CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187

Available online at: http://www.iajps.com *Review Article*

# IMMUNOLOGY PERSPECTIVE OF DENTISTRY- REVIEW

**[1]Moaaz Alem Fadelelahy, [2]Basem Saad AlGhamdi, [3]Hassan Ahmed Darwish, [4]Nawal Mohammed Alotaibi, [5]Hussain Nasser Almashhadi, [6]Nada Atif Alessa, [7]Afaf Hamid Alharbi, [8]Ahmad Adnan Samara, [9]Ayman Mohammed Alshareef**

[1]General Dentist, ministry of health / PHC Al-nwarya.
[2]General Dentist, Alnawariyah Healthcare Center
[3]General Dentist, Alnawariyah Healthcare Center
[4]Technician-Dental Assistant, Alnawariyah Healthcare Center
[5]General Dentist, Alzaher Healthcare Center
[6]Specialist Dental Assistant, Hera General Hospital
[7]Dental Assistant, Alnawariyah Healthcare Center
[8]General Dentist, Ministry of Health, Taif Dental Center, Taif, Saudi Arabia
[9]General Dentist, Ministry of health , western alhawiya PHC ,Taif ,Saudi Arabia

**Abstract:**
*The early pulpal responses to caries involve a variety of cells and inflammatory mediators. Typically, innate immunity is not specific to antigens but relies on receptors to identify shared chemical patterns seen in germs. This recognition triggers the process of internalizing and eliminating bacteria through phagocytosis. For instance, mannose- and scavenger-receptors are well-established receptors for phagocytosis that are found on neutrophils and macrophages. The recent discovery and analysis of mesenchymal stem cells (MSCs) in dental tissues represents a significant advancement in the progress of novel therapeutic approaches. Mesenchymal stem cells (MSCs) play a crucial role in the restoration of tooth pulp and are vital for the effectiveness of regenerative endodontic treatments. It is crucial to comprehend that immune cells and cytokines have the ability to influence the functionality of stem cells, hence potentially affecting their capacity for healing. However, stem cells possess immunoprivileged properties and possess the capacity to regulate immunological and inflammatory reactions, hence offering potential for enhancing therapeutic outcomes.*

**Corresponding author:**
**Moaaz Alem Fadelelahy,**
*General Dentist, ministry of health / PHC Al-nwarya.*

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*Please cite this article in press Moaaz Alem Fadelelahy et al.,* ***Immunology Perspective Of Dentistry- Review,*** *Indo Am. J. P. Sci, 2023; 10 (12).*

## INTRODUCTION:

The activation of innate immunity occurs when microorganisms first invade. If the initial response is unable to eliminate the insult, the body activates adaptive immunity, which involves cellular (cell-mediated immunity) and specific antibody (humoral immunity) responses. These responses work together to augment the protective mechanisms of the innate immunity. The innate immune system in the oral mucosa is comprised of epithelial barriers, circulating cells, and proteins that prevent bacterial invasion and destroy invading germs by identifying and responding to pathogens or chemicals produced during infection [1,2].

Typically, innate immunity is non-specific to antigens, but instead relies on receptors to identify chemical patterns that are often found in germs. This recognition triggers the process of internalizing and eliminating bacteria through phagocytosis. Neutrophils and macrophages express mannose- and scavenger-receptors, which are well-known receptors for phagocytosis [3].

The innate response of the dentin/pulp complex to caries involves several components, including the following six: the outward flow of dentinal fluid and the deposition of intratubular immunoglobulins; odontoblasts; neuropeptides and neurogenic inflammation; innate immune cells such as immature dendritic cells (DCs), natural killer (NK) cells, and T cells, along with their cytokines and chemokines. While the first two elements are not traditionally considered integral components of innate immunity, they have a distinct role in the early inflammatory reaction to caries (as shown below). The extensive innervation of the dental pulp can impact the immune response through two mechanisms: direct stimulation of immune cells via neuropeptides, and increased vascular permeability, which aids in the transportation and accumulation of immune cells and macromolecules to the inflamed tissue [4,5].

