REVIEW ARTICLE

Local Immune Response to Mineral Trioxide Aggregate: A Narrative Review

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Abstract

Aims and background: Mineral trioxide aggregate (MTA) is a bioactive calcium (Ca) silicate-based material that is commonly used in endodontic and restorative procedures. The material interacts with living host tissues in close proximity to promote tissue healing. This paper reviews the interaction and effect of MTA on the various components of the local immune response cascade.

Results: Mineral trioxide aggregate (MTA) is capable of releasing Ca ions (Ca^{2+}), increasing the alkalinity of surrounding tissues, and altering enzymatic activity within cells. By recruiting cells to the application site, MTA is capable of eliciting a local immune response. MTA has been found to enhance the actions of interleukin-1α (IL-1α), IL-6, and IL-12, upregulate macrophage M2 polarization, promote angiogenesis, and suppress proinflammatory interferon (IFN) and messenger RNA (mRNA) expression of IFN-γ. However, MTA has no effect on cytokines tumor necrosis factor-α (TNF-α), RANKL, and IL-10. MTA's anti-inflammatory properties facilitate tissue healing, and the mineralization induced by MTA is significant even in the presence of systemic diseases such as diabetes mellitus and hypertension. MTA modulates the expression of various components and enzymes involved in the immune response cascade, resulting in antiinflammatory effects, angiogenesis, and optimal healing of inflamed or injured tissues.

Conclusion: Mineral trioxide aggregate (MTA) has demonstrated bioactivity and is capable of promoting healing without any cytotoxic effects. The activation and suppression of specific immune responses by MTA are responsible for its antiinflammatory properties, making it a valuable tool for clinicians in various endodontic, and restorative applications.

Clinical significance: The MTA's clinical significance lies in its ability to promote healing and modulate the immune response cascade in a manner that facilitates optimal tissue repair.

Keywords: Cytokines, Immunity, Inflammation, M2 macrophage, Mineral trioxide aggregate.

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Introduction

The placement of a filling material in either an orthograde or retrograde manner necessitates the prevention of communication pathways between the root canal and adjacent tissues. This objective requires the use of a nontoxic, biocompatible, stable, and insoluble material that is noncarcinogenic and nongenotoxic in nature.[1] In restorative dentistry, a number of materials such as dental amalgam, interim restorative material, super-ethoxy benzoic acid, and glass ionomers have been employed. However, the aforementioned materials are subject to various limitations including corrosion susceptibility, electrolysis, staining and expansion upon contact with moisture, poor marginal adaptability leading to leakage, sensitivity to moisture, and adverse toxic effects on tissues.[2]

Since its introduction in 1993 by Torabinejad et al. as a root-filling material, mineral trioxide aggregate (MTA) has become a valuable tool in operative dentistry and endodontics. MTA is commonly used for various procedures, including vital pulp therapy, root end closure, root perforation repairs, and surgical and regenerative procedures. MTA is a bioactive Ca silicate-based material that is placed in close proximity to tissues to elicit a local immune response and stimulate the repair of both hard and soft periradicular tissues.[3] MTA's properties of being osteoconductive, osteoinductive, and biocompatible contribute to its effectiveness.

The MTA's patented composition includes CaO and silica. The fine hydrophilic particles of these components constitute 70–95% of the material. These components form tricalcium silicate, dicalcium silicate, tricalcium aluminate, and tetra-Ca aluminoferrite, which in the presence of moisture, form a colloidal gel made of calcium hydroxide [$Ca(OH)_2$] and Ca silicate hydrate.[4] Additionally, bismuth oxide is included as a radiopacifier.[5] As the material sets, the Ca from Ca silicate precipitates, forming $Ca(OH)_2$. The dicalcium silicate and tricalcium silicate formed or the tricalcium aluminate

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formed after the hydrogenation of the powder are the sources of $Ca(OH)_2$ and are responsible for the alkalinity of MTA after hydration.[6,7] The freshly mixed material has a pH of 10.2, which increases to approximately 12.5 after 3 hours. The solidified gel has a very hard structure with a compressive strength of 45 MPa after 21 days.[8]

