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LITERATURE REVIEW

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Insights on the role of cytokines in carious lesions

Insights sobre o papel das citocinas em lesões cariosas

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ABSTRACT

Objectives: The dentin-pulp immune response to caries pathogenesis is still poorly understood due to the complex interplay of the involving processes. The aim of this review was to explore the role of cytokines and its relevance in the pathogenesis of dental caries. **Results:** Dental caries can result in a host inflammatory response in the dental pulp, characterized by the accumulation of inflammatory cells leading to the release of inflammatory cytokines such as Interleukin-4 (IL-4), Interleukin (IL-6), Interleukin-8 (IL-8) and Tumor necrosis factor–α (TNF-α). IL-4 seems to be correlated to the depth of carious lesions; IL-6 is strongly correlated to caries disease and is considered a potent biomarker; IL-8 can be a potent biomarker for both caries and other changes present in the pulp and, its release is correlated to TNF-α and IL-6; TNF-α plays an important role not only in caries progression, but also in other pathological processes. **Conclusion:** Specific mediators have a great potential to serve as biomarkers alluding to the presence and progress of caries disease, urging further investigations in the field.

KEYWORDS

Biomarkers; Cytokines; Dental caries; Dental pulp; Interleukins.

RESUMO

Objetivo: A resposta imune da dentina-polpa à patogênese da cárie ainda é pouco compreendida devido à complexa interação dos processos envolvidos. O objetivo desta revisão foi explorar o papel das citocinas e sua relevância na patogênese da cárie dental. **Resultados:** A cárie dentária pode resultar em uma resposta inflamatória do hospedeiro na polpa dental, caracterizada pelo acúmulo de células inflamatórias levando à liberação de citocinas inflamatórias como, Interleucina-4 (IL-4), Interleucina (IL-6), Interleucina-8 (IL-8) e fator de necrose tumoral–α (TNF-α). IL-4 parece estar correlacionada com a profundidade das lesões cariosas; IL-6 está fortemente correlacionada com a doença cárie e é considerada um potente biomarcador; IL-8 pode ser um potente biomarcador tanto para cárie quanto para outras alterações presentes na polpa e sua liberação está correlacionada com TNF-α e IL-6; TNF-α desempenha um papel importante não apenas na progressão da cárie, mas também em outros processos patológicos. **Conclusao:** Mediadores específicos têm um grande potencial para servir como biomarcadores quanto à presença e progressão da doença cárie, o que incita a necessidade de mais investigações nesse campo.

PALAVRAS-CHAVE

Biomarcadores; Citocinas; Cárie dentária; Polpa dentária; Interleucinas.

INTRODUCTION

Dental caries is one of the most common chronic human diseases worldwide which is multifactorial, biofilm-mediated, diet modulated, non-communicable and dynamic disease. It is determined by a variety of factors such as biological, behavioral, psychosocial, and environmental. As consequence of this process, a carious lesion develops as a result of net mineral loss of dental hard tissues [1-3]. During caries process the pulp immune response is triggered to respond in inflammation [4].

Pulpal tissues are equipped with defense cells and inflammatory mediators that mediate and maintain the host response to microbial infection. Odontoblast cells direct response to caries is the release of cytokines and antimicrobial peptides, while indirectly causing the migration of immunocompetent cells such as cytokines [4].

Cytokines are products of activated monocyte–macrophage cells that may play an important role controlling the inflammatory response to bacterial infection contributing to the initiation and progression of dental caries [5]. The literature accepts the arrangement of cytokines into major structural families such as chemokines, interferons, tumour necrosis factors, and interleukins [6].

Dental caries process is responsible to trigger a host inflammatory response in the dental pulp, characterized by the accumulation of inflammatory cells leading to the release of inflammatory cytokines such as IL-4, IL-6, IL-8 and TNF-α [6]. Some studies have pointed out that these mediators could be potential targets for therapeutic strategies in the treatment of inflammatory diseases [7]. However, the diagnostic process of caries disease till these days relies on clinical, visual, and radiographic methods, and its inflammatory component remains unexplored, which is a recognized source for diagnosis at the molecular level [6]. Therefore, the role of cytokines in the pathogenesis of dental caries entails further investigation. Accordingly, regarding the importance of the immune system and its components in inflammation of the dental tissue, this review was designed to explore the role of cytokines and its relevance in the pathogenesis of dental caries.

DENTAL CARIES

Nowadays, dental caries is defined as a result of dysbiotic changes in the oral biofilm community with predominant acid-tolerant and acid-producing microbiota and low levels of beneficial bacteria mainly mediated by frequent intake of fermentable sugars and carbohydrates [3,8].

The dynamic caries process consists of rapidly alternating periods of tooth demineralization which is caused mainly by the action of lactic acid and, remineralization through the buffering action of saliva but, the presence of fluoride can also prevent demineralization. Caries lesions occurs when the demineralization takes place over enough time bypassing remineralization process at teeth surface [9-11].

