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Maresins: anti-inflammatory pro-resolving mediators with therapeutic potential

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Abstract. – Although inflammation is protective of the body, uncontrolled acute inflammatory reactions may inflict tissue damage and lead to chronic inflammation. There is a fast-growing research interest in mechanisms that mediate regression of inflammation and actions of anti-inflammatory factors. Studies of inflammatory and anti-inflammatory mechanisms have uncovered roles for new lipid mediators, including lipoxins, resolvins, protectins, and maresins, collectively referred to as specialized pro-resolving mediators (SPM). Maresins have recently been discovered and are biosynthesized from docosahexaenoic acid (DHA) by macrophages and display strong anti-inflammatory and pro-resolving activities. Here, we summarize the actions and mechanisms of maresins in different diseases and suggest possible therapeutic uses.

Key Words:
Inflammation, Lipid mediators, Maresins.

Introduction

Although inflammation is a predominantly self-protective bodily response, acute excessive levels of inflammation may cause great damage to our health[1]. The inflammatory response involves interactions between many different cell types and cytokines[2]. Typical symptoms accompanying inflammatory responses include fever, redness, swelling, pain and loss of function[3]. Today, excessive inflammation is widely recognized as an important factor in chronic diseases such as metabolic syndrome, cardiovascular disease, and nervous system diseases[4-8], and it has therefore become a major public health concern. Anti-inflammatory mediators form a class of factors preventing further inflammation and tissue damage[9]. The therapeutic use of anti-inflammatory mediators may reduce inflammation-induced damage and have curative effects on the resulting chronic diseases.

Fatty acids act as metabolic fuels for the human body and form an important part of the cell membrane[10]. Besides these functions, fatty acids affect human health by acting as signaling molecules[11]. They not only have an impact on the health of cardiovascular diseases but also have impacts in a range of other diseases, including metabolic and inflammatory diseases, and cancer[12]. ω-6 Fatty acids (e.g., linoleic acid; LA) and ω-3 fat acids (e.g., α-linolenic acid; ALA) are essential fatty acids that cannot be synthesized by humans or other higher animals[13]. After a series of complex desaturation-and elongation reactions acting in concert to transform LA and ALA to their higher unsaturated derivatives: arachidonic acid (AA) from LA, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from ALA[14,15]. The conversion pathways are shown in Figure 1, and the produced derivatives will undergo further biochemical processing in the body and are converted into molecules that affect metabolism directly.

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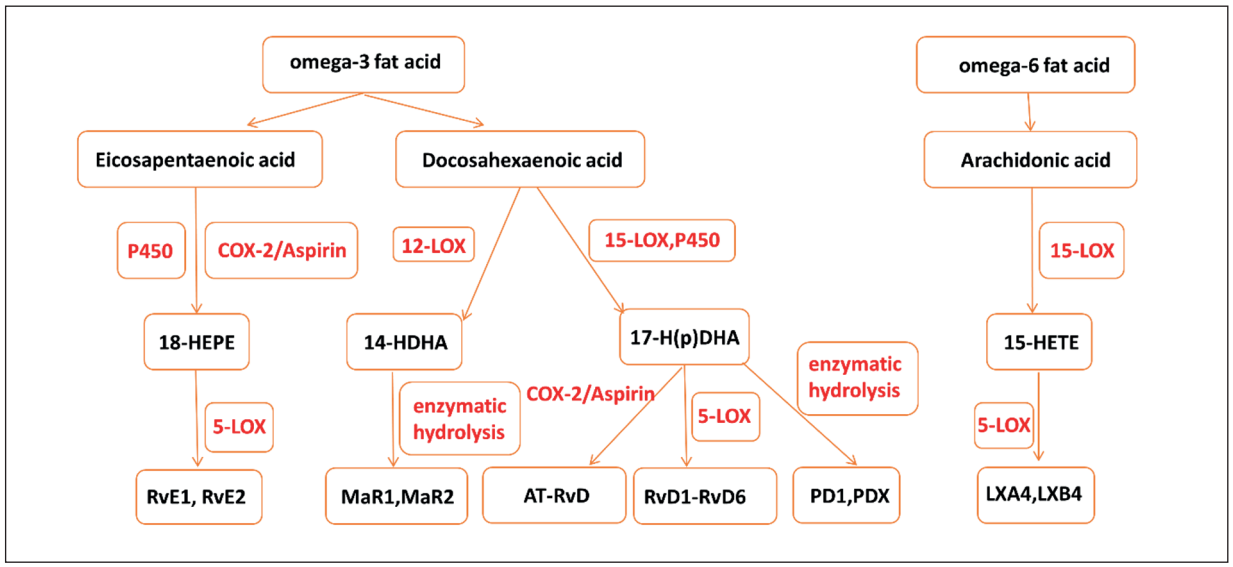

Figure 1. The production of biosynthesis of pro-resolving lipid mediators. Abbreviation: 5/12/15-LOX, 5/12/15-Lipoxygenase; COX-2, Cyclooxygenase-2; RvD, resolving D series; RvE, resolving E series; MaR, maresin; PD1, Protectin D1; PDX, Protectin DX; LXA4, Lipoxin A4; LXB4, Lipoxin B4.