Identifying the exact initiation of the natural immune response in the dentin/pulp complex is challenging due to the typically gradual advancement of carious lesions into the tooth pulp. There is evidence to suggest that adaptive immune responses take place in pulps that are irreversibly inflamed and located less than 2 mm away from a deep carious front. The shift from an inherent to a flexible reaction likely takes place during the advancing stages of reversible pulpitis in the presence of superficial caries [6,7].

Following their synthesis in the bone marrow, immune cells undergo migration to secondary lymphoid organs located throughout the body. These organs vary in their respective functions. The cells in the spleen and lymph nodes respond to antigens that enter the body by the blood, skin, or lymphatic system. The antibodies generated in these locations are mainly of the IgM and IgG isotypes and go throughout the bloodstream. The mucosal immune system comprises immune cell groups that reside in the lamina propria and submucosal regions of the gastrointestinal, salivary, respiratory, and genitourinary systems. The B cells located in these specific areas predominantly generate IgA and IgM isotypes. These antibodies are capable of being produced in forms that are resistant to the degrading enzymes found in mucosal secretions. Antibodies that are generated in the salivary glands are actively released into saliva, where they penetrate the oral cavity and attach to numerous germs. These complexes of antibodies and microbes can subsequently be eliminated and expelled without being taken up by phagocytic cells [8,9]. The oral cavity is safeguarded by cells and antibodies derived from the blood, lymphoid organs, and the mucosal system. Significant modifications in any of these divisions of the immune system can lead to oral illness [10]. The aim of the review is to emphasizes and overview the immunological perspectives in dentistry, including innate immunity and to go through other way of immune response in different types of oral health problems.

## DISCUSSION:

### Innate Immune Cells in the Dental Pulp

The primary intrinsic effector cells found in the majority of tissues consist of neutrophils, mononuclear phagocytes (monocytes and macrophages), and innate lymphocytes such as NK cells. Both T cells and immature dendritic cells (DCs) play a crucial role in immunosurveillance within the tooth pulp, contributing to the innate response against caries. The diagram in Figure 1 depicts potential interactions among innate immune cells, cytokines, odontoblasts, and neuropeptides in the pulps of teeth affected by shallow caries, both in normal conditions and during reversible pulpitis. Neutrophils and macrophages are proficient phagocytes involved in innate immune responses. Neutrophils are not significant in reversible pulpitis as only a small number of neutrophils were found in the pulpal tissues around shallow cavities. Additionally, the dentin acts as a physical barrier that hinders direct interaction between neutrophils and bacteria. However, odontoblasts have been proposed to have a fascinating phagocytic function [12].

Tissue macrophages originate from circulating monocytes and exhibit significant variability, which is regulated by their surrounding microenvironment. For example, alveolar macrophages have a high level of pattern recognition receptors that can induce the production of cytokines. On the other hand, macrophages found in the lamina propria of the gut have strong phagocytic and bactericidal activity but produce fewer proinflammatory cytokines [13]. Activated macrophages are highly efficient at eradicating pathogens in both the innate and adaptive immune responses. They also play a crucial role in maintaining tissue balance by removing senescent cells and facilitating tissue remodeling and repair following inflammation. While the specific traits of macrophages in the normal dental pulp have not been investigated, it has been observed that when mouse macrophages are exposed to LTA, they release VEGF, a powerful stimulator of angiogenesis and vascular permeability. In addition, the quantity of macrophages rises as caries advances and consistently surpasses that of DCs at every stage of caries invasion [14,15]. Thus, it is possible that these macrophages produced from monocytes get activated during the initial phase of pulpitis in order to safeguard the dental pulp. This activation involves enhancing the permeability of blood vessels and eliminating foreign antigens and injured tissues from the affected pulp.

Natural Killer (NK) cells are present in the bloodstream and have the ability to migrate to sites of inflammation in response to inflammatory chemokines. Due to the presence of shared chemokine receptors and the ability to produce chemokines that can attract one other, both NK cells and immature DCs are expected to coexist in inflamed tissues. The interactions between DCs and NK cells can lead to mutual activation and enhanced production of cytokines by both cell types [17]. Natural Killer (NK) cells that have been activated stimulate the maturation of Dendritic Cells (DC) and the production of cytokines. This, in turn, increases the proliferation of NK cells, the generation of Interferon (IFN-), and their ability to kill target cells [18]. Natural Killer (NK) cells play a crucial role in the early generation of interferon (IFN-), which serves to activate macrophages in order to eliminate engulfed microorganisms. Additionally, NK cells selectively enhance type-1 T-cell responses in the adaptive immune system [18]. The existence of NK cells in the tooth pulp may contribute to the elevated occurrence of IFN- mRNA in the pulpal tissue underlying shallow caries lesions, as depicted in **Figure 1** [19].