The enamel barrier disruption makes dentin more susceptible to degradation by Gram-positive bacteria such *as streptococci*, *lactobacilli*, and *actinomyces*, which further becomes the leading cause of pulpal inflammation [12]. The metabolic activity and proliferation of these microorganisms release bacterial components into dentinal tubules and lead to diffusion toward the peripheral pulp. The recognition of bacterial components by host cells such as odontoblasts at the dentin-pulp interface triggers host protective events including antibacterial, immune, and inflammatory responses including the production of pro-inflammatory mediators such as chemokines and cytokines [13,14]. However, the host immune response also plays a pivotal role in tissue destruction [12].

When dentin is demineralized, collagenases are uncovered and activated, playing an important role in caries progression [7]. The progression of caries also induces degradation of the collagen matrix. Host-derived proteolytic enzymes such as matrix metalloproteinases (MMPs) and cysteine cathepsins are activated by low pH. Cysteine-B and -K, and many types of matrix metalloproteinases such as MMP-2, -8, -3 and -9 have been identified in dentin carious lesions [7,15,16]. In addition, host proteases are not only found in dentin but also in saliva [7]. MMPs-8 and -9 are the most predominant salivary MMPs and efficiently degrade exposed dentinal collagen [7,15]. During dentin demineralization as the disease progress, high levels of cytokines and growth factors, such as TNF-α and TGF-β are released [17]. Previous studies have reported increased expression of

different cytokines in caries-affected dental pulp and/or odontoblasts [18].

Despite several studies exploring mediators of the immune response, little is still understood about the impact of cytokines on caries disease because of its complexity. Clearly understanding the role of cytokines and their correlation with caries disease is important to establish useful tools for diagnosis and treatment.

CYTOKINES - IMMUNE AND INFLAMMATORY RESPONSE

Cytokines

Cytokines are classified as soluble proteins with low molecular weight (≈6–70 kDa), secreted by a variety of cells (macrophages, lymphocytes, natural killer (NK) cells, stromal cells, and mast cells) which have a specific effect on communications and interactions between cells. Cytokine is a general name; other names are based on its origin or functions such as lymphokine (generated by lymphocytes), monokine (generated by monocytes), chemokine (cytokines with chemotactic activities), interferons (IFNs), tumor necrosis factors (TNFs), colony-stimulating factors (CSFs), and transforming growth factors (TGFs), and interleukin (cytokines generated by one leukocyte and acting on other leukocytes) [19,20]. Cytokine production can play an important role on health conditions as they are responsible for de dynamic regulation of the maturation, growth, and responsiveness of immune cells [20].

Cytokines can generate and maintain host responses to microbial infection. These molecules are secreted by the host living cells as paracrine or autocrine signals to recruit cells of the immune system (chemokines), proinflammatory cytokines, or anti-inflammatory cytokines [18]. Pro-inflammatory cytokines facilitate inflammatory reactions and contribute to the stimulation of immunocompetent cells, they are interleukin 1 beta (IL-1β), interleukin 6 (IL6), interleukin 8 (IL-8), interleukin 12 (IL-12), tumor necrotic factor-α (TNF-α), and interferons among others. On the opposite side, anti-inflammatory cytokines such as IL-1 receptor antagonist (IL-1RA), interleukin 4 (IL-4), IL-6, interleukin 10 (IL-10), interleukin 11 (IL-11), interleukin 13 (IL-13), and transforming growth factor (TGF-β), suppress immune cells and inhibit inflammation [21]. This classification helps to understand the pathways triggered by the host response in consideration of, a single cytokine may be secreted by different cells and act as shows both anti-inflammatory or pro-inflammatory activities depending on the context, generating multiple immune responses [20].

Cytokines can be classified based on their cellular source as type 1 cytokine response which is produced by a cluster of differentiation 4 (CD4)+ T-helper 1 (Th1) cells and characterized by cell-mediated response, with interferon-γ (IFN-γ), as the typical cytokine in association with interleukin 2 (IL-2), Tumor Necrosis Factor-β (TNF-β) and interleukin 12 (IL-12) and, type 2 which is produced by CD4+ Th2 cells and marked by the production of one or more B-cell activities, with IL-4 being the classical cytokine and an association with interleukin 5 (IL-5), IL-6, IL-10, and IL-13 [20,22,23].

Cytokines are redundant in their activity, because analogous functions can be stimulated by different cytokines. They are often produced in a cascade, as one cytokine stimulates its target cells to make additional cytokines. Cytokines can also act synergistically, additively, or antagonistically as a network (Figure 1) inhibiting or enhancing the action of other cytokines in complex ways [19].

