Article

Mines of cytokine: A treasure trove in pulpal and periapical diseases

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Abstract

Pulpitis is a special disease of dental pulp. It causes localized inflammation, due to various inflammatory mediators such as cytokines and chemokines. These inflammatory mediators are responsible for various reparative and resorptive processes in the dental pulp. The balance between these processes ultimately determines the viability of the tooth. Due to the important properties of various inflammatory markers, the correlation of cytokinin gene expression in various stages of inflammation becomes necessary to focus on. Several studies in the past have focused on the importance of such correlation to help in diagnostic applications. The nature of these inflammatory mediators can help us in diagnostic evaluation. Several attempts have been made to focus on these associations so that it can assist in making clinical decisions effectively. The data available are vast but are the most neglected topic. This review article briefly outlines and summarizes the importance of various inflammatory mediators such as cytokinin and chemokines in various pathways of pulpal and periapical inflammation in explanatory and diagrammatic forms. Knowledge gained about pulpal inflammatory response may aid in understanding the molecular level of inflammatory pulpal and periapical diseases, which shall modify our future diagnostic modalities. Several medicaments are used in the treatment of minimal to advanced dental caries which leads to periapical infections. Thorough understanding of these medicaments can resolve secondary infection and can improve the prognosis of the treated tooth.

Keywords: Chemokines; cytokines; interferons; interleukins; periapical inflammation; pulpal diseases; pulpitis

INTRODUCTION

Pulpitis is a special disease of dental pulp. It causes localized inflammation, due to various inflammatory mediators such as cytokines and chemokines. These inflammatory mediators are responsible for various reparative and resorptive processes in the dental pulp. The balance between these processes ultimately determines the viability of the tooth. Due to the important properties of various inflammatory markers, the correlation of cytokinin gene expression in various stages of inflammation becomes necessary to focus on. Knowledge gained about pulpal inflammatory response may aid in understanding the molecular level of inflammatory pulpal and periapical diseases, which shall modify our future diagnostic modalities. Several medicaments are used in the treatment of minimal to advanced dental caries which leads to periapical infections. Thorough understanding of these medicaments can resolve secondary infection and can improve the prognosis of the treated tooth.

IMMUNE RESPONSE

If induced in a host by any antigen stimulus, the specific reactivity is called as immune response. There are two types of immunity, innate and adaptive. The initial exposure of microbes activates innate immunity. If the initial or innate

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immunity fails to abolish the response, then adaptive immunity comes into role, which includes cellular or cell-mediated immunity and antibody-specific or humoral immunity. The components of innate or nonspecific immunity in the dental pulp tissue include dentinal fluid, odontoblast, neuropeptides, immune cells, cytokine, and chemokines: interleukin 2 (IL2), IL4, IL5, and IL13 induced by activated T-cells. The components of adaptive immunity in the pulpal tissues include T- and B-cells, mast cells, and their cytokines and antibodies.[1]

INITIAL PULP RESPONSE TO CARIES

The initial pulpal response to caries is mediated by various pathways causing inflammatory response it involves the dentinal fluid, odontoblasts, cellular, neuronal (neuropeptides such as calcitonin gene-related peptides and substance P), and vascular components. These components are not classic and nonspecific but show active participation in the initial response and as the disease progresses.

There are different groups of cells involved in innate immunity and adaptive immunity. The lymphocytes, natural killer cells (NK cells), T-cells, dendritic cells, monocytes and macrophages, tumor necrosis factor (TNF), IL1, IL6, IL10, IL10, and IL18, and interferons (IFN) participate in innate immunity. On the other hand, interleukins such as IL2, IL4, IL5, and IL13 and activated T-cells participate in adaptive immunity. Chemokines are a special group of secreted proteins that help in cell migration.

