Review Article
Advancements in Life Sciences – International Quarterly Journal of Biological Sciences

ARTICLE INFO

Date Received: 16/10/2022;
Date Revised: 27/12/2023;
Available Online: 31/03/2024;

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How to Cite:
Al-Ghurabi BH, Mahmood MA, Aldhaher ZA (2024). Immunomodulatory Role of Cytokines in Periodontal Disease. Adv. Life Sci. 11(2): 670-681.

Keywords:
Periodontal Disease; Cytokines; Inflammation; Immune Response

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Immunomodulatory Role of Cytokines in Periodontal Disease

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Abstract

Periodontal disease is an inflammatory condition that affects the periodontium and results in the destruction of periodontal tissue. Cytokines are small, non-structural proteins with inferior molecular weights which have a intricate organizational effect on inflammation and immunity. Immune reaction against products of bacteria and the resulting generation of inflammatory cytokines, are significant contributors to periodontal tissue injury. In this disease inflammatory cytokines are generated by immune cells to attack the periodontal bacteria. A persistent or strong immune response may cause inflammation and the creation of cytokines that are essential in the development of periodontitis, even though the immune response can defend an organism from a variety of diseases. Clarifying the immunomodulatory role of cytokines in periodontitis was the main goal of this review. Using suitable keywords, relevant papers would be searched in the scientific databases Scopus, Google Scholar, PubMed, and Web of Science. In conclusion cytokines are control and modulate the immune response in periodontitis. Covered studies were posted between 2000 and 2023 and detect great variance in patients selection, clinical assessments, and cytokines measures. A significant association between cytokines and periodontitis developments was reported in some studies. Cytokines are control and modulate the immune response in periodontitis

Introduction

A group of infectious, inflammatory oral diseases known as periodontal disease impact the periodontal structures of the tooth. Progressive tooth loss and destruction come from the breakdown of the synergistic interaction among the bacteria in the mouth and the immune reaction. It is distinguished by times of microbiological aggravation followed by times of recovery [1]. Heterogeneous periodontitis is distinguished by the gradual loss of bone and eventual decay of teeth. It starts with microbes and spreads because of environmental conditions [2]. Microorganisms and their metabolites cause the host immune system to become activated, which releases cytokines and other proinflammatory biomarkers that cause tissue damage. The interplay between bacterial biofilm and immune reaction, which is predominantly controlled by cytokines and chemokines of permanent and emigrant cells in the region of inflammation, determines the course of periodontal disease [1,3].

Cytokines are soluble proteins that cells release in order to communicate with other cells. They have the ability to govern cellular development and differentiation, thereby as well as mediate and control immunological and inflammatory responses [4]. A growing variety of illnesses, including periodontitis, are characterized by a central role for cytokines in their development. They are essential inflammatory mediators involved in the development, progression, and host modulation of periodontitis [5, 6]. Immune and inflammatory responses are initiated, maintained, and amplified in part by cytokines [7]. They play intricate and perhaps conflicting roles in the immune system. Based on their overall function, they can be categorized into pro- and anti-inflammatory groupings [8]. It has been proven that pro-inflammatory groups have a significant part in the development of periodontitis. As a result of an infection or injury, they cause inflammation [9]. Pro-inflammatory cytokines' activity and synthesis are restrained by anti-inflammatory cytokines [10]. Therefore, this study was established to clarify the immunomodulatory role of cytokines in periodontitis.

Methods

Literature search and selection criteria

Using keywords like "periodontal disease, periodontitis, cytokines, immune response regulation," relevant papers would be searched in the scientific databases Scopus, Google Scholar, PubMed, and Web of Science.

Discussion

Periodontal Disease

A group of infectious, inflammatory oral diseases known as periodontal disease impact the gum tissues of the teeth. Chronic tooth loss and destruction come from the breakdown of synergistic interaction among the bacteria in the mouth and the immune reaction. It is distinguished by times of microbiological aggravation followed by times of recovery [1]. Periodontal disease is typically divided into two categories: gingivitis, an intense, treatable infection limited to the gum tissues, and periodontitis, a more severe, permanent, and damaging condition [12]. Severe gum pockets, loss of the ligament and cement connection, and erosion of the alveolar bone are all signs of periodontitis, which ultimately results in the loss of teeth [13].