Cytokines, dentin and pulp tissue

An association between the dentin or the pulp and the presence of cytokines is not a newly

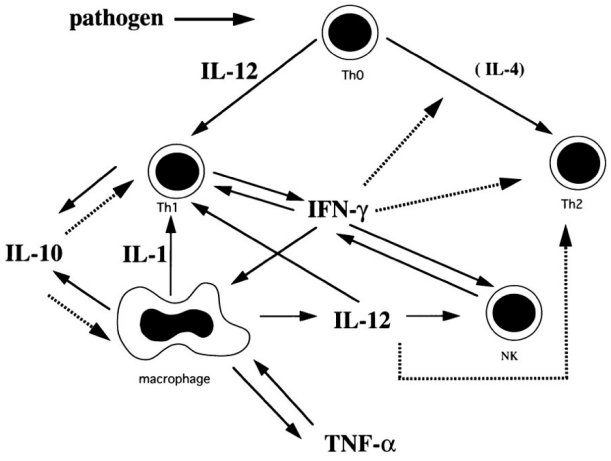

Figure 1 - Cytokine network. When pathogens interact with cells close to the pulpal core, inflammatory events occur leading to increase in the number of different cytokines. During these events, cytokines can play a role synergistically or antagonistically with one another, which lead to enhancement or inhibition of actions of other cytokines. This relationship among the different cytokines (IL-1, IL-4, IL-10, IL-12, IFN-γ, and TNF-α shown in the image) is complex.

observed concept. In 1991, McFarlane and Meikle were among the first to see a relation between cytokine levels and oral diseased conditions [24].

Dentin has been recognized as a bioactive matrix which stores numerous collagenous and non-collagenous proteins. Growth factors and cytokines in dentin have been also identified in several studies. These studies reveal dentin as a source of signaling molecules and highlight dentin's bioactive ability to regenerate tissues following injury [25]. During an inflammatory response complex, biological and biochemical processes are involved with cells of the immune system. Biological mediators such as cytokines also play an extremely important role in mediating the process of inflammation [26]. In 2004, a study conducted by Silva et al. [27] evidenced that the release of dentin-derived bioactive factors resulting from exposure or destruction of dentin matrix could contribute to chemotaxis and aggregation of inflammatory cells, and determine the maintenance or resolution of the inflammatory process. They demonstrated that dentin factors orchestrate at least one part of the scenario, favoring building or destruction of the tissue. Some of these biologic mediators show potential for clinical use in areas such as periodontology and restorative dentistry. This led to speculation that the physiological and natural biochemical properties of dentin could be exploit for the development of novel treatment modalities and diagnostic technologies [12].

Pulpal fibroblasts synthesize and secrete the pulpal collagen matrix and, also produce inflammatory mediators in response to caries-related bacteria. Dendritic cells exist underneath the odontoblast layer and are known to increase during carious challenge to identify foreign bodies for immune cells [28,29]. When bacterial infection is present, the invading pathogens and their products or components, and the dentin matrix constituents secreted during demineralization are first encountered by odontoblast cells located at the periphery of the pulp. As bacterial infection invades the underlying dental tissue and deeper, pulpal inflammation exacerbates, becoming more intense and prevalent. This is characterized by elevated pro-inflammatory gene expression and concurrent elevation of immune cell infiltrates. In addition, the dentin matrix contains a complex variety of pro- and anti-inflammatory molecules. Furthermore, increase in the number of immune system cells that infiltrate the pulp (such as lymphocytes, neutrophils, macrophages, and plasma cells) is shown with further progression of the lesion [30].

Odontoblasts protect the underlying dental tissue against the bacterial invasion, functioning as a barrier [31]. The cells are immunocompetent and have the ability to orchestrate an inflammatory response [32]. As the bacterial infection progresses into deeper underlying dental tissue, changes in the bacterial biofilm composition are seen, and destructive effects on the host cells such as pulpal cell deaths may occur [33]. Thus, further progression of molecular interactions between the cells and pathogens close to the pulpal core results in an aggravation of inflammatory events. In such events, the increase of some cytokines (both pro- and anti-inflammatory) such as IL-1β, IL-2, IL-4, IL6, IL-8, IL-10, IFN-γ, tumor necrotic factor-α (TNF-α), TGF-β1, vascular endothelial cell growth factor (VEGF), C-C chemokine ligand 2 (CCL2), human beta-defensins (hBDs) and CXC chemokine ligand 10 (CXCL10), has been reported to happen [4,18,34].

Expressed in a wide range of host and immune structural cells are the toll-like receptors (TLRs), a class of proteins consisting of cell membrane-bound and endosome-bound receptors [35]. TLRs have regulatory functions in the innate immune system, by recognizing pathogen-associated molecular patterns (PAMPs). Bacterial surface components are TLR ligands; some of them are lipotechoic acids, flagellin, lipopolysaccharides, lipoproteins and peptidoglycans. Other ligands detected by toll-like receptors are nucleic acid ligands originating from pathogens. Following the invasion of the underlying tissues, TLRs-1, -2, -3, -4, -5, -6, and -9 are expressed on pulpal fibroblasts and odontoblasts and further bind to the bacterial components. The binding stimulates activation of the nuclear factor kappa B (NF-κB) intracellular signaling pathway, which is responsible for molecular inflammatory response regulation [34]. In fact, a number of cellular signaling pathways are active during inflammation. In response to nuclear factor kappa B signaling pathway, cytokines and chemokines are released as potent signaling proteins. Cytokines and chemokines regulate inflammatory and immune responses and functions via detection and binding of specific membrane-bound receptors. Furthermore, through second messenger signaling systems, these molecules act to modulate biochemical responses and gene expression in target cells [36].

