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MARESINS: THE PRODIGAL DOYENNE OF THE RESOLUTION REALM

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ABSTRACT

Inflammation plays a crucial role in protecting the human body from harmful external antigens and microorganisms. Nevertheless, an exaggerated inflammatory response can lead to tissue damage and interfere with organ functions. Hence, it is imperative to understand anti-inflammatory processes and resolution mechanisms. A controlled and dynamic process known as "resolution of inflammation" helps the body regain equilibrium by removing cell debris from the injured tissue. Specialized pro-resolving mediators (SPMs), endogenous bioactive lipids such as lipoxins (LXs), resolvins (Rvs), protectins (PDs), and maresins (MaRs) are responsible for coordinating this physiological response. Macrophages, in particular, produce maresins (MaRs), which have tissue-regenerating, pro-resolving, and anti-inflammatory qualities. The underlying molecular processes of maresin in periodontitis have been the subject of an expanding body of clinical and experimental studies. MaRs has recently shown a direct correlation with the periodontal disease's ability to reduce inflammation.

KEYWORDS: Periodontitis, macrophage, maresins, inflammation, resolution, Specialized pro-resolving mediators (SPMs).

INTRODUCTION

Inflammation is a pathophysiological response to infection or tissue damage.[1] Inflammatory processes that include changes in vascular permeability, recruitment and accumulation of leukocytes, and release of inflammatory mediators, are important in the regeneration of injured tissues.[2] However, an abundance of chronic inflammatory disorders can arise from tissue damage caused by uncontrolled or unresolved inflammation.[3] The generation of inflammatory mediators is also triggered by certain bacteria-induced periodontal diseases. The periodontium, or the tissues that support the teeth, is lost or destroyed as a result of these processes.[4] The primary agents responsible for the destruction of periodontium can be generally classified into two categories: those originating from the subgingival microbiota and those originating from the inflammatory response of the host immune system. Of the two, it is now evident that the inflammatory processes of the host account for the majority of periodontal deterioration. Therefore, in order to stop periodontitis progression, this inflammation needs to be reduced.[5] Acute inflammation resolution is typically an active process rather than a passive one, requiring the production of SPMs such as , resolvins (Rvs), protectins (PDs), and lipoxins (LXs), maresins (MaRs).[2]

GENERATION OF SPMs

Bioactive autacoids known as SPMs are derived from the omega-6 fatty acids arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) through enzymatic production. These autacoids, which are typically found in inflammatory environments, include lipoxins (LXs), resolvins (Rvs), protectins (PDs), and maresins (MaRs), which are produced by lipoxygenases (LOXs), cytochrome p450 (CYP450), and cyclooxygenase-2 (COX-2) enzymes. While a wide variety of cell types are capable of producing SPMs, immune cells, including neutrophils, monocytes, and macrophages, are thought to be principally in charge of producing these SPMs.[9,10]

MARESIN

Macrophages are important for regulating the innate host response to tissue regeneration and local inflammation. These cells play a key role in the coordination of various other processes, such as wound healing and neovascularization. Recently, a new family of pro-resolving mediators from macrophages was identified and named maresins (macrophage mediators in resolving inflammation).[11]

MaRs are thought to function as highly protective mediators of macrophage function, aiding in tissue regeneration and the resolution of acute inflammation. MaRs have been shown in recent research to stimulate inflammatory activity in macrophages. Moreover, culturing human macrophages with MaRs enhances resolution by enhancing phagocytosis and efferocytosis. These effects are probably caused by different substances that are produced by macrophage-releasing receptors (MaRs), which change the way macrophages function and may help to reduce inflammation. To promote tissue regeneration and inflammation resolution, for instance, biosynthesized MaRs downregulate proinflammatory cytokines such TNF-α, IL-1β, and IL-6.[12,13]

On the other hand, defective or delayed resolution results in persistent inflammation, which may ultimately cause chronic inflammatory pain. According to reports, the following functional issues with macrophages and lipid mediator family cause decreased inflammatory resolution.