Mineral trioxide aggregate (MTA) is commercially available as both gray and white MTA. The introduction of white MTA in 2002 was due to the discoloration caused by gray MTA on overlying tissues.[9] White MTA contains a lower amount of tetra-Ca aluminoferrite and magnesium. The pH of white MTA is higher than gray after 60 minutes of mixing. The presence of bismuth in MTA hampers the precipitation of $Ca(OH)_2$ after the hydration of MTA powder. Therefore, the placement of MTA in any inflammatory site may result in the dissolution and release of bismuth oxide in an acidic environment.[10] This may negatively affect the biocompatibility of the material since bismuth oxide also inhibits cell proliferation.[11] However, it has been reported that MTA performs better when applied for root repair and bone formation in comparison with other restorative materials.[12] MTA's bioactivity induces interfacial interactions between tissues. The resultant deposition of carbonate apatite lays down the mineral phase of hard tissues such as dentin, cementum, and bone. The release of ionic components regulates enzymatic activity within the cells and their interaction with surrounding tissues. This allows for the adhesion, proliferation, and growth of cells while creating a mineralized matrix that improves its marginal seal.[13]

Owing to its isolation from collateral blood circulation and encasement by dental hard tissues, dental pulp response to external irritants is limited.[14] The degree of inflammation in the pulp is inversely proportional to the extent of irritation; thus, it is essential to prevent further irritation to prevent reversible inflammation from becoming irreversible. In endodontic procedures, MTA triggers a localized immune response by recruiting inflammatory cells to the MTA application site. The initial stage of inflammation is characterized primarily by polymorphonuclear cells and monocytes, while the chronic phase is characterized by T and B lymphocytes, plasma, and natural killer cells. These inflammatory cells contribute to debris scavenging and promote the repair of dental tissues. MTA promotes the recovery of diseased pulp without exerting cytotoxic effects. When combined with sterile water, MTA does not prompt apoptosis or any adverse impact on fibroblasts and macrophages.[15] Nonetheless, MTA stimulates the expression and activity of alkaline phosphatase (ALP) in cultured fibroblasts. It also triggers the upregulation of molecules in the dental pulp, such as bone morphogenic protein (BMP), dentin sialophosphoprotein, and ALP.[16]

The present paper provides a comprehensive review of the extant literature pertaining to the impact of MTA on the local immune response in dental procedures, with a focus on the response of the individual components of the inflammatory cascade.

Pulpal Response to MTA

It has been observed in animal models that following pulp exposure, pulpal necrosis begins after 2 days, and periapical bone destruction begins after 7 days. Rapid destruction of the periapical tissues occurs after 2 weeks. Following this acute phase of destruction, the rate of bone resorption reduces, and the chronic phase begins. The inflammatory cytokines and chemokines help recruit the leukocytes to the diseased or injured tissue. But this process may further cause tissue damage.[17] The CC chemokine ligand 5 (CCL5) is significantly active toward eosinophils, monocytes, and cluster of differentiation 45^+ ($CD45^+$) T cells. It upregulates the interleukin IL-12 and IFN-γ[18] while stimulating the migration of T helper cells Th1 and the memory T cells.[19]

The most important goal of vital pulp therapy of pulp capping is reducing or eliminating inflammation of the underlying pulp. The biocompatibility of pulp-capping agents is indicated by low pulpal inflammation. Dentin bridge formation under the capping material alone does not signify the healthy status of pulp, rather, the lower induction of inflammation is a success factor. MTA reduces the CCL5 mRNA expression during the initial 10 days of inflammation, resulting in lower IFN-γ mRNA levels. Hence, MTA acts as an antiinflammatory agent.

It has been reported that MTA, $Ca(OH)_2$, and Portland cement caused mild to moderate inflammation with some giant cells in the subcutaneous tissue of rats after 7 days of implantation of dentine tubes filled with the materials. After 30 days, mildly inflamed fibrous connective tissue with scarce giant cells was observed.[20] The mechanism of action of MTA is similar to that of $Ca(OH)_2$, producing calcite crystals which are evidenced by necrosis and multinucleate foreign body giant cells.[4] In a long-term clinical study evaluating direct pulp capping in carious teeth using $Ca(OH)_2$ and MTA, it was observed that over time, $Ca(OH)_2$ group teeth turned nonvital. No such time-dependent failure was seen in the MTA group.[21] This time-dependent decline in the $Ca(OH)_2$ group could be attributed to poor bonding to dentin, material instability, and resorption. Comparatively, in the group where direct pulp capping was done using MTA, a better histologic response was observed. The odontoblastic layers appeared earlier, lesser hyperemia, inflammation, and necrosis were observed, and the dentinal bridges as compared to the $Ca(OH)_2$ group were more pronounced. Upon Scanning electron microscopy and electron probe microanalysis, a hard tissue bridge formed of collagen bundles with Ca phosphate $[Ca_3(PO_4)_2]$ calcification in the center and irregular dentinal tubules toward the pulpal surface were observed.[22]