SPMs are derived from essential fatty acids and play crucial roles in orchestrating the resolution of tissue inflammation[16]. The new pro-resolving lipid mediators include separate families of molecules: lipoxins, resolvins, protectins and maresins, which are derived from AA and omega-3 polyunsaturated fatty acids[17-20]. Lipoxins and aspirin-triggered lipoxins, generated from AA, reduce inflammation and promote resolution. In contrast, resolvins, maresins and protectins are derived from omega-3 polyunsaturated fatty acid[21,22]. Maresins are a class of 14S-dihydroxyl-containing molecules with conjugated triene double bonds, which are synthesized from DHA through an oxidative (e.g., lipoxygenase-related) pathway during inflammation regression[23]. In general, the biosynthesis of maresins occurs in M2 macrophages[24]. Abdulnour et al[25] report that maresin 1 is synthesized in the interaction of platelets with neutrophils. This review addresses the contributing roles of maresins to the regression of inflammation and highlights their potentially beneficial roles in the resolution of various diseases.

Biosynthesis and Stereochemistry

Polyunsaturated fatty acids (PUFAs) play an important role in the initiation, development and regression of inflammation[26,27]. Two classes of PUFAs are distinguished: n-3 (ω-3) PUFAs and n-6 (ω-6) PUFAs[15]. DHA and EPA are derived from the simplest ω-3 fatty acid, ALA, are especially abundant in e.g., fish oils, and play important roles in organ function and health[28]. In humans, metabolites of PUFAs are known to trigger inflammation. However, prostaglandin E3 and leukotriene B5 produced by ω-3 PUFAs are much less biologically active than the prostaglandin E2 and leukotriene B4 produced by ω-6 PUFAs[29]. Furthermore, lipid mediators such as resolvins and protectins produced by EPA and DHA metabolism promote the regression of inflammation[30].

Maresins form the third-largest family of SPMs derived from DHA20. The biosynthesis of maresins occurs primarily in M2 macrophages and is initiated by a reaction involving human macrophage 12-lipoxygenase (12-LOX)[31]. The lipoxygenation reaction involves insertion of an oxygen atom into DHA on the fourteenth carbon atom. This generates 14S-HpDHA, which is further transformed into 13S,14S-epoxide maresin, followed by a conversion, performed by different enzymes, e.g., maresin 1, maresin 2, and maresin conjugate in tissue regeneration (MCTR)[32].

Maresin 1 was the first discovered member of the family of maresins[33]. By the action of 12-LOX, DHA was found to be converted to 14S-HpDHA[34]. 12-LOX is a key enzyme in the synthesis of maresins[35]. When 12-LOX is absent in macrophages, the production of 14S-HpDHA is reduced by > 95%. By the action of 12-LOX,

14S-HpDHA is converted to 13S,14S-epoxy-maresin. Next, by an epoxide-hydrolysis reaction, the double bond in the 13S, 14S-epoxy-maresin is reconfigured to a Z/E configuration, yielding the final product 7R, 14S-dihydroxydocosa-4Z, 8E, 10E, 12Z, 16Z, 19Z-hexaenoic acid (maresin 1). In addition, maresin 1 is produced by combined actions of platelets and neutrophils[25]. Through the action of 12-LOX in platelets, DHA is converted into 13S, 14S-epoxy-maresin, which is then transformed into maresin 1 by neutrophils. The substrates and initial steps for the biosynthesis of maresin 2 are the same as for maresin 1. The difference is that when DHA is converted to the intermediate 13S,14S-epoxy-maresin, it is oxidized to 13R,14S-dihydroxy-docosahexaenoic acid (13R, 14S-diHDHA) (maresin 2) by soluble epoxide hydrolase (sEH) within human macrophages[36]. MCTR is a conjugate in the process of maresin-induced tissue regeneration, including MCTR1 (13R-glutathionyl, 14S-hydroxy-4Z, 7Z, 9E, 11E, 13R, 14S, 16Z, 19Z-docosahexaenoic acid), MCTR2 (13R-cysteinylglycinyl, 14S-hydroxy-4Z, 7Z, 9E, 11E, 13R, 14S, 16Z, 19Z-docosahexaenoic acid), MCTR3 (13R-cysteinyl, 14S-hydroxy-4Z, 7Z, 9E, 11E, 13R, 14S, 16Z, 19Z-docosahexaenoic acid)[37]. The biosynthesis of MCTRs (like that of maresins 1 and 2) is initiated by 12-LOX. The 13S, 14S-epoxy-maresin is converted to MCTR1 by the catalysis of glutathione S-transferase MU 4 (GSTM4) and leukotriene C4 synthase (LTC4S). MCTR1 is a precursor of MCTR2 and is converted to MCTR2 under the catalysis of gamma-glutamyl transferase (GGT). The biosynthesis of MCTR3 is based on MCTR2, with the catalysis of dipeptidases (DPEP), MCTR2 is converted to MCTR3[38]. Conversion relationship between DHA and maresin isomers is shown in Figure 2.