CYTOKINES

Cytokines are said to regulate immunity and inflammation. (Cyto is "cell" and kinos is "movement"). These are small, low-molecular-weight proteins secreted by immune cells. They travel through lymph, blood, or other tissues to reach their target immune cells. A variety of exogenous and endogenous signals regulate the expression of cytokine receptors.[2]

Types of cytokines [Table 1]:

- IL
- IFN
- TNF.

Growth factors: Transforming growth factor (TGF), Vascular Endothelial Growth Factor (VEGF), platelet-derived growth factor, etc.

- Colony-stimulating factor (CSF)
- Chemokines (C, CC, CXC, and CX3C).

Interleukins

This broad subgroup family of cytokine originates from hematopoietic cells and primarily acts on leukocytes. They are produced by one leukocyte and act on another leukocyte. This cross-talk between the leukocytes gives the name signaling molecules. As per the order of discovery, they are numbered from 1 to 38. They have a significant role in acute inflammation.

Interferons

IFN-gamma, a family of cytokinin, is secreted by NK cells in innate immunity and T-cells in adaptive immunity. They play a role in phagocytosis.

Tumor necrosis factor

Earlier TNF was regarded as an antitumor agent, but with further added research, it shows that they have multiple roles including adhesion, emigration, and secretion. It has a role in stimulating the endothelial adhesion molecules, emigration of macrophages and neutrophils, and secretion of various other cytokines. The two types of TNF are:

- TNF alpha produced by mono- and macrophages (innate immunity)
- TNF beta produced by activated helper T-cells, TH0, and Th1 cells (adaptive immunity).

Transforming growth factor-beta

This cytokinin has a major role in cell growth. The production of this family is regulated by macrophages and odontoblast

Table 1: Cytokines in pulpal diseases

Cytokine	Family	Sources	Functions
IL1β	IL1	Macrophages, monocytes	Pro-inflammation, proliferation, apoptosis, differentiation
IL6	IL6	Macrophages, T-cells, adipocyte	Pro-inflammation, differentiation, cytokine production
IL 8	CXC	Macrophages, epithelial cells, endothelial cells	Pro-inflammation, chemotaxis, angiogenesis
IL 12	IL 12	DCs, macrophages, neutrophils	Pro-inflammation, cell differentiation, activates Nk cells
TNF α	TNF	Macrophages, NK cells, CD4 lymphocytes, adipocytes	Pro-inflammation, cytokine production, cell proliferation, apoptosis, anti-infection
IFN -γ	INF	T-cells, NK cells, NKT cells	Pro-inflammation, innate adaptive immunity, antiviral
GM-CSF	IL 4	T-cells, macrophages, fibroblasts	Pro-inflammation, macrophage activation, increase neutrophil and monocyte function
Il 4	IL4	Th cells	Anti-inflammation, T cells and B cell proliferation, B cell differentiation
Il 10	IL 10	Monocytes, T-cells, B-cells	Anti-inflammation, inhibition of pro inflammatory cytokines
IL 11	IL 6	Fibroblast, neurons, epithelial cells	Anti-inflammation, differentiation, induce acute phase protein
TGF-β	TGF	Macrophages, T-cells	Anti-inflammation, inhibition of pro-inflammatory cytokine

NK: Natural killer, TNF: Tumor necrosis factor, TGF-β: Transforming growth factor - beta, CSF: Colony-stimulating factors, GM: Granulocyte-macrophage, IFN: Interferons, IL: Interleukins, CXC: Chemokines, DCs: Dendritic cells

in innate immunity and regulatory T-cells (Treg) in adaptive immunity. There are three main functions of TGF which include inhibition of cell proliferation, enhancement of extracellular matrix deposition, and tissue repair.

Colony-stimulating factors

They stimulate the stem cells and hematopoietic cells to become specialized cells to fight against invaders. The family members of this group include monocyte M-CSF, granulocyte-CSF, granulocyte-macrophage-CSF, and erythropoietin.