In fact, cytokines are the modulators of the immune and inflammatory response and other factors [12]. Therefore, cytokine measurements are important as these proteins can be widely used as biomarkers [4]. The analysis of cytokines levels in various biological fluids such as serum, blood, stool, saliva, and sweat, provides valuable information regarding the diagnosis, stage, and prognosis of various diseases, which makes possible to understand and predict disease progression and monitor the effects of treatment [20,37], including oral diseases such as caries [38].

Cytokines and dental caries

The inflammatory and immunological response of the dentin-pulp to caries is complex and initiates acute and chronic activation of the innate immune responses leading to pulpitis. This process involves several factors that can lead to increase levels of cytokines. Some studies have shown that cytokines can contribute to initiation and progression od dental caries. However, their role in the pathogenesis of dental caries still not totally understood [5,14].

The progress of carious infection into pulp-dentin can affect the microflora composition, lowering the proportion of Gram-positive aerobic bacteria and increasing levels of Gram-negative anaerobic bacteria [39]. Consequently, the environment at deep carious lesion becomes more anaerobic and complex with a high bacterial diversity. The odontoblasts barrier can recognize caries-related pathogens, such as *Streptococcus mutans*, which has an important impact on the initial lesion and pulpal pathology, prevails on shallow lesions and, play important roles in the innate immune system of dental pulp tissues [14,40]. Host cells, including odontoblasts and other immune cells, will increase their expression in response to infection. Moreover, components of dentin released by carious bacterial acids during the demineralization process can contribute to the increasing levels of inflammatory mediators [13,41].

Several previous studies have shown increased expression of various cytokines in caries-affected dental pulp and/or odontoblasts including IL-1β, IL2, IL-4, IL-6, IL-8, IL-10, IL11, IFN-γ and TNF-α, TGF-β1, and others [13,18,32,34,40,41]. The induction of these cytokines was also shown in odontoblast-like cells and cultured pulp-derived fibroblasts exposed to bacteria or their products *in vitro* [23,40] such as *Lactobacilli* and *Streptococci* microorganisms particularly associated with the development of caries lesions [42].

Some authors have even correlated levels of expression of certain cytokines with the severity of the caries disease [43].

Relevant interleukins in carious process

Several studies have been carried out to explore cytokines as possible biomarkers for caries disease. A biomarker act as an indicator of a normal biological process, a pathological process, or a response to a pharmacological treatment and, provide information about the susceptibility or risk to develop a disease [44].

Cytokines acts modulating the immune and inflammatory response among other factors therefore, can help to diagnose and monitor several oral cavity diseases, including caries [12,38]. Among these studies, some cytokines draw attention with great potential as a tool to aid in the diagnosis of caries such as IL-4, IL-6, IL-8 and TNF-α and, seems to be correlated to each other (Table I).

The evidence of increasing levels of IL-4 in deep carious lesions associated with a close association between IL-4 and IL-6 expression shed light on the importance to better investigate the role of IL-4 in caries [54,55]. The TNF- α and IL-6 are considered key mediators of acute inflammation. Higher levels of the TNF- α and IL-6 can lead to a lower number of fibroblasts and osteoblasts that contributes in the demineralization process of teeth and development of caries disease [6,45] IL-8 and TNF-a play an important role in immunity of the oral cavity [50] TNF-α is an effector cytokine and its production leads to oral diseases besides. Moreover, it is a stronger inducer of interleukin-8 [45]. According to ElSalhy et al. [46], the ratios of IL-6/IL-10 and IL-8/IL-10, and levels of IL-8 have the potential to indicate pulpal inflammation in caries exposure cases.

Interleukin-4

Interleukin-4 is an important cytokine that is responsible for the secretion of other cytokines. It functions as a potent regulator of immunity secreted primarily by mast cells, Th2 cells, eosinophils and basophils [56,57].

Among several interleukins, IL-4 has a significant influence on shaping immune responses.