Biological Actions and Possible Mechanisms of Maresins

Inflammation is a defense-based pathological process that occurs in the stimulation of various damage factors in living tissues, which is the result of interaction between inflammatory cells, inflammatory factors and tissues in the body[39]. As emerging lipid mediators, SPMs inhibit inflammation-induced tissue damage by down-regulating inflammatory mediators, up-regulating anti-inflammatory mediators, and limiting tissue infiltration by neutrophils[40]. Maresins as a category of new effective anti-inflammatory mediators, have a strong protective effect in inflammation, oxidative stress and immune diseases. As far as the current research proves, the cell actions of maresins mainly promote the polarization and phagocytosis of M2 macrophages[41], inhibit the infiltration of neutrophils[25], and induce Treg generation[42]. Maresin 1 inhibits the differentiation of naive T cells into T-helper 1 (TH1) and T-helper 17 (TH17) and promotes differentiation into Treg[43]. In various inflammatory environments, maresins inhibit the expression of pro-inflammatory cytokines such as IL-6, TNF-α and IL-lβ by inhibiting TLR4/MAPK/NF-κB signaling pathway. Not only that, maresins can inhibit the expression of TGF-β1, thereby inhibiting the phenotype transformation of fibroblasts by inhibiting the ERK/Smad signaling pathway. Maresins increase the expression of oxidoreductase and detoxification enzymes by activating the Nrf-2 signaling pathway, while reducing ROS generation by inhibiting the NF-κB signaling pathway[44]. By activating AMPK and PPARα, which can inhibit endoplasmic reticulum (ER) stress, thereby protecting the body. The molecular identification of mareisns signal through its receptor has not yet been identified. The actions of maresins were shown in Figure 3. Inferred from current research, maresin 1 blocked transient receptor potential V1-mediated currents in neurons[45], acts as a ligand for Retinoid related orphan receptor α (RORα), inhibits TLR4 signaling. Chiang et al[46] has revealed that maresin 1 can activate LGR6, a member of the glycoprotein hormone receptor subfamily of rhodopsin-like GPCR, which initiates cAMP and impedance change, as well as stimulates innate immune responses on PMN, monocytes, and MΦ. Further research may reveal the receptors and mechanisms of maresins.

The Actions of Maresins in Diseases

Maresins in Lung Disease

Nordgren et al[47] showed that maresin 1 can protect human bronchial epithelial cells that are exposed to organic dust by activating protein kinase C subtype α (PKCα) and protein kinase C subtype e (PKCϵ) thus reducing the release of pro-inflammatory cytokines like IL-6 and IL-8. In a mouse model of acute restrictive pneumonia caused by repeated exposure to organic dust, it was observed that maresin 1 can significantly limit neutrophil infiltration in bronchial inflammation, down-regulate the production of pro-inflammatory mediators such as IL-6, TNF-α,