Chemokines

Chemokines are short forms of chemotactic cytokines. A specific group of cells is attracted toward the wound site; this recruitment is taken care of, by the chemokines and is called the chemoattractant property. They include four major subgroups such as C, CC, CXC, and C × 3C.[3]

Chemokines are grossly differentiated into two types:

- Pro-inflammatory cytokines: Those cytokines which produce fever, inflammation, tissue destruction, and in some cases shock and death are called as pro-inflammatory cytokines. These include IL-1, IL-1β, IL-6, IL-8, TNF, and IFN. They favor or upregulate inflammation and are predominantly produced by activated macrophages[4]
- Anti-inflammatory cytokines: Those cytokines do not produce inflammation or inhibit the pro-inflammatory cytokines. They have a major role in the regulation of the intensity and duration of the immune response. Anti-inflammatory cytokines include IL-4, 10, 11, and TGF.[4]

Properties of cytokines

The major properties of cytokines are grouped as follows:

1. Pleiotropy: This is the property of cytokines to affect multiple cell types
2. Redundancy: This is the property in which multiple cytokines affect the same type of cells
3. Synergy: The property in which cytokine acts in concert on the same cell
4. Antagonism: Competing actions of cytokines
5. Cascading: Sequentially acting cytokines
6. Cytokines mediate their effects by binding to various target receptors
7. Other properties: Production and regulation of inflammatory response influence synthesis of other cytokines.

CLINICAL IMPLICATIONS

Diagnosis of pulpitis

The four stages of any pulpal condition, considering signs and symptoms can be classified as normal, reversible inflammation, irreversible inflammation, and necrosis. Histology remains the gold standard in exact differentiating these stages, but there still lies a huge gap when it comes to the clinical diagnostic evaluation. The clinical diagnosis does not consider the present inflammatory condition; hence, there is always a scope for improving our diagnostic decisions if we consider the same. The normal and necrotic pulp can have a straightforward histological presentation; the challenge lies in the diagnosis of reversible and irreversible pulpitis. All the current diagnostic procedures do not consider the inflammation as a factor, so it is unfortunate to differentiate between vital pulp therapy (VPT) and root canal treatment. This review article highlights the difference between reversible and irreversible pulpitis using cytokinin as biomarkers.[5]

The inflammatory biomarkers include IL-2, IL-6, IL-8, IFN-C, and TNF-a, whereas anti-inflammatory biomarkers include IL-4, IL-10, and IL-13.[5]

THE ROLE OF DOMINANT CYTOKINE IN VARIOUS STAGES OF PULP INFLAMMATION

As the pulpal inflammation starts, IL-2 is secreted by CD4+ T-cells, stimulates T-cells proliferation, activates NK cells, and promotes B-cells. In addition, they activate the transcription of other inflammatory cytokines and increase the cytolytic activity of NK cells. As pulpal inflammation starts, the level of IL-2 increases [Figure 1a].

As the disease advances to the irreversible stage, the concentration of IL-2 decreases. This decrease may represent the tissue may be in the late phase of irreversible inflammation and might be progressing toward necrosis. The absence of IL-2 indicates the end of the acute phase and the development of chronic inflammatory disorder.[6] IL-8, an inflammatory chemokine, is heat and proteolysis resistant. It induces chemotaxis and activation of inflammatory cells. It is rapidly synthesized in local sites of inflammation to combat infection continuously. Due to this property, it becomes ideal to function at sites of inflammation [Figure 1b].

The levels of IL-8 at the inflammatory sites play an important role in combating infection. On the other hand, IL-10 acts as a potent anti-inflammatory marker that promotes healing at inflammatory sites. The ratio IL8/IL10 is of significance in diagnosing pulpal and periapical diseases. Furthermore, an increase in IL-8 and IL-10 has been observed in inflammatory conditions of pulpal and periodontal diseases[7] [Figure 2a].