Interleukins

Interleukin (IL)-1α found in the early stages of pulpitis, and apical periodontitis promote the migration of leukocytes to the inflamed tissue by inducing the endothelial cells to express the adhesion molecules. It indicates the resorption of bone and the production of IL-6 by bone. In the presence of MTA, the expression of IL-1α mRNA is lower, suggesting an antiinflammatory effect. However, some studies have reported an increased *in vitro* level of IL-1α and IL-6 after osteoblasts were in contact with MTA for >6 days.[23]

IL-12 is a proinflammatory cytokine that acts as a link between innate and adaptive antigen-specific immune responses.[24] It was reported that MTA-based sealer stimulates the production of IL-12 p70 by M1 macrophages.[25]

Tumor Necrosis Factor

Tumor necrosis factor-α (TNF-α) promotes inflammation by recruiting lymphocytes and monocytes to the inflamed or injured tissue and stimulates the expression of adhesion cells by the endothelial cells and the secretion of chemokines.[26] TNF-α also induces the inflammation of pulpal and periapical tissues and resorption of bone. The overexpression of TNF- α in later stages of inflammation, when tissue was treated with MTA is indicative of its proinflammatory effect. However, it has been reported that following the initial

proinflammatory effect, there is a regulatory effect in later stages that reduces the immune activity. It has also been reported that MTA does not have any negative impact on the production of TNF-α by macrophages.[27] This indicates that MTA and MTA-based sealers do not affect TNF-α by macrophage subtype. MTA may help in the clearance of microbes by antigen-presenting cells.

Interferons

The natural killer cells, $CD4^+$, and the $CD8^+$ T lymphocytes produce IFNs. IFN-γ contributes to innate and adaptive immunity by activating macrophages. The expression of IFN-γ mRNA was reported to have dramatically decreased after 3 weeks of treatment with MTA, indicating antiinflammatory properties.

The proinflammatory cytokine IL-6 that is secreted in response to antigens and other cytokines activates osteoclasts to cause bone resorption.[28] When osteoblasts are exposed to MTA, an increase in IL-6 production has been reported; however, no expression of IL-6 has been reported in the pulp.

Rezende et al. examined the effect of MTA on the adaptive immune response. They reported that MTA exposure led to an increase in immunoglobulin G (IgG) antibodies and inhibited the antigen-specific proliferation of *Fusobacterium nucleatum* (*F. nucleatum*) and anaerobic reactive memory T cells. In their experiment, BALB/c mice were immunized with heat-killed *F. nucleatum*, and exposure to MTA was found to result in the upregulation of IgG antibodies, while suppressing the antigen-specific proliferation of *F. nucleatum* and *Peptostreptococcus anaerobius* (*P. anaerobius*) reactive memory T cells. The production of IL-4 was inhibited by *F. nucleatum* reactive memory T cells, and that of IFN-γ was inhibited by *P. anaerobius*-reactive BALB/c memory T cells. However, cytokines TNF-α, RANKL, and IL-10 remained unaffected, indicating that MTA did not have any effect on memory T cell-mediated inflammation.[29]

Macrophages

Macrophages are cells involved in chronic inflammation or healing phases.[30] They function by eliminating bacteria and foreign substances by phagocytosis along with neutrophils, recruitment of cells, and production of cytokines and chemokines.[30,31]

These are two types, M1 and M2 that differ in relationship with their receptors, functions, and production of cytokines. M1 macrophages produce IL-12 in high concentrations and IL-10 in low concentrations; whereas M2 macrophages secrete IL-10 in high concentrations and IL-12 in low concentrations.[32] M1 cells are proinflammatory, mediate resistance to pathogens, and metabolize through inducible nitric oxide synthase.[33] M2 cells metabolize through arginine, which results in collagen synthesis and cell proliferation and is involved in healing. It has been reported that MTA does not affect the antibacterial functions and viability of M1 and M2 macrophages. These include bacterial phagocytosis, production of reactive oxygen species and nitrogen species, and arginase activity. However, MTA-based sealer Fillapex Angelus includes salicylate resin, bismuth trioxide, and silica nanoparticles which may have resulted in negative results.[34]