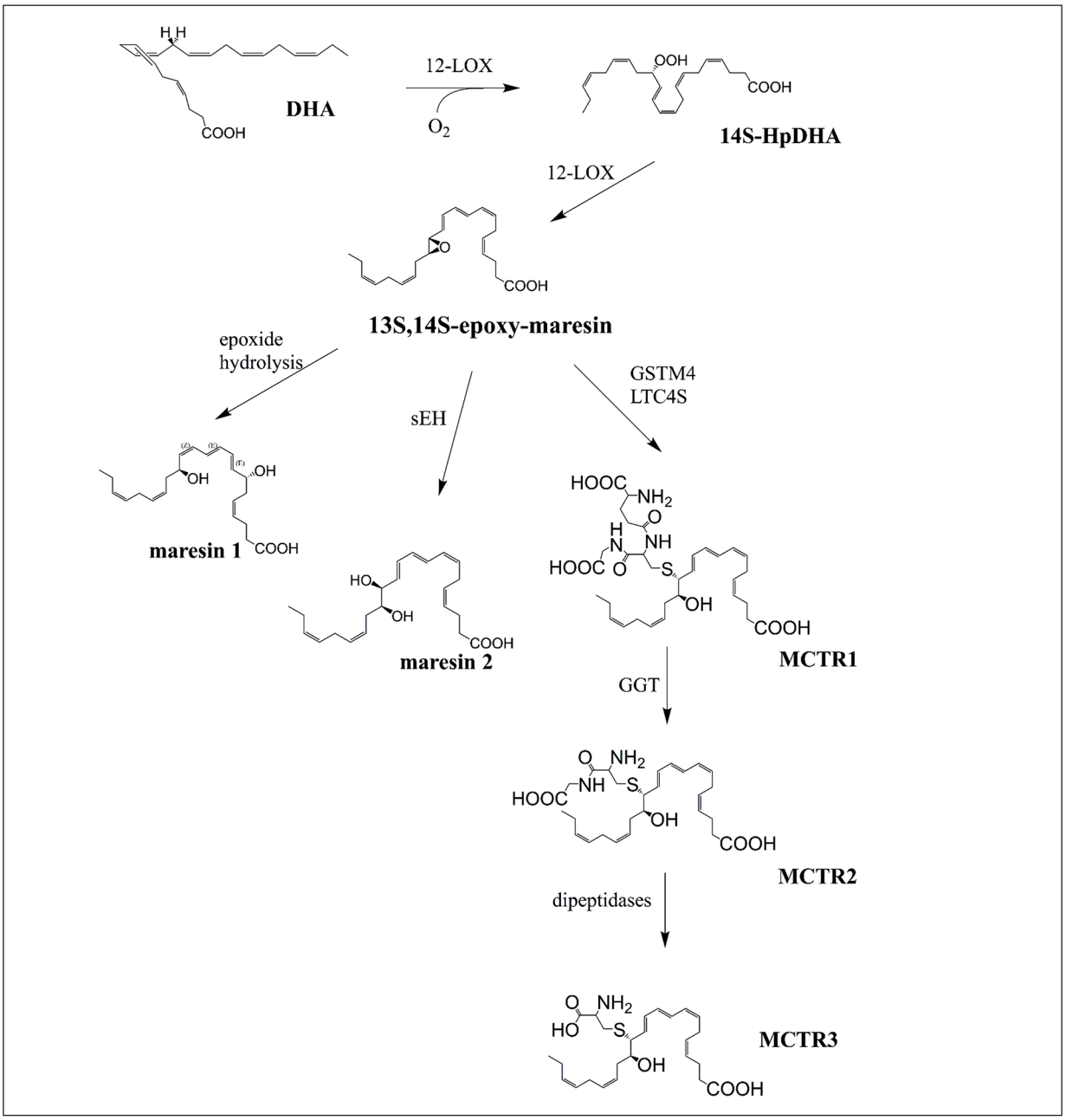

Figure 2. The production of maresins. Abbreviations: GSTM4, glutathione S-transferase MU 4; LTC4S, leukotriene C4 synthase; GGT, gamma-glutamyl transferase.

chemokines and lung-cell adhesion molecules[48]. In another experiment, high doses of maresin 1 attenuated LPS-induced lung injury in mice by inhibiting neutrophil adhesion and decreasing levels of pro-inflammatory cytokines[49]. In a rat model of pulmonary edema, it was found that maresin 1 can effectively regulate alveolar fluid clearance (AFC), promote the expression of Na, K-ATPase, increase the activity of Na, K-ATPase and of the epithelial sodium channel (ENaC) *in vivo* and *in vitro*, which proved that maresin1 increases Na, K-ATPase expression to promote AFC via the ALX/PI3K/Nedd4-2 signaling pathway[50]. ENaC and Na, K-ATPase are generally considered to be the major determinants of AFC, which is the driving force for the removal of edema fluid from the alveolar space by ion transport-dependent mechanisms[51].