IFN-gamma predominantly participates in the maintenance of periapical immune response in cases of endodontic failure.[8] It plays a crucial biomarker in innate as well as adaptive immunity. It triggers the production and release of

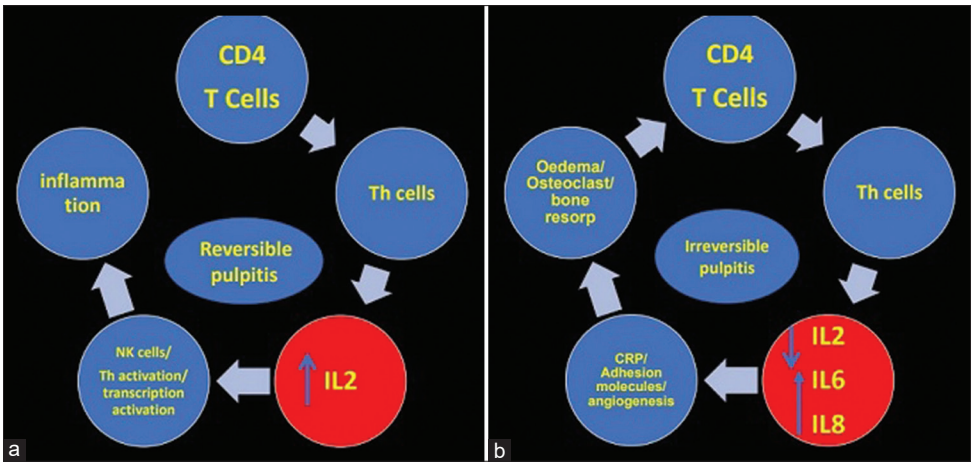

Figure 1: (a and b) Cytokines as diagnostic markers in reversible pulpitis and irreversible pulpitis

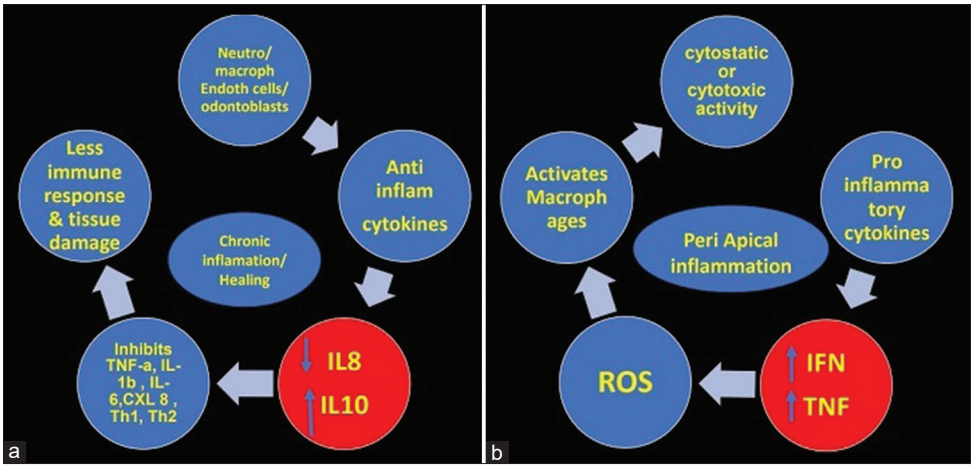

Figure 2: (a and b) Cytokines as diagnostic markers in chronic inflammation/healing and periapical inflammation

various reactive oxygen species (ROS) from macrophages. This gives an added advantage of cytotoxicity against various bacteria, virus, and tumor cells. IL-1β, TNF-α, and PGE2 are important inflammatory biomarkers in apical diseases, which might correspond to the development of bone destruction in clinical scenario[9] [Figure 2b].

