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REVIEW OF INFLAMMATORY CYTOKINES IN DENTISTRY

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Abstract. *Pro-inflammatory cytokine is a type of signaling molecule that is secreted from immune cells like helper T cells and macrophages, and other cell types that promote inflammation like interleukin 1(IL-1), (IL-12) (IL-18), TNF-α, interferon gamma, granulocytes, macrophages and colony stimulating factor (GM-GSF). They play important role in mediation in initiate immune response. Inflammatory cytokines are predominantly produced and are involved in up regulation of inflammatory reaction. Most frequently Inflammatory diseases in dental medicine are periodontal diseases. Many studies have indicate that biological activity of variety of cytokines may be directly relevant to periodontal destruction. Draw of the initiation is well documented and the end result is destruction of alveolar bone and periodontal connective tissue. This is readily observe but the events between this two points in time remain obscure and are the focus of this paper. Bacteria from plaque formation induces tissue destruction indirectly by activating host defense cells, and tissue breakdown components of dental plaque have the capacity to induce the initial infiltrate of inflammatory cells including lymphocytes macrophages, PMNs. Bacteria can cause damage directly and indirectly. Cytotoxic cellular immune responses to self and pro-inflammatory responses are involved in releases of many cytokines and chemokines.*

1. INTRODUCTION

The first line of defense against molecules that are either pathogen-derived or endogenous danger signals (or quite often both) has evolved over millions of years. It is composed of players and mediators that are common to most vertebrates and invertebrates, as well as even plants [1]. In general, immunity does not only differentiate between self and not-self but also between dangerous and not dangerous [2]. Inflammatory cytokines play a role in initiating an inflammatory response and to regulate the host defense against pathogens mediating the innate immune response. Some inflammatory cytokines have additional rules such as acting as a growth factors. Pro-inflammatory cytokines such a IL-1 beta, IL-6 and TNF-α also trigger pathological pain. While IL-1 beta is released by monocytes and macrophages it is also present in nociceptive DRG neuron. IL-6 plays a role in neuronal reaction to an injury. TN-alpha is well known pro-inflammatory cytokine present in neurons and the glia. TNF alpha is often involved in different signaling pathways to regulate apoptosis in the cell. Excessive chronic production of inflammatory cytokines contribute to inflammatory decease that have been linked to different decease such a arteriosclerosis and cancer. This regulation of pro-inflammatory cytokines have also been linked to depression and other neurological decease. Pro-inflammatory and anti-inflammatory cytokines should be in balance for health to be maintained. Aging and exercise also play a big role in the amount of the release of pro-inflammatory cytokines.

Summarized, the messenger molecules such as cytokines are highly important in the orchestration of the inflammatory response to self- or not-self danger molecules. Meanwhile, the role of the immune system in various inflammatory diseases, in dental medicine as a periodontal decease, pulpitis bone pathologies such as atherosclerosis and distraction. But most frequently decease in dental medicine are periodontal diseases.

Periodontal diseases or periodontitis, are heterogeneous group of diseases characterized by inflammation and subsequent destruction of the tooth-supporting tissue. Today it is quite clear that periodontal diseases are of an infection nature and that the microorganisms present in the sub gingival bacterial plaque are the primary etiological agents [3, 4, 5, 6]. Initiation and progression of periodontitis are dependent on the presence of gram-negative anaerobic bacteria localized in the sub gingival region and include typically, *Porphoromonas gingivalis* (Pg), *Prevotela intermedia* (Pi), *Actinobacillus actonomycetascomitans* (Aa), and *Bacteroides forshytas* (Bi). One periodontal pocket can contain more than 700 microorganisms. The bacterial colonizing the sub gingival region multiply and extend in the apical direction, and, in the process, bring about loose epithelial and connective tissue attachment. The bacterial may give rise to destruction process by both direct and indirect mechanisms due to the activation of the hosts ' immunological and inflammatory reaction.

Although is not possible to attribute the etiology of periodontal diseases in a specific bacterial agent, there are a number of studies pointing to a group of bacteria believe that play a special role in the triggering and subsequent development of the disease.