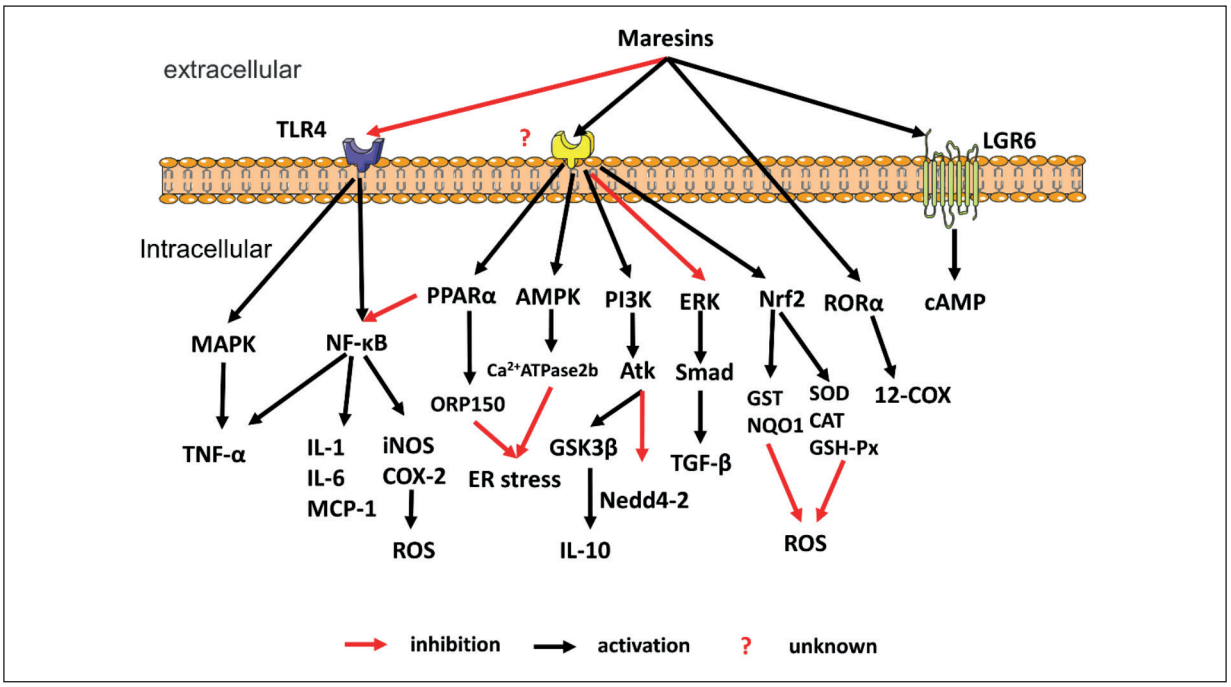

Figure 3. Biological actions and mechanisms of maresins.

Recently, in a mouse study, it was observed that maresin 1 promoted de novo generation of regulatory T cells and interacted with type 2 innate lymphoid cells to inhibit TGF-β-dependent cytokine production, which effectively reduced lung inflammation. This also revealed a new mechanism by which maresins address-allergic inflammatory diseases[42]. In a recent study, maresin 1 was shown to attenuate pulmonary fibrosis by inhibiting epithelial-mesenchymal transition *in vitro*. In addition, maresin 1 inhibited TGF-β1-induced proliferation, migration and differentiation of human lung fibroblasts[52,53]. This suggests that a new ant-inflammatory drug based on maresin 1 could treat chronic lung inflammatory diseases such as pulmonary fibrosis.

Maresins in Liver Disease

Hepatitis is one of the most common liver diseases[54]. Previous studies[55,56] demonstrated that various pathogenic factors such as drugs, viruses, parasites, bacteria, chemicals, alcohol and other hepatotoxic agents can cause damage to liver cells. Long-term inflammatory stimuli can cause liver tissue fibrosis and progression to cirrhosis or even liver cancer[57]. As an anti-inflammatory mediator, maresin 1 plays an important role in reducing hepatocyte inflammation, fibrosis and steatosis[58]. In a CCl4-induced liver injury test in mice, maresin 1 attenuated liver oxidative stress by reducing the level of oxygen free radicals and thiobarbituric-acid reactive substances in liver tissue. Moreover, maresin 1 significantly reduced serum levels of several pro-inflammatory cytokines, including IL-6, IL-1β, TNF-α and MCP-1. At the same time, expression of the anti-inflammatory cytokine IL-10 was promoted by maresin 1. In addition, maresin 1 inhibits the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) in liver treated with CCl4, indicating that the key protective effect of maresin 1 in the liver is anti-inflammatory in nature. In terms of signal transduction, maresin 1 inhibits the classical MAPK and NF-κB inflammatory pathways, thereby reducing oxidative stress and inflammation[44]. Non-alcoholic fatty liver disease (NAFLD) is the most common disease of the liver[59], characterized by an excessive accumulation of triglycerides in hepatocytes[60]. Activation of ER stress and the unfolded protein response (UPR) are hallmarks of NAFLD[61]. Jung et al[62] of HFD mice showed that maresin 1 attenuates NAFLD by inhibiting ER stress via the AMPK-SERCA2b pathway. Maresin 1 also led to an increase in oxygen-regulated protein 150 (ORP150) expression which is responsible for the inhibition of ER stress. Furthermore, maresin 1

was found to act as a ligand for RORα and enhanced RORα expression. In turn, RORα effectively enhances M2 polarization in liver macrophages via Kruppel-like factor 4, which facilitates the regression of inflammation, the pathway is shown in Figure 4. Moreover, RORα can increase the expression of 12-LOX, a key enzyme in maresin 1 biosynthesis, thereby further enhancing the biological effects of maresin 1[63].