APICAL PERIODONTITIS

It is known that T-helper responses, such as Th1 and Th2 lymphocytes drive the inflammatory periapical reaction. These are considered significant sources of cytokines. Treg cells have a crucial role in inhibiting apical periodontitis and periodontitis. TGF β released from Treg cells contributes to tissue repair.[10,11]

Effect of intracanal medicaments on cytokines

The most commonly used intracanal medicament (ICM) is calcium hydroxide. Calcium hydroxide in combination with 2% chlorhexidine gel has been found to be effective in increasing TH-2 type cytokines in the apical inflammatory process. Adding chlorhexidine gel to ICM increases its antimicrobial activity and makes it more effective against resistant microorganisms such as *Enterococcus faecalis*.[11,12]

Propolis has a major role in the production of cytokines. It is found to restore the expression of IL-1β, IL-6, and TNF-α to a basal level.

There is a huge association noted between phytotherapeutic agents and inflammatory mediators. Curcumin inhibits matrix metalloproteinases and upregulation of ROS. Chlorhexidine acts on IL-4 secretion. Neem leaf extracts act on NF-KB pathway. In triple antibiotic paste, ciprofloxacin is found to have more anti-inflammatory properties than the other contents.[13]

Cytokines and bone resorption in apical periodontitis

As the disease progresses to apical periodontitis, bone resorption occurs. Inflammation is the driven force for bone destruction. Osteoclasts are the major cells responsible for bone resorption, which are most active during the presence of inflammation. The correlation of clinical or radiographic

findings with that of responsible biomarkers can help us determine the exact treatment to be undergone in that situation.[14]

Osteoclasts mediate bone resorption by acting on two receptors. They are cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) on Treg cells and receptor activator of nuclear factor kappa-B ligand (RANKL).

Treg cells secrete inhibitory cytokines such as IL-10, IL-4, and TGF-β that inhibit the differentiation of osteoclast precursor cells into osteoclasts. CTLA-4 on Treg cells when comes in contact with osteoclast precursors can induce apoptosis of cells. Th17 cells upregulate the nuclear factor kappa-B ligand (RANKL) activator by releasing inflammatory cytokine IL-17 which plays an essential role in stimulating the release of local inflammatory factors. A better understanding of the pathophysiology of inflammation and bone resorption in apical periodontitis could be the basis for developing new root-filling materials with superior immunomodulatory properties which can be more effective.[14]

Apical periodontitis can appear as apical granulomas or radicular cysts. Radicular cysts or apical granulomas can cause apical periodontitis. Pro-inflammatory cytokines such as IL-1 and IL-6 have been shown to function as growth factors for ERM cells, which could lead to the formation of radicular cysts.[15] Compared to apical granulomas, macrophages in radicular cysts exhibited a notably greater degree of M1-like polarization. Macrophage polarization (M1 vs. M2) determines whether immune responses are pro-inflammatory (directed toward inflammation, antigen clearance, and tissue destruction) or immunomodulatory (directed toward peripheral tolerance, tissue regeneration, and wound healing) (M2). It was demonstrated that the formation of radicular cysts was linked to an increase in M1-like pro-inflammatory polarization macrophages.

Dentigerous cysts differ from radicular cysts in that they have a high degree of M2 polarization and low macrophage infiltration, which may indicate that they have a developmental rather than an inflammatory origin. It suggests that immunological mechanisms, such as modifications in macrophage polarization, may regulate the progression of apical periodontitis toward apical granulomas or radicular cysts.

Consequently, the development of radicular cysts may be inhibited by the use of root filling materials with anti-inflammatory qualities, such as mineral trioxide aggregate (MTA).

By upregulating TGF beta, vascular endothelial growth factor, and IL 10, MTA can cause macrophage polarization toward the M2 phenotype.