Table I - Cytokine expression during caries progression

Study	Objective	Method	Key findings
Hahn et al. (2000) [40]	Evaluated the hypothesis that cytokines induced by antigens from *Streptococcus mutans* could play a major role in inducing the initial T-cell response in the pulp	Examined *S. mutans* ability to elicit cytokines by stimulating T cells and analyzed the presence of cytokines in dental pulp at mRNA level	Inflammatory cytokine mRNAs (IL-4, IL-10, IFN-γ) were identified in dental pulp. All three cytokines of different frequencies- IFN-γ (67%), IL-10 (29%), and IL-4 (19%) - were observed in shallow caries. However, there was no differences in the frequencies of cytokines in deep caries. The presence of *S. mutans* correlated with the IFN-γ levels in the pulp.
McLachlan et al. (2004) [41]	Examined the expression levels of potential molecular mediators for pulpal inflammation, and correlated the levels with oral disease severity	Semi quantitative reverse transcriptase PCR analysis was used to examine the pulpal tissue samples of S100 family members, multiple cytokines and ENA-78	In carious teeth, significantly positive correlation between the expression of IL-1β and S100A8, between IL-6 and epithelial neutrophil-activating peptide 78 ENA-78), between S100A8 and collagen-1α, and among IL-1β, IL-6, IL-8, TNF- α and ENA-78. Thus, a complex molecular immune response involving many cytokines occurs during caries infection.
Horst et al. (2011) [18]	Examined gene expression profiles of cytokines that are generated in response to caries disease and aimed to build a mechanistic response model and downstream signaling network	Described gene expression profiling of cytokines and related immune components induced in odontoblast layer and pulp of normal teeth. cDNA array analysis was conducted to study the expression levels of cytokines, chemokines and receptors in response to caries in human teeth.	Interleukins, chemokines and receptors were differentially upregulated in odontoblast layer during carious infection. Also, pro-inflammatory cytokines Interleukin-1 alpha (IL-1α), IL-1 β, and TNF-α- were highly expressed in odontoblast layer of carious teeth.
Gornowicz et al. (2012) [45]	Investigated to test the hypothesis that changes in the levels of IL-6, IL-8, and TNF-α in saliva are seen in patients with dental caries	Presence of IL-6, IL-8, and TNF-α were examined in caries and healthy patients through Enzyme Linked Immunosorbent Assay (ELISA)	The results showed a positive correlation between IL-8 and TNF-α. Also, the study indicates that significant increased levels of TNF-α, IL-6 and IL-8 in saliva and dental caries disease.
ElSalhy et al. (2013) [46]	Measured and compared the levels of cytokine molecules TNF- α, IFN-γ, IL-2, IL-6, IL-8, and IL-10 found in pulpal blood from normal pulps, pulps with asymptomatic caries exposure, and pulps with irreversible pulpitis	Blood samples from pulp exposure sites in teeth with normal pulps, those with asymptomatic caries-exposed pulps, and those with irreversible pulpitis were obtained. High-sensitivity ELISA was used to determine their cytokine levels.	High levels of TNF- α, IFN-γ, IL-6, IL-8, and IL-10 were found in teeth with caries-exposed pulps and those with irreversible pulpitis. Teeth with irreversible pulpitis showed higher concentrations of IL-2 and IL-10, and lower levels of IL-8 were found in those with caries-exposed pulps. The IL-6/IL-10 ratio and IL-8/IL-10 were higher in irreversible pulpitis cases. Levels of IL-8 levels and IL-6/IL-10 and IL-8/IL-10 ratios may have the potential to act as indicators for pulpal inflammation in caries-exposed teeth.
Menon et al. (2016) [47]	Evaluated the level of salivary IL-6 in children with early childhood caries (ECC) and to compare its levels before and after full mouth rehabilitation.	Saliva samples were collected from children with ECC prior and 3-month post dental treatment. The salivary IL-6 levels were analyzed using the ELISA method.	High levels of salivary IL6 were found. Full mouth rehabilitation significantly contributed to reducing salivary IL6 levels.
Ribeiro et al. (2018) [21]	Evaluated salivary concentrations of the proinflammatory cytokines- VEGF, TNF-α, and IL-6-, and associated them with sugar intakes, obesity, and the presence of dental caries in mothers and in their children.	Case-control study involving caries-free children and children with early childhood caries (ECC), and their mothers. Salivary levels of VEGF, IL-6 and TNF-α were analyzed.	Children with caries had a 63% higher median salivary VEGF and twofold higher mean IL-6 levels compared to caries-free children. Mothers of children with ECC showed higher mean of salivary IL-6 levels compared to those of children without ECC.
Sharma et al. (2017) [6]	Evaluated levels of inflammatory cytokines in saliva of children with early childhood caries (ECC), in order to assess their potential use as non-invasive biological markers.	ELISA was used to determine salivary concentrations of TNF- α, IL-6, and IL-8 in healthy children and children with ECC, before and after rehabilitative intervention.	The severity of caries disease and the cytokine concentrations were correlated. Significant increase in the TNF- α, IL-6, and IL-8 concentrations may act as indicators as non-invasive, diagnostic and prognostic markers in early childhood caries.
Nazemisalman et al. (2019) [48]	Evaluated the level of TNF-α in saliva and its association with caries in different age groups of adolescents and children.	In this case-control study, 128 children and adolescents were divided to four age groups. In each group, half of the individuals had no decay (control group) and the other half had more than 4 decayed teeth (case group). Salivary level of TNF-α was measured using ELISA.	Decay plays an important role in increasing of TNF-α in non-stimulatory saliva. However, there is no confirming evidence of the direct effect of age on immune function yet.
Giudice et al. (2020) [49]	Evaluated salivary immunoglobulin A (s-IgA) and IL-6 in saliva of children and its correlation to tooth decay severity.	Fifty-nine patients were divided into two groups: caries free and caries active. Saliva levels of IgA and IL-6 were analyzed by ELISA.	Salivary IL-6 levels were significantly higher in children with active caries when compared with the caries-free group, while the s-IgA rate showed no significant differences between the two groups.
Hussein et al. (2020) [50]	Evaluated the level of pro-inflammatory cytokines such as IL-6, IL-8, and TNF-α in the saliva of smokers with dental caries and non-smokers (control group).	Whole saliva from 32 smokers aged 35-46 years with dental caries and 16 healthy subjects were analyzed, to measure IL-6, IL-8, and TNF-α levels by ELISA.	The results indicated links between production of TNF-α, IL-6, and IL-8 in smokers saliva and dental caries disease.
Taso et al. (2020) [51]	Estimated the effect of caries disease and treatment on concentrations of IL-2, IFN-γ, IL-12, Interleukin-17A (IL-17A), IL-13, IL-10, IL-6, IL-5, IL-4, interleukin 22 (IL-22), TNF-α, and IL1-β in gingival crevicular fluid (GCF) of caries affected teeth before (B), 7 (7D) and 30 (30D) days post-treatment and to compare them with concentrations from healthy teeth.	GCF samples were collected baseline as well as 7D and 30D. The biomarker measurement was performed using multiplex flowcytometry.	Significantly higher levels of IFN-γ, IL-1β, IL-2, IL-4 and IL-6 were found in caries affected teeth when compared to healthy teeth. The levels of cytokines post-treatment showed general trend of increase when compared to baseline, that was significant for IL-22 and interleukin 17 (IL-17) at 7D, while IFN-γ was significantly increased at 7D compared to the healthy teeth. At 30D, IFN-γ, TNF-α, IL-17 and IL-4 levels were significantly increased when compared to healthy teeth, while IL-2 levels were significantly higher than baseline levels.
Govula et al. (2021) [12]	To assess and compare the salivary levels of IL-6 in patients before and after caries removal.	A pre-treatment saliva sample was collected. The post-treatment saliva samples were collected. The IL-6 levels were analyzed through ELISA.	After the complete removal of caries and restorative procedures the levels of IL-6 reduced significantly.
Paqué et al. (2021) [52]	Evaluated the potential of protein and salivary bacterial markers for evaluating the disease status in healthy individuals or patients with gingivitis or caries.	Saliva samples from healthy individuals, patients with gingivitis and, patients with deep caries lesions were collected and analyzed for 44 candidate biomarkers.	Computational analysis revealed four biomarkers (IL-4, IL-13, Interleukin-2 receptor alpha chain (IL-2-RA), and eotaxin/CCL11) to be of high importance for the correct depiction of caries. These findings suggest IL-4, IL-13, IL-2-RA, and eotaxin/CCL11 as potential salivary biomarkers for identifying non-invasive caries.
Ramírez-De los Santos et al. (2021) [53]	Evaluated the concentrations of IL-6, IL-8, IL-15, and interleukin 18 (IL-18) in the salivary samples of children with caries and obesity.	Salivary samples of children with normal weight and with obesity were used to measure the cytokine levels via the ELISA technique.	The results of this study suggested that IL-6 has a significant effect on both obesity and caries. However, IL-8 is more related to caries, and IL-15 is more related to obesity.