Maresins in Vascular Disease

Atherosclerosis is a common chronic cardiovascular inflammatory disease that is characterized by the deposition of large amounts of lipids and inflammatory cells onto the vessel wall[64]. Vascular inflammation increases the likelihood of atherothrombotis, which may manifest as plaque ruptures or erosions[65]. Viola et al[66] in mice confirmed that as atherosclerosis progresses, levels of anti-inflammatory factors such as resolvin D2 and maresin 1 decrease. Of note, in therapeutic settings, maresin 1 and resolvin D2 were found to act on local macrophages, inducing macrophage phenotypic changes and facilitating the breakdown and metabolism of lipids. As a consequence, surrounding smooth muscle cells were stimulated to produce collagen fibers, which stabilized the atherosclerotic plaque and prevent rupture. It was also demonstrated that neointimal hyperplasia was attenuated after systemic administration of resolvin D2 and maresin 1. Maresin 1 reduced the thickening of vascular endothelium by inhibiting the activation of vascular smooth muscle and by attenuating the proliferative response at vascular injury sites[67]. M2 macrophages contribute to the maintenance of homeostasis during inflammation and atherosclerosis, and maresin 1 is one of the most important mediators of this function[68-70]. Chatterjee et al[71] demonstrated how maresin 1 resolved inflammation in the vascular system. It was observed that, during inflammation, TNF-α induces oxidative stress in vascular endothelial cells and promotes the expression of NADPH oxidase. Additionally, monocytes and other intravascular cells release large amounts of cytokines, also in response to TNF-α. In contrast, maresin 1 attenuates ROS production induced by TNF-α. Also, pro-inflammatory transcription factors activated by TNF-α, were found to be attenuated by maresin 1. Finally, maresin 1 was found to increase the production of cAMP, thereby effectively inhibiting the activation of NF-κB and the expression of adhesion molecules. A recent study found that MCTR1 and MCTR2 reduce Leukotriene D4-induced vascular leakage in mouse cremaster vessels and that MCTRs inhibited Leukotriene D4-induced reductions of heart rate. This study clearly demonstrated that MCTRs interact with human cysteinyl leukotriene receptor-1 to attenuate leukotriene D4-stimulated vascular responses[37]. In short, maresins provide a promising therapeutic target for the treatment of vascular inflammatory diseases.

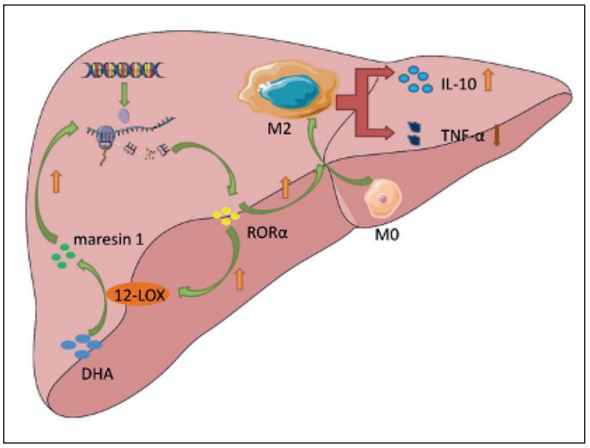

Figure 4. Maresin 1 activates M2 macrophage polarity shift in liver. Maresin 1 acts as a ligand for RORα and enhanced RORα expression. In turn, RORα promotes the synthesis of maresin 1 by up-regulating the expression of LOX-12. At the same time, RORα enhances the polarization of M2 macrophages, which promotes the expression of anti-inflammatory factors such as IL-10 and inhibits the expression of pro-inflammatory factors such as TNF-α, thereby inhibiting liver inflammation.

Maresins Control Pain

Pain, whether caused by mechanical or chemical stimuli, counts as a universally unpleasant experience. In the periphery, cytokines that are released by inflammatory cells stimulate nerve endings, thereby causing pain, while in the spinal cord, pain is primarily mediated by growth factors and chemokines released from glial cells[72]. The use of analgesics can alleviate pain symptoms, but at the same time may also cause adverse reactions[73]. The transient receptor potential channel V1 is expressed in primary sensory neurons and facilitates the transmission of pain signals[74]. Serhan et al[75] observed that maresin 1 dose-dependently blocked transient receptor potential V1-mediated currents in neurons, thereby inhibiting neuropathic pain caused by inflammatory factors and chemicals. Maresin 1 also reduces temporomandibular arthritis pain by regulating synaptic plasticity in the trigeminal nervous sys-

tem[45]. Maresin 1 has crucial roles by inhibiting NF-κB activation, stimulating the release of neuropeptides, and activating astrocytes and microglia[76,77]. The activation of astrocytes and microglia, and secretion of cytokines by neurons mediate neuropathic pain[78]. This suggests that SPMs, including maresins, may be suitable as new anti-inflammatory/analgesic agents.