Due to the high prevalence of S. mutans in first carious lesions, their antigens may be among the first antigens processed by pulpal dendritic cells or macrophages. They have shown that S. mutans efficiently stimulated peripheral blood mononuclear cells to produce significant levels of IFN- and IL-12. Furthermore, the induction of IFN- by S. mutans was dependent on NK cells and IL-12. NK cells and S. mutans-induced type-1 cytokines (IFN-, IL-12) likely contribute to the initiation of the pulpal inflammatory response to caries by triggering a cell-mediated type-1 immune response. In addition, S. mutans has the ability to efficiently convert monocytes into fully developed dendritic cells (DCs) over a 24-hour period in laboratory conditions. This process is believed to have a role in the local development of DCs in inflamed dental pulps [20].

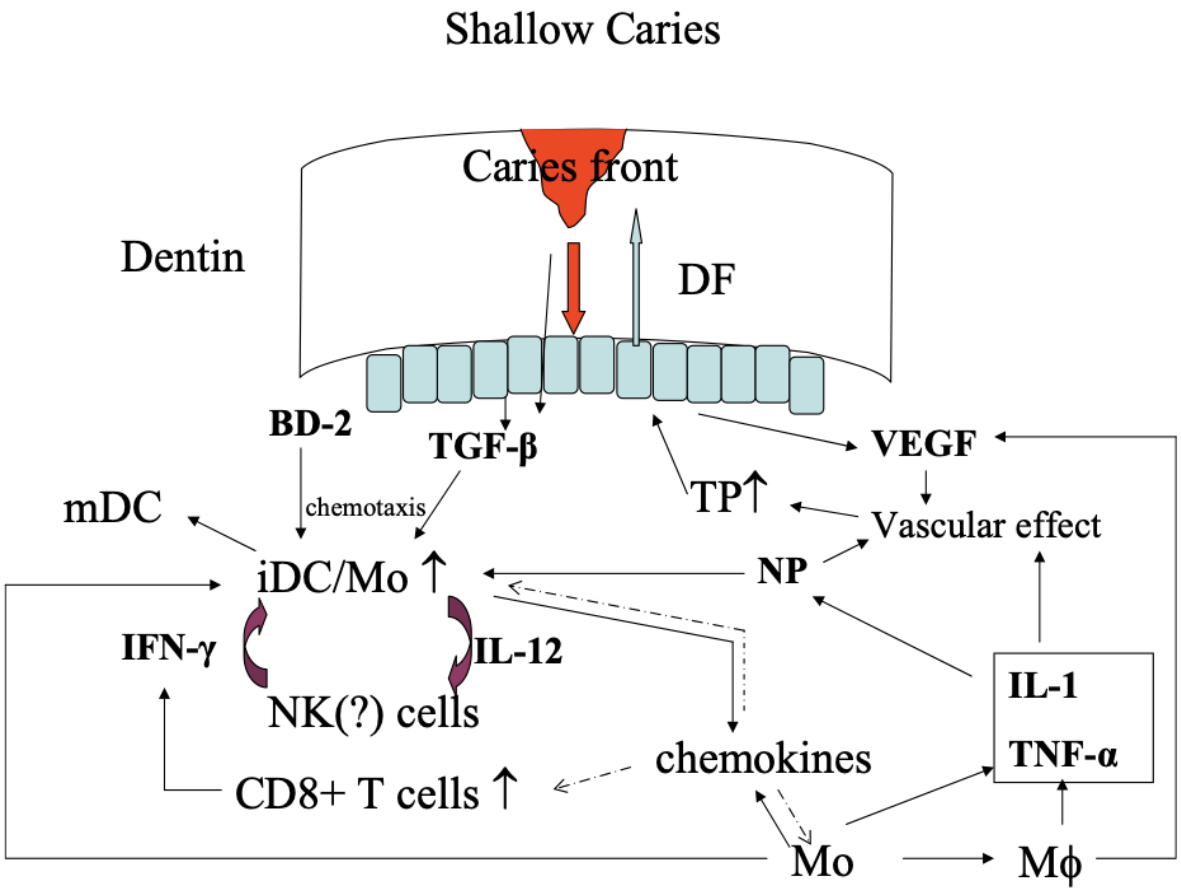


**Figure 1.** Cellular and molecular events in the dental pulp beneath shallow caries. Increasing pulpal tissue pressure from neurogenic inflammation results in an outward flow of dentinal fluid. TGF- released from the demineralized dentin and odontoblasts along with BD-2 attracts immature DCs. VEGF, IL-1, and TNF- secreted from activated macrophages and monocytes promote the vas- cular effect of neuropeptides. The presence of NK cells in the inflamed pulp is not determined yet. Chemokines for recruiting CD8 T cells, macrophages, and monocytes in reversible pulpitis tissues are presently unknown (long dashed-dotted lines). Abbreviations: BD-2, beta defensin-2; DF, dentinal fluid; iDC, immature dendritic cell; Mo, monocyte; M, macrophage; NP, neuropep- tide; TGF-, transforming growth factor-; TP, pulpal tissue pressure; VEGF, vascular endothelial growth factor.

**Impact of inflammatory milieu on mesenchymal stem cells activity:**

Mesenchymal stem cells (MSC) possess surface marks that indicate their capacity to engage with the immune system. The extensive documentation of this phenomenon is especially evident in bone marrow-derived MSCs, as they possess receptors for numerous cytokines (such as IL-1, IL-4, IL-6, IFN-c, TNF-a), growth factors (including fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), TGF-b, epidermal growth factor (EGF), insulin-like growth