IL-4 is a protein that has pleiotropic effects on multiple cell types. IL-4 receptor is composed of an α subunit that is associated with IL-4's binding affinity and a γ subunit which also act as a component of other cytokine receptors. When IL-4 binds to its receptor, T cell proliferation and differentiation into helper T cells are induced [55]. Once activated, peripheral $CD4^+$ T cells produce and secrete various cytokines. These cytokines act as autocrine growth/differentiation factors, and consequently, T cells proliferate in number and differentiate into effector cells [55].

Effector helper T (Th) cells can be categorized into subsets according to the pattern of the cytokine secretion. Type 1 Th cells secrete IL-2, IFN-γ, and TNF-α; and Type 2 Th cells produce interleukin 3 (IL-3), IL-4, IL-5, and IL-6 [56]. For instance, Type 1 Th cell functions are essential for cell-mediated immunity; and Type 2 Th cells aid in B cell function and immunoglobulin class switching. The vital immune responses dominated by IL-4 may be reflective of the influences of Type 2 Th cells during microbial infections [58]. As host immune responses are activated, and different cytokines are secreted, Type 2 Th cells produce, among other cytokines, IL-4 and IL-6 [56]. The type 2 immune response promotes B-cell activities, with IL-4 acting as the prototypic cytokine molecule and in association with IL-6 [59]. Therefore, action on Th 2 lymphocytes to secrete cytokines during pulpal inflammation leads to production and increased levels of IL-4 and IL-6, releasing the two pro-inflammatory cytokines within the diseased tissue [60].