A bacterial illness known as periodontitis is caused by a variety of microorganisms in the mouth [14] and causes soft tissue pockets to form. Severe cases of periodontitis can result in bone loss and tooth movement. Although the presence of germs is necessary for periodontal disease to develop, a susceptible host is also crucial. Although the host's inflammatory response is a protective response, both hypo- and hyper-responsiveness can cause progressive tissue death [15]. Advanced periodontal disease is defined by the development of pathological periodontal pockets and the breakdown of the periodontal ligament fibers that link teeth to the alveolar bone. Advanced periodontal disease is caused by a prolonged microbial attack that induce ongoing infection in the periodontal tissues [16]. Therefore, inflammatory reactions are crucial in the emergence of chronic periodontitis [17].

Host Immune Response in Periodontal Disease

Both types of immune responses are engaged in immunological response of host during periodontitis, which causes persistent inflammation and extensive loss of tooth-supporting tissues [18]. The interaction between the bacteria and the immune response, comprises a complex network of cells and humeral elements of the system of immunity, determines the extent and severity of periodontal disease. As a result, host defense mechanisms trigger innate and adaptive immune responses [19]. The innate defense mechanism relies on neutrophils, which can recognize, move toward, and engulf microorganisms through phagocytosis before killing them, like macrophages. These cells also play the role of producing and secreting molecules that are biologically active throughout the bloodstream. The mediators include cytokines, and chemotactic lipids, that operate as a guide for some blood cells to move to the areas of infection and participate in the damage the microorganisms. These include polymorphonuclear

leukocytes, natural killer cells, eosinophils and monocytes.

By means of toll-like receptors (TLRs), which are expressed by host cells in the contaminated microenvironment, this form of immune response recognizes the presence of microorganisms. The PAMPs specific to microbial classes bind to and stimulate particular TLRs [20], permitting the human body to learn more about the traits of the invasion microbe through the ensuing promotion of distinct engagement cascades which change the amounts of TLRs, cytokines, and biomarkers of inflammation. The characteristic's pathogens with host defenses that contribute to illness parthenogenesis are revealed by changes in TLR and cytokine expression in tissue [21].

The formation of antigen-specific T and B cells, as described by Alexandrina [22], is the first step in the specific immunity. T cells then transform into functional T cells, that release various kinds of cytokines to kill the targets, whereas B cells emit immunoglobulins, that kill foreign microorganisms. The first cells to be impacted by periodontitis are the cells of epithelium. The contact cause causes the inflammation that occurs and promote connective tissue cells and PMN in the gingival crevice. The engaged cells are producing Interleukins; IL-1, IL-6, IL-8, and TNF-. Periodontitis is caused by a disparity among the immune defense and the microbe. Furthermore, the epithelia cells will stimulate the local host cells (macrophage, fibroblast, and mast cells) to secret pro-inflammatory cytokines "IL-18, IL-6, IL-12, TNF-", PGE2 , histamine, chemotactic molecules, and MMPs that cause damage collagen from connective tissue. Leukocytes is going through the cells and arrive at infected area whereby destroy of pathogen take place as a result of leukocyte extravasation caused by endothelium activation [23].

Cytokines

Cytokines are tiny proteins which have a crucial role in the transfer of signals among cells, as well as in cell interactions and actions. Interleukins, interferons, and the tumor necrosis factor family are a varied set of low-molecular-weight protein molecules with significant biological functions for regulating the amplitude and duration of immune responses. Furthermore, the family of chemokine has lately evolved has distinct category having functions resembling several interleukins. In addition, a variety of substances that weren't previously assumed to be cytokines have been shown to be cytokines due to the way they work that modulating immune reaction, such as growth factors like TFG-b and adipocytokines [24].

The genetic control that leads to the production of proinflammatory cytokines by a number of cells is usually reliant on NFkB transcriptional activity. PAMPs such as LPS activate the NFkB-regulated systems via the TLR axis [25]. Cytokines promote natural immunity, which protects the tissues of the host immediately as well as communicate acquired antibody and cell mediated immunity. Actions of these biomarkers to produce harming infection in the midst of continuous bacterial excitation are among the most essential features in the etiology of periodontitis [24]. During the immediate and initial persistent stages of inflammation, resident cells such as epithelial cells and fibroblasts release cytokines, as do phagocytes (neutrophils and macrophages) and lymphocytes in entrenched and major lesions [26]. Lymphokines "cytokines released by T cells that control the immune reaction)", pro-inflammatory cytokines "cytokines which enhance and sustain the inflammation pathway", growth factors "encourage cell viability and lead to alteration in structure of airways", chemokines "They are chemotactic for inflammed cells", and anti-inflammatory cytokines "which are adversely impact the inflammation process) are four types of cytokines [27]. TNF-, IL-1, IL-2, IL-6, IL-8, and TNF- are all proinflammatory type. Proinflammatory cytokines boost killing of bacteria, attract fresh non-specific immune cell types to area of infection, enhance dendritic cell development, and direct the resulting specific immune reaction to invader pathogens. Whereas others that inhibit inflammation such as IL-4, IL-10, and IL-13 prevent or at least reduce the strength of the cascade [28].