factor (IGF), bone morphogenetic proteins (BMPs)), and chemokines [21]. In addition, they exhibit surface chemicals that facilitate cell-to-cell contacts with hematopoietic and immunological cells, including a range of adhesion molecules. Currently, there is no comprehensive analysis of surface markers specifically for dental stem cells. However, it is likely that a comparable vast range of markers can be anticipated. Several receptors for various mediators, including as TGF-b, VEGF (vascular endothelial growth factor), FGF, IGF, or BMPs, have been found in dental MSCs. As elucidated in the preceding section, immune cells generate many cytokines and growth factors. In addition to immune cells, various other types of cells have the ability to produce mediators that might influence the activity of MSCs. For example, in the case of dental pulp or endothelial cell injury, mediators such as PDGF-AB, VEGF, and

FGF-2 can be produced. Therefore, it is highly probable that the impact of immune cells and mediators on MSCs has a significant effect in the repair of pulp and periapical pathoses [22].

Increasing data is gathering to illustrate the ability of many cytokines and growth factors to regulate (i) the attraction, (ii) the multiplication, and (iii) the specialization of dental stem cells. Examples of dental stem cell recruitment include the mediation of TGF-b1, VEGF, and FGF-2, which can also serve as positive regulators of chemokine production. Additionally, chemokines like as stromal cell-derived factor-1 (SDF-1) play a role in this process. More generally, it has been demonstrated that the damage to endothelial cells also triggers the recruitment of stem cells. Dental stem cell proliferation can be enhanced by various stimuli, including FGF-2, platelet-derived growth factor (PDGF-BB), VEGF, insulin-like growth factor (IGF-1), and TGF-b1 [23]. Various factors that have been demonstrated to promote the development of dental stem cells include TGF-b1, TGF-b3, FGF-2 (either alone or in combination with the latter two), bone morphogenetic protein-7 (BMP7) and BMP-2, VEGF, IL-11, IFN-c-2b, TNF-a, and IL-1. Through the stimulation of stem cell recruitment, proliferation, and differentiation, these factors facilitate the process of healing [24,25,26].