IL-4 is considered an inflammatory mediator with a significant increase in the reversible and irreversible stages of dental pulp inflammation compared to normal pulp tissue [61]. Although there are several investigations on IL-6 levels and its link to dental caries, there is limited data in the literature in general on the levels of different interleukins in pulp in association with carious lesions, especially IL-4.

Hahn et al. [40] observed the existence of IL-4, along with IFN-γ and IL-10, in the pulpal carious lesions. Also, it showed that *S. mutans*, which is associated to shallow lesions, promoted minimal induction of IL-4. These findings suggested that there may be a correlation between the level of IL-4 and the depth of carious lesions; in other words, the concentration of IL-4 may act as a differentiator among shallow and deep carious lesions. Paqué et al. [52] investigated the potential protein markers for evaluating the disease status in healthy individuals or patients with gingivitis or caries. They observed that the presence of IL-4 in deep caries lesions was remarkable in comparison to healthy teeth, suggesting that this cytokine can be considered an excellent marker to make distinction among caries, healthy, and gingivitis. Moreover, Taso et al. [51] verified the increased level of IL4 even in the presence of shallow caries lesions.

Although there are several investigations on IL-6 levels and its link to dental caries, there is limited data in the literature in general on the levels of different interleukins in pulp in association with carious lesions, especially IL-4. Therefore, investigations on the expression and/or pathways that lead to the expression of IL-4 in association with carious lesions may render interesting findings on the role of the cytokines in caries process. Not only its association with IL-6 may be indicative of the important role of IL-4, but also its differing levels of expression with regards to the depth of the carious lesions.

Interleukin-6

The human interleukin 6 is a helical-shaped protein composed of 212 amino acids, is a pleiotropic cytokine produced by a variety of nonimmune and immune cells which is responsible to regulate many aspects of the local immune response, such as T-cells and macrophage cells. IL-6 have pro- and anti-inflammatory effects, involved in inflammation response, tissue injury and regenerative processes [12,62]. This cytokine is strongly upregulated in bacteria-challenged inflamed pulps *in vivo* and in odontoblasts *in vitro* upon TLR2 engagement [63,64]. IL-6 has an important role in the differentiation and regulation of T helper (Th)2, Th17, and T regulatory (Treg) phenotypes, and it stimulates the secretion of acute-phase proteins including lipopolysaccharide-binding protein. This cytokine plays an important role accelerating pulpal inflammation and it may also participate in the edema formation by an increase in vascular permeability induced by the intradentinal penetration of Gram-positive bacteria [12,13].

The presence of IL-6 has been correlated to different oral diseases such as oral lichen planus, periodontitis and dental caries [50,62]. Gornowicz et al. [45] showed that the levels of IL-6 were increased in patients with dental caries.

Menon et al. [47] observed that caries activity and poor oral hygiene may increase the level of IL-6 in saliva. Giudice et al. [49] in a clinical study observed high levels of salivary IL-6 in children with active caries in comparison to the caries-free group. In another study conducted by the same research group [62] the authors suggested that low-quality plaque control, plaque accumulation and gingival inflammation can induce an increase of IL-6 levels in gingival crevicular fluid in children. Govula et al. [12] showed that there is a strong correlation between IL-6 levels and the extent and severity of carious lesions and, that the levels of IL-6 reduced significantly after the complete removal of caries and restorative procedure. Taso et al. [51] in controlled split-mouth study observed that caries affected teeth exhibited significantly higher levels of IL-6 when compared to healthy teeth.

The role of Interleukin-6 in caries disease has been extensively studied and the results are promising. The literature has pointed this cytokine as potent biomarker for caries disease since it has shown a strong correlation with pulpal inflammation and immunosenescence with dental caries [10].

Interleukin-8

Interleukin- 8 (IL-8) is considered the prototype molecule in the chemokine class and is classified as an inflammatory stimulant cytokine [50]. IL-8 is synthesized by a vast number of different cells, such as monocytes, macrophages, neutrophils, fibroblasts, T-cells, endothelial cells, and chondrocytes [6,50]. The main function of IL-8 is to attract and activate neutrophils cells [4,6]. IL -8 seems to be involved in processes such as inflammation, immune response control, hematopoiesis, and oncogenesis. This cytokine is synthesized in acute inflammatory response contributing to host defence and persists for a relatively long time at the site of inflammation [65]. IL-8 is normally released, following the cells' stimulation by lipopolysaccharide molecules, early pro-inflammatory cytokines such as TNF-α and interleukin 1 (IL-1) or bacteria. Therefore, can be rapidly synthesized at local sites of inflammation, as one of the most potent cytokines and the main neutrophil chemo-attractant. Moreover, it is speculated that elevated levels of IL-8 lead to stimulation of TNF-α [4,45].