Cytokines in Periodontal Disease

Interleukins and interferons are examples of cytokines that are immunomodulating agents. Although bacterial infection has generally been the focus of periodontitis pathogenesis, research in immune reaction mechanisms caused gum disease was grown in the last several decades. An immediate inflammatory reaction which engages the non-specific immune response was the earliest reaction to infection by bacteria. The increased expression of this originally limited activity results in the synthesis of several cytokines and other mediators, as well as the spread of inflammation throughout the gum tissues [29]. Unable for protect that "inflammatory attack" in gum tissue causes the response with spread to the alveolar bone. Inflammation then destroys connective tissue and alveolar bone, that is the hallmark of gum illness [30].

To attain critical quantities of inflammatory mediators leading to bone resorption, pro-inflammatory cytokines like IL -1, -6, -11, and -17, TNF, and M oncostatin must be produced [31, 32]. Kinins including bradykinin, thrombin, and other chemokines can also stimulate bone resorption. This is

in contrast to the anti-inflammatory cytokines along with other molecules such as IL-4, -10, -12, -13, and -18, plus interferon-beta (IFN-b) and gamma (IFN-g), decrease bone repair [33]. CD4 T helper cells (Th0) interact with antigen-presenting cells, they differentiate into several subsets, including Th1, Th2, Th17, and regulatory T cells (Tregs), based on the cytokines they produce. In the presence of IL-12, Th1 initiates the immune response mediated by cells and produces interferon- (IFN-), transforming growth factor- (TGF-), interleukin-2 (IL-2) and TNF. In the presence of IL-4, Th2 promotes the humeral immune response by producing IL-4, IL-5, IL-6, L-10, IL-13, and TGF-. The remaining CD4 T cells, Th17 and Tregs, play an important role in autoimmunity and the maintenance of immunological homeostasis. In the presence of TGF-, IL-1, and IL-6, the TH17 subset secretes IL-17, IL-23, IL-22, IL-6, and TNF, whereas Tregs arise in the presence of TGF- and generate immunosuppressive IL-10 and TGF- β [34]. IL-17, in particular, increases the synthesis of inflammatory substances such as TNF, prostaglandin E2 (PGE2), IL-6, and IL-1, increasing bone resorption via osteoclast activation. Changes in immune system regulation by Treg cells, which are known to mediate inflammation resolution, are thought to have a role in the development of various autoimmune disorders [35, 36].

A research involving experimental periodontitis on the Macaca fascicular is monkey model revealed that cytokines that promote inflammation play a part involved in the spread of the inflamed reaction to bone proximal areas. Silk ligatures embedded with *Porphyromonas gingivalis* have been placed to the mandibular posterior teeth in this animal model to generate experimental periodontitis. For 6 weeks, primates were given local injections of TNF- and IL-1 antagonists (soluble TNF- and IL-1 receptors). In control primates, examination of oral tissue samples in the close proximity of the bone revealed considerable migration of cells associated with inflammation, development the osteoclasts around the bone. Cytokines, chemokines, and other agents activate periostal osteoblasts during an inflammatory response by modifying the production amount of a molecules termed factor-kappa B (RANKL) receptor activator on the osteoblast surface. Osteoblasts express RANKL as a protein membrane bound or as a soluble form. RANKL is produced by a variety kind of cells, like fibroblasts, T and B lymphocytes, in addition to osteoblasts. RANKL is produced at a tiny amount in fibroblasts, but it increases due to toxic chemical produced by *Aggregatibacter actinomycetemcomitans* [37].

Conclusion: Cytokines are control and modulate the immune response in periodontitis.If future research makes the link between cytokines and periodontitis clearer, a simple, cheap, and safe new way to prevent and treat periodontitis would become available.

Author Contributions

Al-Ghurabi BH. conceived of the presented idea. Mahmood MA and Aldhaher ZA. developed the theory and performed the computations. Al-Hindawi SH. verified the analytical methods. All authors discussed the results and contributed to the final manuscript.

Conflict of Interest

The authors declare that there is no conflict of interestregarding the publication of this paper.

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