Typically, inflammation is an initial reaction that swiftly eliminates germs and initiates the healing process. Nevertheless, in the field of endodontics, bacteria can be found in areas that are generally inaccessible to the immune system, such as the dentinal tubules in decayed lesions or the intracanal space in periapical lesions. Prior to the occurrence of direct contact between bacteria and pulp or periapical tissues, which may happen later in the pathological process, inflammation is initiated by toxins and by-products of bacterial metabolism that are transferred through diffusion. Various degrees of inflammation can be noticed in the pulp and periapical tissues when exposed to bacterial assault. The tissues typically exhibit a mixture of different components, with simultaneous presence of inflammation, necrosis, and healing processes [27,28]. Furthermore, the precise assessment of the inflammatory condition of the dental pulp and the tissues around the tooth root cannot yet be ascertained in a clinical environment. Hence, it is necessary to create novel diagnostic tools that rely on biological measurements. One such tool is the evaluation of matrix metalloproteinase 9 (MMP-9) levels, which has been suggested as a means to quantify pulp inflammation. However, it should be noted that MMP-9 alone does not seem to accurately predict pulpal inflammation. Therefore, it may be beneficial to expand this experiment to include multiple factors in order to obtain more reliable results [29].

Elevated levels of CGRP and SP, together with an increased number of nerve fibers that react to CGRP, SP, VIP, and NPY, are observed in the inflamed pulp during the course of caries. Spleen (SP) attracts T lymphocytes and enhances the production of interleukin-2 (IL-2) and interferon-gamma (IFN-) in response to antigens and mitogens [30]. Additionally, SP enhances the expression of interleukin-12 (IL-12) in antigen-presenting cells (APCs) and stimulates the production of IL-8 in pulpal cells. The presence of CGRP and VIP in the injured pulp can quickly attract immature DCs to areas of acute inflammation and prevent mature DCs from migrating to nearby lymph nodes. VIP can also stimulate the maturation of immature dendritic cells (DCs), resulting in an increased production of IL-12 and CD83 [31,32].

Inflammatory cytokines and chemokines, such as interleukin-1 beta (IL-1), tumor necrosis factor alpha (TNF-), interleukin-6 (IL-6), and IL-8, have the ability to cause intense hyperalgesia. This occurs indirectly through the secretion of prostanoid or nerve growth factor (NGF), which increases the expression of bradykinin receptors, or by influencing sympathetic nerve fibers. In addition, IL-1 and other substances that cause inflammation, including as prostaglandins, histamine, and NGF, can stimulate the release of neuropeptides and create a cycle of reinforcement in the inflammatory process [33].

Immune cells secrete somatostatin and β-endorphin in order to maintain homeostasis of neurogenic inflammation. CD3 T cells exhibit heightened production of somatostatin and β-endorphin in inflamed pulps compared to uninflamed pulps. Somatostatin is a neuropeptide that does not have vasoactive properties. Its main function is to prevent the antidromic release of substance P. Both somatostatin and CGRP have a general inhibitory effect on T cell proliferation and the generation of cytokines IL-2 and IFN-.Endorphin, which is a type of opioid peptide, counteracts the impact of vasoactive neuropeptides. The involvement of these molecules in inflammation and pain perception has yet to be established [35].

Periapical inflammation is caused by bacteria or bacterial by-products present in the necrotic root canal. The observed heightened sensitivity to percussion can

typically be attributed to mechanisms of peripheral and central sensitization [36]. Notably, the ability to feel vibrations caused by tapping on a tooth is occasionally linked to the presence of healthy nerves beneath extensive tooth decay. The hypothesis that periapical inflammation is caused by the diffusion of bacterial by-products from the radicular pulp into the periradicular tissues lacks sufficient evidence. Matsumoto and colleagues (1994) showed that the mechanoreceptors in the periodontal ligament become more sensitive when the vital pulp is inflamed with mustard oil. Animal investigations have demonstrated that periapical inflammation initiates prior to complete pulpal necrosis. Hence, the sensitivity to percussion experienced in teeth with reversible or irreversible pulpitis may arise due to central sensitization caused by prolonged inflammation of the dental pulp and/or by an axon reflex in the branching nociceptive nerve fibers [37].