Maresins in Sepsis

Sepsis refers to a systemic inflammatory response syndrome that is triggered by infections, and that can lead to organ dysfunction and circulatory disorders[79]. The pathophysiological causes of sepsis may include the excessive production of inflammatory factors, as well as a lack of anti-inflammatory factors[80]. Fatty acid intake can effectively inhibit inflammation and protect tissues from damage[81]. In a mouse study, maresin 1 exhibited protective effect in sepsis by decreasing the levels of alanine aminotransferase, aspartate aminotransferase, and blood urea nitrogen in serum[82]. Additional findings were that maresin 1 reduces levels of lipopolysaccharides and pro-inflammatory cytokines such as IL-6, TNF-α and IL-1β. At the same time, maresin 1 alleviated damage of organs such as liver, kidney and lungs following cecal ligation and puncture surgery of the mice. In addition to these observations, another relevant finding is that maresin 1 may reduce the concentration of reactive oxygen species, reduce the number of neutrophils, and reduce the concentration of lactic acid in the inflammatory environment. Moreover, by increasing the concentration of cAMP to alleviate damage to mitochondria, further progression of inflammation is halted[83]. Intestinal infections and inflammation caused by bacteria can also be alleviated by maresin 1[84]. Two new molecules derived from maresin 1 in infectious exudates, i.e., 14-oxo-maresin 1 and 22-OH-maresin 1, enhance human macrophage phagocytosis of bacteria. A new family of macrophage-derived pro-resolving and tissue-regenerative molecules was recently identified and coined MCTR[37]. MCTR3, which is produced from DHA by E. coli-activated human macrophages, was identified in sepsis patients and was found to accelerate resolution of E. coli infection[85]. Moreover, MCTR3 was shown to be a potent bioactive molecule found in human lymph nodes, serum, and plasma, which is capable of enhancing human neutrophil- and macrophage responses. However, further studies are needed to determine how MCTR3 enhances human neutrophil- and macrophage responses. These observations suggest that pharmaceuticals targeting the levels of anti-inflammatory mediators such as lipoxins, resolvins, protectins and maresins may be an effective approach to prevent or manage sepsis.

Maresins in Nervous System Diseases

Innate immunological activation plays an important role in the pathology of many neurodegenerative diseases. However, over the past few decades, it has become clear that abnormal inflammatory activity within the central nervous system (CNS) may lead to neuronal dysfunction[86]. Although inflammation is considered a physiologically beneficial response that promotes clearance of debris and that contributes to tissue repair, sustained inflammation can cause damage to the CNS[87]. Given the limited regenerative capacity of neurons, excessive neuronal damage in the CNS has dire consequences for motor- and cognitive functions. Common inflammation-related neurological diseases include Parkinson's disease, Alzheimer's disease (AD), multiple sclerosis, and amyotrophic lateral sclerosis[88]. One of the pathological hallmarks of many neurodegenerative diseases is the accumulation of misfolded proteins within the ER of neurons and glial cells[89]. In the previous section of this article, we mentioned that maresin 1 reduces hepatocyte damage by inhibiting ER stress and by inhibiting the formation of NAFLD[62]. Ohuchi et al[90] showed that maresin 1 also protected neurons from damage by inhibiting ER stress and inhibiting NF-κB activation. All in all, maresins are involved in the resolution of neuronal inflammation and are protective of the nervous system.

Because of demographic developments, AD is becoming more common among the elderly. With the rapidly increasing number of AD patients, more and more researchers are paying attention to this topic[91]. Among the pathological hallmarks of AD are amyloid plaques and neurofibrillary tangles. Amyloid plaques are extracellular accumulations composed of abnormally folded Aβ, while neurofibrillary tangles were composed of hyperphosphorylated tau protein[92]. Maresin 1 has potent pro-resolving actions on microglia and by stimulating the phagocytosis of Aβ42 and downregulating pro-inflammatory markers[88]. In addition, maresin 1 significantly downregulated the levels of the 67 kDa transmembrane glycoprotein, CD33. This molecule is expressed by microglia,

and its levels are generally increased in AD patients in association with decreases in cognitive functioning[93].