Elevated levels of IL-8 were associated to gingivitis and periodontitis. A systematic review performed by Hirsch et al. [4] correlated the presence of IL-8 to irreversible pulpitis in comparison to normal pulp samples. In regard to caries disease, Ramírez-De los Santos et al. [53] observed the correlation between the presence of IL-8 and caries. Hussein et al. [50] investigated salivary levels of pro-inflammatory cytokines (IL-6, IL-8, and TNF-α) in the saliva of smokers with dental caries and the control (non-smokers) and, they observed a high level of IL-8 in the presence of dental caries. In a study conducted for Gornowicz et al. [45] the saliva cytokines levels in patients with dental caries were investigated, the author observed a high level of IL-6, IL-8, and TNF-α in dental caries in comparison to healthy patients. Sharma et al. [6] investigated salivary levels of inflammatory cytokines in children with early childhood caries in early and severe stages and, before and after restorative procedures and from the healthy controls in order to assess their potential as non-invasive biomarkers. The salivary levels of IL-6, IL-8 & TNF-α were significantly higher in patients before the intervention and got significantly reduced after the restorative procedure. This result indicated that these cytokines are significantly associated with severity of dental caries. Moreover, the authors found correlation among IL-6, IL-8 & TNF-α with each other in both pre-operative and post-operative groups.

Studies indicate that IL-8 can be a potent biomarker for both caries and other changes present in the pulp. It is worth mentioning that many studies correlate the presence of these three cytokines that seem to act in similar situations.

Tumor necrosis factor–α

Tumor necrosis factor–α is a pleiotropic cytokine that stimulates inflammation by leading to recruitment of leukocytes, inducing vasodilation, and stimulating the production of pro-inflammatory cytokines [66]. This cytokine is considered a cell signaling protein involved in systemic inflammation that composes the acute phase reaction and chronic inflammation and immune response. Besides, TNF-α stimulates phagocytes for cellular apoptosis, bone resorption, and the synthesis of IL-1, IL-6, and chemokines [6,67].

TNF-α is a pro-inflammatory cytokine originally discovered as a protein with necrotizing effects in mouse-transmissible tumors. This cytokine has an important role in host defense and inflammatory responses with multiple biologic effects. TNF-α acts on the growth, differentiation, and function

of all cell types and seems to be an integral part of inflammatory and immunological events [45,48].

TNF-α is present in all vital human pulpal tissues it is considered an important cytokine for evaluating the inflammatory process [67]. A previous study [68] showed that irreversible symptomatic pulpitis presented a high concentration of TNF-α which were slightly less in irreversible asymptomatic pulpitis, although healthy samples got the lowest TNF-α concentration.

It is well known that bacterial antigens of caries disease can induce the release of proinflammatory cytokines such as IL-1 and TNF-α which are rapidly produced by activated monocytes/macrophages to recruit neutrophils and monocytes to the site of infection [69]. Gornowicz et al. [45] found an elevation of salivary cytokines such as TNF-α in dental caries patients and, that there is correlation among this cytokine, IL-6, IL-8 in saliva and dental caries disease. Sharma et al. [6] evaluated salivary levels of inflammatory cytokines in children with early childhood caries and found an elevated level of TNF-α and, that the presence of this cytokine is correlated with the severe stage of the caries disease. The study conducted by Nazemisalman et al. [48] concluded that tooth decay plays an important role in increasing cytokine TNF-α in non-stimulatory saliva. In contrary, Hussein et al. [50] observed that the level of TNF-α in the saliva of smokers with dental caries were not significant in comparison to control. However, for Hirsch et al. [4] TNF-α may be a notable objective marker for laboratory determination of the extent of inflammation, which could be useful for caries diagnosis.

TNF-α plays an important role not only in caries progression, but also in other pathological processes [70, 71]. Therefore, further studies should be conducted in order to better understand the correlation of this cytokine with the other mediators present in the carious process.

CONCLUSION

The dentin-pulp immune response to caries pathogenesis is still poorly understood due to the complex interplay of the involving processes. This literature review showed that the presence of IL-4 seems to be strongly correlated with the progress of the carious lesion. Whereas, IL-6, IL-8, and TNF-α are markers of the presence of caries disease. Moreover, the expression of these interleukins are correlated with each other. The latest findings on the role of cytokines on caries process shows that some specific mediators have a great potential to serve as biomarkers alluding to the presence and progress of caries disease, urging further investigations in the field.

Author's Contributions

LLG: Conceptualization. LLG: Methodology. LLG, EK, JFB: Writing – Original Draft Preparation. AP: Writing – Review & Editing. MRB, LA, AP: Visualization. MRB, LA, AP: Supervision.

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