Within the framework of maintaining homeostatic equilibrium between the host and its microbial composition, it has been suggested that the commensal microbiota plays a vital role in preserving good health [38]. Dysbiosis refers to the disturbance of the balanced state of the body, known as homeostasis, specifically in relation to the makeup of beneficial microbial communities compared to their healthy state. Dysbiosis can arise from alterations in the composition of the microbiota or the host's capacity to interact with its microbiome. The intricate equilibrium between homeostasis and dysbiosis is now recognized as a crucial process in the initial development of local and systemic immune control, involving both innate and acquired regulators [39]. From a conceptual standpoint, this idea may be demonstrated in germ-free animals, where the absence of exposure to a normal commensal microbiota results in an underdeveloped or untrained immune system [40]. Conversely, the "old friends" theory refers to the way in which the human body with a functioning immune system responds to microbial challenges, as a result of early exposure and immune training. The disruption of the immune system's training, as observed in humans, has been demonstrated by subjecting the baby commensal microbiota to antibiotics, which can alter this state of equilibrium [41]. Furthermore, the administration of antibiotics to young mice can alter their intestinal (and possibly oral) microbiota, inhibit the usual (eubiotic) beneficial microbiota, and contribute to increased body weight (obesity) and height in these mice treated with antibiotics [42].

This need for training and balance is further supported by a study where the intestinal microbial contents were removed from mice that were not treated with antibiotics. Then, the intestinal microbiota from mice that were treated with antibiotics as infants were transplanted into these animals. The results were compared to mice who were not treated with antibiotics. Upon being challenged, the two transplanted populations exhibited unique reactions in the mice that received the transplants. The newborn mice that received transplants from antibiotic-treated animals had a greater body weight and size compared to the mice that received transplants from mice with a "normal" non-antibiotic microbiota. The primary objective was to create a system that could bypass the requirement for germ-free mice, with the purpose of documenting the development of the microbiome and its impact on the host. The colonization of transplanted animals was evaluated by comparing donors from lean or obese mice. The transplantation effect shown in these trials, albeit lasting only for a duration of 6 weeks, was adequate to educate the immune system and facilitate the examination of disease development in mouse models [43].

The significance of the "early" commensal gut microbiota in brain development has been documented in research involving both mice and humans [44]. The maintenance of a healthy microbiome seems to be closely connected to the proper development of the nervous system, while changes or imbalances in the microbiome are associated with schizophrenia, autism spectrum disorders, and hyperactivity disorders [44]. Gnotobiotic mice were humanized by transplanting early fecal microbiota from preterm newborns with either good or poor growth. Subsequently, samples of mouse brain, liver, feces, and serum were collected for the purpose of analyzing histology, protein, fatty acid, and RNA expression levels in these transplanted mice [45]. Mice that were inhabited by bacteria that hindered growth had reduced levels of indicators of early brain development, as well as delayed development of oligodendrocytes and myelination, suggesting a delay in neuronal development. Moreover, the mice with poor growth exhibited changes in neurotransmitter levels and experienced the development of neuroinflammation. There was a subsequent alteration in the composition of short chain fatty acids produced by the gut flora. This work provided evidence for the significant impact of the colonizing microbiome on the early development of the brain, confirming existing theories and previous data that connect the gut-brain axis to neuronal development [45].

## CONCLUSION:

The tooth pulp possesses the ability to initiate an inherent reaction against invading caries bacteria, potentially impeding bacterial infiltration. Nevertheless, the distinctive positioning of caries bacteria appears to hinder their eradication or elimination by phagocytes. However, when an infection persists, it triggers the activation of adaptive immunity and causes excessive inflammation. This results in increased swelling and pressure within the pulp, which is harmful to the pulp enclosed in an environment with limited flexibility. Mesenchymal stem cells, particularly those derived from dental sources, possess receptors for several inflammatory mediators. These mediators can be generated by inflammatory cells, damaged pulp/periapical cells, or secreted from dentine and/or materials used during therapy. Cytokines and growth factors have the ability to modulate the recruitment, proliferation, and differentiation of MSCs, either by promoting or inhibiting these processes. Mesenchymal stem cells have immunosuppressive characteristics, perhaps due to the secretion of soluble substances.

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