Unbalanced M1/M2 macrophages
(b) decreased production of SPM or MaR
(c) deficient DHA synthesis
(d) aging.[2]

RECEPTORS

Maresin1 (MaR1) is able to promote the regeneration of tissues in an experimental model. In human cells, it is produced by platelets and PMN interactions. MaR1 promotes tissue regeneration and repair.[6]

One receptor, known as leucine-rich repeat-containing G-protein-coupled receptor 6 (LGR6), was found in many different organs and possessed the structure of GPCRs. This discovery was made recently. A different receptor has been discovered in the nucleus, which is called retinoic acid-related orphan receptor α (RORα). The precise molecular mechanisms behind the resolution of inflammation, host defense, tissue homeostasis, and wound healing remain unknown, despite the importance these two receptors play in maresin-1's action mechanism.[14]

RESOLUTION HOMEOSTASIS

Tissue edema and vascular dilatation, which permit leukocyte migration from the lumen to the interstitial space, are the first steps in the mechanisms implicated in acute inflammatory diseases. Proinflammatory mediators, specifically leukotrienes (LTs) and prostaglandins (PGs), which are produced from the omega-6 fatty acid AA, mediate this process. The initial neutrophil migration into the injured tissue, followed by the blood's monocytes and macrophages.

The first PUFA-derived mediator with anti-inflammatory and pro-resolving properties has been identified as LXA4. LXA4 and LXB4, which are produced as a result of platelet leukocyte contact, promote the lipid signaling class transition by preventing the recruitment of additional polymorphonuclear cells from capillary venules. To preserve homeostasis, the inflammatory response needs to be controlled until the harmful substances have been eliminated by phagocytosis. SPMs actively manage the process of acute inflammation resolution. Through the inhibition of leukocyte trafficking to the inflammatory site, the reversal of vasodilation and vascular permeability, and the promotion of the removal of inflammatory cells, exudates, and tissue debris, these SPMs aid in the restoration of body equilibrium.

Similar biological roles of SPMs in the lipid class-switch process include boosting macrophage phagocytosis, promoting pro-to-anti-inflammatory cytokine profiles, and restricting neutrophil invasion.[2]

IMMUNE CELLS AS EMERGING PLAYERS IN RESOLUTION

Tissue inflammation exacerbate by external pathogens and apoptotic cells. Macrophages, on the other hand, reduce the intensity of these inflammatory reactions by eliminating these pathogens and apoptotic cells to bring an end to inflammation. By encouraging anti-inflammatory activity, maresin-1 has been demonstrated to increase phagocytotic activity in macrophages. The M2 macrophages release cytokines that are anti-inflammatory, like TGF-β and IL-10, which hasten tissue remodeling and the phagocytosis-mediated removal of apoptotic debris. Maresin-1's activity regulated the inflammatory response negatively.

T Cells

Maresin-1 upregulates T-bet and Rorc expression, which suppresses the induction of CD4+, CD8+, and Th17 cells. It also induces Tregs and increases the production of IL-10, an anti-

inflammatory cytokine. Therefore, maresin-1 suppresses effector cell induction, increases Treg formation, and causes T cells to produce anti-inflammatory cytokines.

Neutrophils

Maresin-1 has been demonstrated to inhibit neutrophil infiltration, reduce CXCL1 production, and promote apoptosis of neutrophils to induce the resolution of inflammatory response.[15]

THE ANTI-INFLAMMATORY ACTIONS OF MARESIN-1

Maresin-1 was initially discovered in human macrophages and demonstrated to be an active lipid mediator in the inflammatory resolution process. Research has demonstrated that the production of maresin-1 by human macrophages is mediated by DHA's 14-lipoxylation and the enzymatic hydrolysis of 13S, 14S-epoxymaresin.[16,17] In terms of its anti-inflammatory properties, maresin-1 has been demonstrated to inhibit neutrophil migration and cytokine production through the activation of Th17, CD4+ T helper (Th1), and CD8+ T cells. Additionally, Maresin-1 has been demonstrated to inhibit the transcription factors T-bet and Rorc, stop Th1 and Th17 development, and concurrently increase the production of Foxp3+ regulatory T (Treg) cells via the GPR32 receptor.[18,19]

BIOLOGICAL ACTIONS AND POSSIBLE MECHANISMS OF MARESINS

Macrophages play a crucial role in wound healing and tissue regeneration. Since maresins are produced by M2 macrophages, it is possible that maresins play a crucial role as mediators between the phases of wound healing and regeneration and the resolution of inflammation. MaR1 was also found to help vascular damage repair. The role of topical maresin administration in extraction socket healing and socket regeneration was investigated in an animal study. MaR1 was discovered to expedite wound healing, encourage bone resorption in the socket, maintain the alveolar ridge, and lessen postoperative discomfort.