There are over 500 bacterial species capable of colonizing in the sub gingival region, but the number of these commonly implicated in the disease process is around 10 or 15 gram negative anaerobes and spirochetes. The designation of periodontal pathogen applies to those bacteria that possess specific mechanism to break down the host's defense systems and cause destruction of the periodontal tissues.

The bacteria are considered to play significant role in the pathogenesis of periodontal diseases and the formation of the periodontal pocket, destruction of connected tissues and desorption of alveolar bone. Oral pathogens are necessary to initiated periodontitis, but they are not sufficient to insure progression of disease, unless it parallels inflammatory responses, in a susceptible host. There is, however, specific host defense mechanism to the bacterial challenge in the adaptive response of the immune system [7, 8]. Innate immunity is the first line of host defense and includes a number of relatively non-specific mechanisms, including the barrier effect of intact epithelium.

The host immune response may be conveniently divided into innate and adaptive immunity. Both innate and adaptive immunity operate together and not in isolation, complementing each other to maintain health and prevent disease.

Oral mucosa bathed in saliva, which contains number protective factors. Bacteria can be recognizing by non-clonally receptors, otherwise known as pattern recognition receptors. These receptors recognize substances such as lipopolysaccharide (LPS) from gram-negative bacteria and peptidoglycan from gram positive bacteria. Innate responses are relative non- specific and there is therefore greater potential for bystander damage of tissues.

Neutrophils appear to be crucial for the maintenance of periodontal health, as disease severity is increased the neutropenia, agranulocytosis and where cellular function in impaired, such as leukocyte adhesion deficiency, lazy leukocyte disease, Papillon Lefèvre and Downs syndromes, as well as diabetes mellitus.

The adaptive immune response is characterized by specificity, memory and the capacity to distinguish self from non-self. One recognition of microbial agents has taken place by the appropriate receptor on macrophages or dendrites cells, then cytokines are released which activate T and B cells, thereby engaging cell- mediated and humeral immune responses..The two arms of immunity therefore function together: the earlier responses being predominantly innate, subsequently helping to focus adaptive immune responses. In humeral or cell-mediated immunity, specificity of the responses is thought to limit by standard damage by focusing the adaptive or specific immune system.

2. CYTOKINES

Cytokines and (chemotactic cytokines) are the messages between the cells. the immune response to infection is regulated by cytokines and chemokines signals. Cytokines are low molecular - weight proteins involved in the initiation of further stages of inflammation, in witch they regulate the amplitude and duration of the response. The genetic regulation leading to the secretion of pro inflammatory cytokines from a variety of cells is generally dependent of the activation of transcription Nuclear factor-kappa B (NF-κB). the Nuclear factor-kappa B (NF-κB) regulation is regulated pathways are activated by pathogen associated molecular pattens, and such as lipopolysaccharides, trough the tall-like receptor pathway. A network of secreted cytokines led to activation of lymphocytes, but the progression of periodontal lesions is caused by deregulations of molecules released by specific cell populations. Many of these secreted factors are involved in bone regulation and maintained, and their imbalance leads to altered periodontal bone remodeling. Thus enhanced osteoblast activity without increase in bone formation occurs and drives the alveolar bone loss [6].

Inflammatory process gives rise to macrophage activation as well as leukocyte infiltration. The activated immunocompetent cells produce and secreted cytokines. These activated host cells include monocytes, macrophages, lymphocytes and fibroblast [9, 10].

Cytokines, are substances that are secreted by specific cells of immune system which carry signals locally between cells, and thus have an effect another cells. The biological effects of cytokines and are extremely diverse as they influence not only the immune response but also inflammatory processes and hematopoiesis.

Various studies have shown that IL-1 alpha, Il-1beta and TNF-α stimulated bone desorption and inhibit bone formation. Research work has sown that IL-1 beta expression is elevated in gingival cervical fluid at sites bone and attachment loss in patients with periodontitis. In another study, it was shown that the exogenous application of recombinant human IL-1 beta in a rat ligature model accelerated alveolar bone loss destruction and inflammation.