Macrophages possess a proton channel that is activated by Ca^{2+} and is pH sensitive. Calmodulin kinase II can phosphorylate and activate these proton channels. Hence, Ca ions regulate the functioning of macrophages and upregulate the receptors. Macrophages also respond to Ca signaling for host cell activation as an immediate response to recognizing vs or bacteria.[35] The silica in MTA turns into a gel in an aqueous environment and attracts Ca and phosphate to form $Ca_3(PO_4)_2$, which is insoluble and affects macrophage activation.[36]

When implanted into the subcutaneous rat tissue, MTA increases the M2 marker-expressing macrophages *ectodysplasin 1 (ED1) (CD68), ED2 (CD163),* and *M2* genes mRNA of CD163 and macrophage mannose receptor (CD206). It also increased M2 polarization and angiogenesis, fibrogenesis, and tissue remodeling.

Takei et al. reported that in the rat molars that underwent pulpectomy, there was a transient accumulation of M2 macrophage-expressing cells beneath the degenerative layer produced under MTA. Pulp-capping using MTA in mechanically exposed human pulp resulted in low inflammation and hyperaemia. The elevated extracellular pH by MTA affects the phagocytosis and polarization of M2 macrophages, NF-κB activation and secretion of cytokines, and superoxide production.[37] It has been reported that MTA activates the Axl/Akt/NF-κB signal that increases the phagocytic removal of apoptotic cells and debris, thus preventing the increase of inflammation.[38]

M2 macrophages also upregulate oxygen free radicals, thereby improving immune response in presence of infection by eliminating pathogens, inducing cell apoptosis and gene expression, and activating signalling cascades.[39]

The implantation of MTA in rats' tissues leads to faster healing, as demonstrated by an increase in CD34 expression in both immunohistochemistry and gene expression analysis. CD34 is a glycoprotein found on the surface of cells that acts as a marker for angiogenesis. This glycoprotein is expressed by hematopoietic stem cells, some macrophages, and dendritic cells, which play a crucial role in promoting neovascularization and improving functional recovery.[40]

Stem Cells

When dental pulp stem cells (DPSCs) are treated with MTA, a significant increase in the levels of p65, both cytoplasmic phosphorylated and nuclear, has been reported. The inhibition of κB phosphorylation and translocation of NF-κB suppresses the odontoblastic and osteoblastic differentiation of the DPSCs induced by MTA. By activating the NF-κB pathway, MTA enhances the odontogenic and osteogenic activity of the DPSCs.[41]

Immune Response

Root canal sealers placed in intimate contact with the inflamed or infected periradicular tissues should not interfere with the phagocytic process in the host. IgG represents 70% of the immunoglobulin-producing cells and the majority of T cells are memory-type T cells in the radicular cysts and periapical granulomas.[42] The antibacterial activity in periradicular lesions induced by MTA is due to the local production of IgG antibodies. The sustained IgG antibody response against the response by bacteria benefits the host.[29] The MTA-induced increased production of RANKL, IFN, and TNF-α by the TCR/CD28-activated naïve T cells affects the periradicular lesions. The cytokines from activated memory T cells affect the periradicular lesions more prominently than those derived from naïve T cells. MTA suppresses the proliferation of memory and naïve T cells. However, IL-10 and RANKL expressed by the memory T cellar are not altered by MTA and it has been reported that bone resorption stimulated by infection is greater in mice due to IL-10.[29]

Cell Migration

Mineral trioxide aggregate (MTA) can boost cell migration through two mechanisms—increasing chemotaxis and the speed of chemokinesis. MTA enhances the migration of immune cells by activating the Ca-sensing receptor (CaSR). The CaSR-PI3K-Cdc42 pathway involved in immune cell chemotaxis is independent of the Rac mechanism. The contractility of the cytoskeleton triggers cell motility, whereas the alteration of myosin light-chain kinase (MLCK)—MLC phosphorylation absolutely shuts off cell motility and the chemical response. MTA promotes immune cell migration, thereby inducing a protective immune response.