In a mouse model of perioperative neurocognitive disorders, maresin 1 was found to exert unique anti-inflammatory effects, e.g., by regulating macrophage- and neutrophil infiltration, NF-κB signaling, and post-inflammatory cytokine release[94]. Similarly, maresin 1 appears to effectively enhance multiple stages of inflammation resolution after spinal cord injury. These effects include a down-regulation of inflammatory cytokines, a reduction of the number of neutrophils and macrophages, promotion of macrophage phenotypic changes, and an enhancement of macrophage phagocytic activity[33]. Therefore, therapeutic interventions based on maresins may be useful for the treatment of acute and chronic inflammation of the nervous system.

Maresins in Kidney Diseases

Acute renal injury is one of the most common renal diseases, which may ultimately lead to acute renal failure[95]. The TLR4/MAPK/NF-κB signaling pathways were identified as mechanisms underlying renal inflammation[96]. Qiu et al[97] showed that maresin 1 significantly reduced TNF-α and IL-6 levels in the kidney, while it increased the level of IL-10. It also prevents renal ischemia/reperfusion injury by inhibiting the TLR4-, MAPK-, and NF-κB pathways and activating the Nrf-2 pathway that mediates anti-oxidative-stress responses. The expression of antioxidant enzymes, including HO-1, SOD and NQO-1, which alleviated kidney injure, were increased by activating the Nrf-2 pathway. Similar mechanisms are activated in response to cerebral ischemia-reperfusion injury[98]. In addition, Tang et al[99] showed that maresin 1 can reduce glomerular fibrosis, thereby reducing the incidence of diabetic nephropathy.

Maresins in Other Inflammation Diseases

Inflammation of tendons and muscles is a common cause of dyskinesia[100]. Injections with non-steroidal anti-inflammatory drugs are commonly used as a treatment for Achilles tendinitis[101]. Dakin et al[102] showed that a range of lipid mediators, including maresins, effectively inhibited inflammation-related processes by reducing inflammatory cell infiltration and the release of inflammatory cytokines. Similarly, a clinical trial confirmed that maresin 1 ameliorated the progression of rheumatoid arthritis by upregulating maresin 1 downstream microRNA, miRNA-21, which increased the proportion of Treg cells while reducing the proportion of Th17 cells[103]. Several recent studies showed that maresin 1 exhibited anti-inflammatory and anti-microbial effects by inducing NF-κB nuclear translocation and Nrf-2 translocation in tuberculosis patients. This is also related to the fact that maresins can promote endogenous anti-inflammatory factor expression, activate macrophage and inhibit the release of inflammatory factors. The experiment found that the application of maresin 1 directly reduced the expression of TNF-α, while indirectly reducing the production of inflammatory cytokines (such as IL-6 and TNF-α) through the Nrf-2 pathway. In addition, the experiment also suggested that the mechanism of action of maresin 1 may be related to GPCR signaling of macrophage. This provides a new direction for maresins' researches[104]. Moreover, the anti-inflammatory effects of maresins were also found in other diseases such as skin inflammation and periodontitis[104-107]. In sum, there is now substantial evidence supporting the clinical potential of maresins as therapeutic targets.

Conclusions

In recent years, the regression of inflammation has become the focus of research, which has elucidated its underlying mechanisms and explored related strategies for inflammation treatment. Many of the published studies suggest the clinical potential of anti-inflammatory and pro-resolving effects of endogenous anti-inflammatory factors and their stable analogues. Of particular interest is the biosynthesis of maresins, which is initiated by human macrophage 12-lipoxygenase. This enzyme converts DHA to the epoxide intermediate 13S, 14S-epoxy-maresin, which itself exhibits anti-inflammatory effects and promotes macrophage phenotypic switching. 13S, 14S-epoxy-maresin, in turn, is enzymatically converted to maresin 1, which exhibits potent pro-resolving, anti-inflammatory and tissue-regeneration effects. The present review highlighted the various roles of maresins in acute and chronic inflammatory processes occurring in different organs and tissues. In acute or chronic inflammatory states, maresins play protective roles by limiting neutrophil infiltration, enhancing phagocytosis of macrophages, reducing the production of pro-inflammatory factors, reducing tissue fibrosis, inhibiting the activation of NF-κB, and stimulating tissue regeneration.

In conclusion, the described roles of maresins as endogenous, self-limiting factors in inflammation suggest maresins as promising new targets for anti-inflammatory, therapeutic interventions.

Conflict of Interest

The paper has not been submitted elsewhere for publication, and all the authors listed have approved the manuscript. There are no conflicts of interest associated with this study.

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Authors' Contribution

Qi-Fan Li wrote the manuscript. Hua Hao revised the manuscript. Wen-Shan Tu was involved in drawing the picture. Ni Guo also contributed to the manuscript. Xiao-Yan Zhou provided the idea for this review and revised the manuscript.

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