Cytokines can be classified into following categories: a. Proinflammatory cytokines; b. Cytokines with predominant immunoregulatory functions; c. Cytokines that regulate lymphocyte growth, activation and differentiation; d. Cytokines that help in hematopoiesis; f. Chemokines.

a. Proinflammatory cytokines: There are cytokine that mediate natural immunity. In this group there are soluble factors that influence inflammatory reaction. These include: interleukin-1 (IL-1), Tumor necrosing factor alpha (TNF-alpha), interleukin 6 (IL- 6), interleukin 8 (IL-8), Macrophage inhibitor factor (MIF).

Interleukin 1(IL-1)

This cytokine exist in two molecular form IL-1 alpha (IL-1 alpha) and IL-beta (IL-1 beta), encoded by two separate genes and displaying only 20% homology to one another. Cells of the monocytemacrophage lineage are the main cellular source of IL-1, while IL-1 beta, synthesized as inactive precursors, is released from the cells after being processed post translational by a cysteine-asparagine protease. IL-1 beta is a proinflammatory cytokine expressed by monocytes, macrophages and dendrite cells. It signals through two receptors, IL-IRI and IL-IRII., both of which are shared with IL-1 alpha. It I multifunctional molecule that effects ranging from inflammation, immunity and haemopoiesis.IL-1 has diverse activities and roles in immunity, inflammation, tissue breakdown, and tissue homeostasis [11, 12].

Interleukin 1 (IL-1), is a proinflammatory multifunctional cytokine, which among its many logical activities enables ingress of inflammatory cells into sites of infection, promotes bone resorption, stimulates eicosanoid (specifically,PGE-2) release by monocytes and fibroblasts stimulates release of matrix metalloproteinases that degrade proteins of the extracellular matrix and participates in many aspects of the immune response [13]. Interleukin-1 levels in general are elevated in both tissues and GCF from diseased [12, 13]. The predominant form in the periodontal tissues is IL-1 alpha, which is produced primary by macrophages. [14].

Release of interleukin-1 beta by epithelial cells, monocytes, macrophages and resident fibroblasts, is accompanied with increased production of prostaglandin E-2, induce osseous resorption by osteoclasts. IL-1 and TNF-alpha increase the production of PGE-2 by epithelial cells, monocytes and fibroblasts. These products can subsequently trigger degradative pathways such as a matrix metalloproteinase (MMPS), plasminogen–depended, and phagocytic polymorphonuclear serine proteinase pathways. The examination of Armitage and Ofenbucher show that MMPS are highly expressed in gingival cervical fluid [15, 16]. MMPS are released in an attempt to kill bacteria: nonetheless, these enzymes end up destroying collagen fibers of the periodontal ligament and gingiva, leading to an apical migration of the junctional epithelium. Hence, pocket form atom the root surface, as the coronal portion of the gingiva separates from the root surface due to these inflammatory events.

3. TNH – ALPHA

TNF-alpha was first described in 1975 by *Carswell et al.* for its cytotoxic activity to tumor cells via immune cells and educed was named TF[18]. it is expressed as a type 2 trans membrane protein (mbTNF-alpha), but can be cut to its soluble forms (sTNF-alpha), with increased biological activity. the enzyme responsible for its cutting is TNF converting enzyme (TACE) or ADAM 17. the membrane bound mb TNF-alpha has a 233 amino acid sequence, Weights 26 K Da and forms homo trimers, the main supple of tNF-alpha are macrophages and many other cell such as neutofils and endothelial cells have been described to produce TNF-alpha. targets for TNF-alpha include two type 1 transmembrane receptors, TNF receptors1 and two TNF receptors 2 where's TNF 1 is expressed on every cell except erythrocytes TNF-2 is found only in endothelial animal cells. The clinical study including 34 patients with at least 20% burn surface area, it was shown that systemic TNF levels correlated with burn severity and predicated aspectability to infection. [20]. In general TNF-alpha surpasses osteoblast activity and some stage of differential and simulate osteoclast proliferation and differentiation. Similar to IL-6 tif alpha can regulated bone metabolism to the endocrine way.