These results highlight the necessity of adequate bacterial clearance during endodontic treatment since bacterial antigens trigger M1 polarization of macrophages, which may prevent an M1 macrophage-derived stimulus for the formation of radicular cysts.[16]

Role of cytokines in vital pulp therapy

One of the main chemokines that controls the migration and infiltration of monocytes or macrophages, a characteristic of inflammation, is monocyte chemoattractant protein-1.[17] The majority of research that has been published states that the healing process begins with a mild inflammatory phase. However, there is growing evidence that inflammation is a necessary precondition for tissue healing, which is followed by pulp repair.[18] Previous research showed that progenitor cells could be stimulated to differentiate into odontoblast-like cells by growth factors such as the TGF family that are released from the dentin matrix.[19] It has been established that MTA stimulates the production of TGF-β1 and bone morphogenetic proteins by human dental pulp stem cells (hDPSCs), thereby promoting dentin repair.[20] According to Zhang *et al*., pulp capping material that has TGF-β1 attached to it can cause the pulp's resident stem cells to differentiate into odontoblast-like cells, which in turn can cause the formation of tertiary dentin.[21] Through the release of TGF-β1, biodentine can promote dentin formation and improve VPT results. The inflammatory pulp is populated by macrophages, which produce TNF-α.[22] Numerous investigations highlight the function of TNF-α protein in maintaining chemotaxis in fibroblasts and inflammatory cells.[23] Consistent with our findings, Silva *et al*. found no discernible variations in TNF-α production between MTA, biodentine, and the negative control.[24] On the other hand, El Karim *et al*. observed that odontoblast-like cells released less TNF-α after receiving biodentine.[25] This disparity might result from different cell types and methods than those employed in our investigation. CXCL8, also referred to as IL-8 (C-X-C motif chemokine ligand 8), is another chemokine that was examined in this investigation. When there is inflammation, IL-8's primary biological effect is to draw in and activate neutrophils.[20] Our findings showed that, in comparison to the control, MTA, CEM, and biodentine had no effect on the amount of IL-8 secreted by hDPSCs.[25] Nonetheless, there was a notable reduction in TNF-α and IL-8 secretion in the TheraCal group. This could be explained by the resin content and decreased cytocompatibility of the material.[26]

Future research implications

- Chairside diagnostics monitoring strategies for pulp inflammation, whether reversible or irreversible
- Predictable outcome in autoimmune diseases
- Resolution of periapical disease
- Successful VPT
- Local tissue and topical drug delivery systems

- Given the strong correlation between microbiological infections and the inflammatory response of the host, it is suggested to develop chairside diagnostic monitoring strategies for measuring levels of inflammatory biomarkers so that it has a role in preventing postendodontic complications and reducing endodontic failure rates
- Dysregulated cytokine networks in autoimmune disease patients cause overexpression of systemic and local pro-inflammatory cytokines; these dysregulated cytokine networks have not yet been reported to have an impact on cytokine levels in periapical tissues and root canals
- Moreover, these techniques will facilitate an enhanced comprehension of the advancement and resolution of periapical disease resulting from root canal infections
- In addition, it is necessary to develop topical and local tissue drug delivery systems that enable the controlled release of therapeutics in areas of inflamed pulp and their targeted application. Antibody/anticytokine receptor therapies, for example, are used to treat inflammatory conditions such as psoriasis, RA, Crohn's disease, spondylitis, and IBS. Specific cytokines are directly bound by anticytokine Ab, thus neutralizing it and stopping it from attaching to its receptors
- Particularly, for patients whose natural inflammatory defenses have been compromised by systemic diseases or local factors, this research may offer more support for the use of intracanal drugs and the development of cutting-edge therapeutic approaches such as inflammatory suppressive therapies or even antigen-specific gene therapies.

CONCLUSION

This review article describes the importance of cytokines to detect pulpal and periapical diseases. The ratio of IL-6/IL-10 and IL-8/IL-10 cytokines can be a useful marker in overall cytokine balance in the pulp. Although enough review literature can be found, this can be regarded as the most neglected topic and should be given due importance. However, further investigation is recommended, as they can prove a milestone in the clinical diagnosis of pulpal and periapical diseases.

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Conflicts of interest
There are no conflicts of interest.

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