Cytotoxicity

It has been reported that MTA is noncytotoxic, does not affect cell death of lymphocytes,[29] and promotes cell viability of macrophages,[25] fibroblasts,[43] and osteoblasts.[44] On the contrary, MTA-based sealer Fillapex reduced the cell viability of macrophages. The component salicylate resin has been evaluated for its effect on human fibrosarcoma cells (HT-1080), and cellular apoptosis was observed.[45] It also impairs cell adhesion and phagocytosis by both subtypes, hence affecting endodontic healing. Owing to these adverse effects, the manufacturer of Angelus MTA changed the radiopacifier to Ca tungstate in 2019.[39]

Interaction with Other Fluids

When used as a root-repair material to seal perforations, MTA comes into contact and interacts with the root canal irrigants before interacting with the periodontal stem cells. The periodontal ligament associated protein-1 and periostin are extracellular proteins found in periodontal tissues, whereas osteoprotegerin is secreted from the periodontal ligament (PDL) cells for the regulation of osteoclastic activity. On interaction with sodium hypochlorite (NAOCl), the levels of these PDL-related markers were found to be low in human osteoblasts. Human osteoblastic cell lines 1–17 exposed to by-products of NaOCl and MTA differentiate into osteoblast-like cells and express lower levels of *BMP2, osteopontin (OPN),* and *ALP* genes. Also, contact between white MTA and NaOCl causes dark brown discoloration of the white MTA.[46] Hence, NaOCl should be thoroughly removed from root canals before the use of MTA for perforation repair to prevent hamper of hard tissue formation.

When white MTA that is mixed with saline, sterile water, or local anesthetic agent, gets contaminated with blood, the resultant mixture does not hamper the properties of MTA but has lower resistance to displacement.

Effect of Systemic Conditions

Inflammatory vascular process such as hypertension results in an increased level of angiotensin II that stimulates the infiltration and proliferation of natural killer cells.[47] It also increases aldosterone, C-reactive protein, IL-1b and 6, TNF-α, and cell adhesion molecules. Inflammatory response to a foreign body is exaggerated in the presence of coexisting hypertension, evidenced by a higher number of neutrophils.[48] The Ca^{2+} released by MTA react with the carbon dioxide in the inflamed tissues to form calcite crystals that deposit in the hard tissues and can be identified by their birefringence under polarized light. Thus, hypertension reduces the capacity of MTA to induce remineralization.[49]

Abnormalities in the metabolism of macronutrients and electrolytes are characteristic features of diabetes mellitus, along with impaired Ca homeostasis and altered bone markers, resulting in bone loss and altered tissue repair capacity and healing. Hyperglycemia due to altered metabolism affects immune response and is associated with the development and progression of periapical and periodontal diseases. MTA induces the contraction of blood vessels by an influx of Ca. Hence, the Ca^{2+} released from MTA enter the systemic circulation. Hence, diabetes may negatively affect the response and mineralization ability of MTA. An increase in the levels of ALP, OPN, and osteocalcin has been reported along with stimulation of cytokines and Ca+ ions upon treatment with MTA.[50]

Future Directions for Research

Further research is needed to explore CaSR as a molecular target for calcimimetics and the potential use of cations for regulating immune cell migration in diverse therapeutic approaches. The mechanism of M1/M2 polarization and its effects on periapical disease pathogenesis requires further investigation. There is a need for long-term clinical trials with large sample sizes and long follow-up periods to elucidate the precise mechanism of action of MTA in modulating the immune response of various cells involved in immunity. Additionally, the systemic effects of bioactive materials need to be better understood.

Conclusion

This review provides a comprehensive overview of the impact of MTA on the enzymes and cells involved in the inflammation and resolution process. The local immune response to MTA is a multifaceted process that requires the concerted efforts of multiple cell types and signaling molecules. The outcome is a well-orchestrated and well-structured repair process that can adequately seal the root canal and prevent reinfection. This enhanced understanding of the actions of bioactive materials would facilitate the identification of new therapeutic targets, thereby achieving superior clinical outcomes for healing pulpal and periapical diseases.

Clinical Significance

Mineral trioxide aggregate (MTA)'s bioactivity and ability to promote tissue healing without any cytotoxic effects make it a valuable tool for clinicians in endodontic and restorative applications.[51] MTA's ability to modulate the expression of various components and enzymes involved in the immune response cascade results in antiinflammatory effects, angiogenesis, and optimal healing of inflamed or injured tissues. These properties make MTA a promising therapeutic agent for it can enhance the actions of certain IL and promote macrophage polarization. Thus, MTA's clinical significance lies in its ability to promote healing and modulate the immune response cascade in a manner that facilitates optimal tissue repair.

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