Tumor necrosing factor (TNF-alpha), is involved in normal inflammatory and immune response. In both autocrine and paracrine inducer of other cytokines like IL-1, IL-6, IL-8, and plate let derived growth factor-B, eicosanoids platelet activating factors and granulocyte monocyte colony stimulating factor. TNF is secreted by macrophages, monocytes, neutrophils, T-cells, Natural-Killer–cells (NK-cells) following there stimulation by bacterial lipopolysaccharides. Cells that are expressing CD-4, secreted TNF-alpha, while CD-8+ve secreted little or no TNF-alpha. Besides the direct effect on the pathogenesis of periodontal diseases, TNF- alpha up regulates the production of other classic proinflamatory innate immune cytokines, such as IL-1B and IL-6 [20, 21].

TNF- alpha can synergized with RANK-L in promoting osteoclastogenesis. Further studies show that TNF-alpha activates C-Jun, NF-kB and calcium signaling leading to NFAT-CL-activation and thus osteoclast differentiation independent of RANKL in human macrophages [22]. TNF-alpha plays a central role in inflammatory reaction, alveolar bone resorption and loose of connective tissue attachment [23]. It is known to be associated in local and systemic inflammation involving bone loose. It is present at high levels in diseased periodontal tissues, where it is positively correlated with RANKL expression [23, 24].

Experimental models of periodontitis are primates demonstrate that local injection of TNF- alpha antagonist reduce the appearance of inflammatory cells in the alveolar bone and the formation of bone resorbing osteoclasts. There studies show spontaneous osteoclast formation and increased bone resorption from circulating PBMCs of periodontitis patients correlating with high levels of TNF-alpha and RANK-L [25, 26]. As a result of the innate immunity response, TNF- alpha is locally produced by neutrophils, which exhibits increased chemotaxis production of proinflammatory [27]. Macrophages represent an important source of TNF- alpha, that, under dysregulations contribute to host tissue destruction.After antigenic stimulation; naïve CD-4+T-cells activate, proliferate and differentiate into distinct effector cell subset characterized by their specific cytokine. This Th-1 lymphocytes subset is characterized by the secretion of TNF- alpha. TNF-alpha contributes to periodontal damage by its direct effect on osteoclastogenesis and by amplification of inflammatory immune reactions. Furthermore, in into data demonstrate and effect of TNF- alpha not only on osteoclasts, but also on osteoblasts by inhibiting differentiation and bone nodule formation [27]. TNF-beta is commonly known as a lymphotoxin. TNF and IL-1 have effects at three different levels: metabolic effects; vascular effect and endocrines pyrogens.

Interleukin-6(IL-6)

IL-6 is shown to play important note in autoimmune decease bacterial infections and metabolic site effects have been observed also. interestingly, IL6 was first described for its effects on adaptive immunity, promoting cluster od differentiations CD-4+ t-cells IL-21 production, and promoting t cells differentiations toward helper 2 cells and t17 cells.

The reason for using IL-6 as a biomarker plays central role inactivating and maintaining inflammatory response. however, unfortunately it is inflammatory properties are so far neglected in clinical practice. while early inflammation is dominated by neutrophils, later stages of inflammations are dominated by monocytes. IL-6 along with IL-1 and TNF-alpha is a major immune inflammatory mediator. It is a pleiotropic cytokine influencing immune responses. One action of Il-6 and B-cells is the increased secretion of Ig M. It also induced T-cell proliferation.

Interleukin – 8 (IL-8)

Il-8 is known for its effects on neutrophils, specifically, its ability to act as a chemoattractant for them. Thus cytokine secreted by many cells, such as monocytes, lymphocytes, fibroblasts and endothelial cells. It induces the adhesion of PMN to endothelial cells and their transendothelial migration, as well as the release of granule enzymes from these cells.

Macrophage migration inhibitor factor (MIF)

MIF is usually efficiently involved in the adaptive immune response through favoring Th1 activation and differentiation. It plays crucial roles in the recruitment of activation of macrophages as well as in helping to kill bacteria. It is also know as a glycosylation inhibiting factor (GIF). MIF plays a major role in innate immunity against bacterial infections through enhancement of TNF-alpha secretion, toll-like receptor 4, (TLR4) expression phagocytosis and intracellular killing mechanisms and is equally efficiently involved in the adaptive immune response through favoring Th 1 activation and differentiation.

b. Cytokines with predominant immune-regulatory functions:

In this group of cytokine are: interferon, Interleukin 12 and interleukin 18.