Researchers found that in an animal model, MaR1 decreased reactive oxygen species and proinflammatory cytokines, which in turn decreased skin edema. TNF-α has been shown in another investigation to suppress keratinocyte growth. TNF-α production is known to be inhibited by MaR1. With all of these variables taken into account, the mechanism by which maresins may facilitate wound healing appears to be indirect and involves the resolution of inflammation.[5]

ROLE OF MARESIN IN PERIODONTAL DISEASES

Patients with aggressive periodontitis (AgP), also known as Grade C periodontitis, typically present with quickly progressing alveolar bone loss around teeth. Periodontal disease is a chronic inflammatory illness. Patients with AgP were shown to have higher serum levels of 14-HDHA (a hydrolysis product of precursor of MaR1), indicating possible dysregulation of the biosynthesis pathway or MaR1 and metabolites in AgP patients.[20]

MaR1 and 12-lipoxygenase (12-LOX) levels were lower in a more homogeneous group of individuals with localized aggressive periodontitis (LAP, also known as Stage IV Grade C molar-incisal pattern periodontitis) than in macrophages (only 36% and 30% the level of healthy control). Patients with LAP have phagocytes that are less capable of phagocytosing and eliminating infections. Nevertheless, further MaR1 injection boosted intracellular ROS production, restored bactericidal capability, and improved phagocytosis (peaking at 1 nM).[13]

Exogenous MaR1 also boosts autophagy and the survival rate of healthy human periodontal ligament cells (hPDLCs). By activating the β-catenin pathway and glycogen synthase kinase-3β (GSK-3) pathways, MaR1 significantly reduces the production of inflammatory molecules, including IL-6, IL-8, TNF-α, and IL-1β, and hPDLCs' apoptosis when stimulated with P. gingivalis (peaking at 10 nM).[21]

MAR1 AS A BIOMARKER IN HUMAN TISSUE FLUID

MaR1 is present in human serum and has been identified in many human tissue fluid sources. It may have applications as a biomarker. It was discovered that patients with periodontitis have higher levels of MaR1 in their saliva. Nevertheless, no association was discovered between the study's observed time and the rate at which periodontitis progressed; rather, data indicated that a rise in MaR1 and a fall in protectin (PD) salivary levels might be indicators of the development of periodontal disease. Furthermore, associations were observed between MaR1, 14-HDHA, and 7(s)-MaR1 and the various subgingival microbiota of subgingival plaque in the healthy group, periodontitis before to scaling and root planing (SRP) treatment, and periodontitis following SRP treatment.[22]

RESEARCH ON THE EFFECT OF SUPPLEMENTING WITH PUFA's ON PERIODONTAL INFLAMMATION

Over the past 20 years, a great deal of research has been done on the advantages of dietary PUFAs in the management of inflammatory diseases. Short-term studies supplementing persons with ω-3 fatty acids showed reductions in cell cultures' generation of TNF-α and IL-1β.[23]

A clinical trial involving patients with chronic periodontitis that received oral hygiene instructions along with either 3 g of polyunsaturated fatty acids daily (test group) or oral hygiene instructions along with a placebo for 28 weeks (control group) produced similar results. Giving PUFAs as a monotherapy for chronic periodontitis did not show any discernible changes in clinical outcomes.[24]

In contrast to SRP with placebo, dietary supplementation with ω-3 fatty acids significantly decreased the gingival index, probing depth, and clinical attachment gain when paired with non-surgical therapy of periodontitis.[25]

CONCLUSION

MaRs are members of the anti-inflammatory lipid mediator family that was newly discovered and is produced from omega-3 or omega-6 fatty acids. It has multiple activities and acts on certain receptors, such as LGR6 and ROR α. MaR activation in macrophages promotes Treg cell production, inhibits neutrophil infiltration, and improves phagocytosis via altering cytokine release. Maresins are beneficial in the treatment of aggressive periodontitis, according to studies. Currently, research on animals is being conducted, and before they can be utilized to treat periodontitis, further clinical trials are necessary.

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