Interferons:

Antiviral effects of interferons are not specific. Interferon alpha and interferon beta, are produced by leucocytes and fibroblast, after challenge with viruses. Interferon- gamma is a polypeptide with 166 amino acids. And it has a wide range of effects. IL-beta induced an increase in the expression of cyclic adenosine monophosphate on the cytoplasmic membrane of endothelial cells egress from the vascular bed. Large number of T-lymphocytes will thus exist in the

vascular bed in areas with hypersensitivity reactions. Interleukin N- gamma has most important effects to activation of monocytes.

Interleukin - 12

Interleukin 12 (Il 12) is an important regulatory cytokine, that has a function central to the initiation and regulation of cellular immune responses. IL-12 is produced by: macrophages, monocytes, dendritic cells and beta cells in response to bacterial products. He is responsible primarily for the production of IFN-gamma and TNF-alpha from both NK cells and helper T-cells [28, 29].

Interleukin -18

It is a recently discovered interleukin, reflecting is major biological role. In many respect it is similar to IL-1, IL-12, IL-18.

c. Cytokine that regulate lymphocyte growth, activation and differentiation.

In this category are: IL-2, IL-4, IL-5, IL-12, IL-15 and transformation growth factor B (TGF-B).

IL-2

It is important for the proliferation of T and B lymphocytes. The receptors of this cytokine are a heterotrimeric protein complex whose gamma chain is also shared by interleukin (IL4) and interleukin 7 (IL 7). IL 2 is also necessary during T-cell development in the thymus for the maturation of a unique subset of T-cells that are termed regulatory T-cells.[30]

IL-4

It is an important factor affecting both T and B cells. It is through IL-4, plays a major role in T-cell development. IL 4 can also act as a mast cells growth factor. IL 4 exerts different effects on B-cells at different stage in the cells cycle. On resting B-cells, IL 4 acts activating factor, inducing them to enlarge in size and increase class II MHC expression. Following activation by an antigen or mitogen<IL4 acts as a growth factor, driving DRNA replication in the B-cells [31].

IL-5

It is known for its activity on B-cells and eosinophiles. It is produced by T-helper-2 cells and mast-cells.

IL-12

It has the capacity to regulate the differentiation of naïve T-cells into TL1 cells. It is produced by macrophages, monocytes, dendritic cells and B-cells in response to bacterial products and intracellular parasites. IL-12 is responsible primary for the subsequent production of TNF-gamma and TNF-alpha from both Nk cells and helper T-cells [26].

IL-15

IL-15 regulates T-cells and NK-cell activation and proliferation. This cytokine and interleukin 2 share many biological activities. They are found to bind common hematopoietic receptors subunits and may compete for the some receptor, and thus negatively regulate each other's activity. The number of SD-8+memory cells, is shown to be controlled by a balance between this cytokine and IL-2.

d. Cytokines that help hematopoiesis

These include: granulocyte-monocyte colony-stimulating factor (GM-GSF),

Interleukin 1 (IL-1), Interleukin 3 (IL-3), Interleukin 6 (IL-6), Interleukin 7 (IL-7).

Thus cytokines stimulated production of new blood cells by acting of hematopoietic progenitor cells. It released by activated T lymphocytes, bone marrow, monocytes, fibroblasts, osteoblast and vascular endothelial cells.

T-Lymphocytes and monocytes

Alpha chemokines: Interleukin 8 (IL 8)

f. Chemokine are a broad and loose category of small proteins that are important of cell signaling. Chemokine can also be involved in autocrine signaling. There are released from lymphocytes and monocytes stimulated with TNF alpha or IL-1In function as a chemotactic and activating factor for granulocytes, the cell population with the highest

level of IL-8 receptor expression. IL-8 recruits granulocytes to areas of inflammation and increasing their phagocyte and pro-inflammatory abilities. It has also been demonstrated to be chemotactic for T- lymphocytes.

Beta chemokines;

In this group are included four major cytokines:

i. RANTES, released by T-cells

ii. Macrophage chemotactic proteins

iii. Eotaxin, chemokine induced by IL-4 that recruits eosinophils and TH 2, CD41 T cells to the sites of inflammation.

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