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**REVIEW**

- 1 New translational and experimental insights into the role of pro-resolving lipid mediators in inflammatory bowel disease

*Pascoal LB, Palma BB, Chaim FHM, de Castro MM, Damázio TA, Franceschini APMF, Milanski M, Velloso LA, Leal RF*

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## New translational and experimental insights into the role of pro-resolving lipid mediators in inflammatory bowel disease

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### Abstract

The resolution of inflammation is an active process, guided by specialized pro-resolution lipid mediators (SPMs). These mediators originate from polyunsaturated fatty acids, such as omega-3. Sufficient evidence suggests that the beneficial effects attributed to omega-3 are, at least in part, the result of the immunomodulatory action of the SPMs, which act systemically by overcoming inflammation and repairing tissue damage, without suppressing the immune response. Recent studies suggest that an imbalance in the synthesis and/or activity of these compounds may be associated with the pathogenesis of several inflammatory conditions, such as inflammatory bowel disease (IBD). Thus, this review highlights the advances made in recent years with regard to the endogenous synthesis and the biological role of lipoxins, resolvins, protectins, and maresins, as well as their precursors, in the regulation of inflammation; and provides an update on the participation of these mediators in the development and evolution of IBD and the therapeutic approaches that these immunomodulating substances are involved in this context.

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**Core Tip:** Much progress has been made in recent decades regarding the understanding of mediators involved in the exacerbated inflammatory response. We discuss the role of specialized pro-resolving lipid mediators and their precursors in the etiology and management of chronic inflammatory diseases, in particular, inflammatory bowel disease (IBD). Our research is based on the data pointed out by the literature and we suggest new therapeutic approaches using these immunomodulatory substances in IBD.

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## INTRODUCTION

### Mediators involved in the inflammatory response

Inflammation is a complex mechanism that aims entirely at the elimination of an aggressor stimulus and the return to tissue homeostasis. The inflammatory process is almost always arranged in two phases: Acute inflammation and resolution[1]. In general, the acute inflammatory response begins with the recognition of a harmful agent by sentinel cells that have pattern recognition receptors [such as Toll-like receptors (TLR) and non-obese diabetic (NOD)] on its surface[2,3]. As a consequence of sensitization of these receptors, there is an increase in vascular permeability and the influx of leukocytes (mainly neutrophils and monocytes) - which translates clinically into the cardinal signs of inflammation[4,5]. All events involved in this phase are mediated by cytokines [tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-1, IL-6, and interferon (IFN)- $\gamma$ ], chemokines, and pro-inflammatory lipid mediators (leukotrienes and prostaglandins). All these acts together by increasing the expression of cell adhesion molecules (integrins and selectins), and the migration of granulocytes and activating T cells, which ultimately signal an acquired immune response that overlaps the innate response[6,7]. As the triggering factor of inflammation is extinguished, the inflammatory process tends to be suppressed from the concomitant production of anti-inflammatory and resolute substances, resulting, then, in the restoration and normalization of the affected tissue[1,8]. However, if the stimulus is not eliminated or failures occur in the resolution of the inflammatory response, the inflammatory process can become chronic, leading to tissue damage due to the permanence, exacerbation of the activity of polymorphonuclear cells (PMNs), and fibrosis at the affected site[1,3,9].

### Resolution of inflammation

The resolution of inflammation was initially reported more than a century ago. However, its understanding as an active process coordinated by endogenous substances is recent[10]. The events involved in the resolution process were first presented by Robbins and Cotran[11], and complemented by Savill *et al*[12], who proposed that during the resolution phase, there is a reorganization of the inflammatory exudate accompanied by a phagocytic activity of macrophages, which act by eliminating dead cells and residues resulting from inflammation[13,14]. Subsequently, this concept was expanded by other researchers who identified a potential action of lipid mediators, derived from omega-6 (n-6) and omega-3 (n-3) polyunsaturated fatty acids (PUFAs), in the coordination of these events[13,15]; resolution was actually revealed to be an active process, after studies conducted by Serhan *et al*[16], which analyzed inflammatory exudate of human cell response *in vitro* and in animals during inflammatory processes. Thus, the resolution of inflammation is recognized today as a dynamic and hierarchical process, whose main actors are lipid mediators specialized

in pro-resolution.

These specialized pro-resolving lipid mediators (SPMs) were identified through lipidomic analysis of the inflammatory exudate cells from the murine air pouch model during the resolution phase. This resulted in the discovery of four distinct families: Lipoxins (LXs), resolvins, protectins, and maresins (MaRs), which are synthesized both temporally and spatially, from PUFAs[17,18]. The main inflammatory mediators involved in this process and the sequence of events are illustrated in [Figure 1](#).

Uncontrolled, excessive acute and chronic unresolved inflammation can result in the development of several human diseases, such as cardiovascular disease, cancer, rheumatoid arthritis, periodontal disease, asthma, diabetes, neurological disorders such as Alzheimer's disease, and inflammatory bowel diseases (IBD). Several studies have shown that, at least in part, the decrease in endogenous biosynthesis or activity of these SPMs could be involved in exacerbating the inflammatory response found in these conditions and that restoring the function of these mediators could help control and treat these diseases[9,13,19].

Therefore, based on this brief presentation of the inflammatory response and imbalances of both pro- and anti-inflammatory mediators involved in this process, this review aims to gather the main recent findings highlighted in the literature on the molecular aspects of the inflammation, and mechanism of action of the SPMs and their precursors. Moreover, the role of these mediators in chronic inflammatory diseases, such as IBD, will be emphasized by depicting its pathogenesis, aspects of the remission maintenance, and the potential of SPMs as a therapeutic approach in this scenario.

## NOVEL PRO-RESOLVING LIPID MEDIATORS THAT ACT IN INFLAMMATORY RESOLUTION

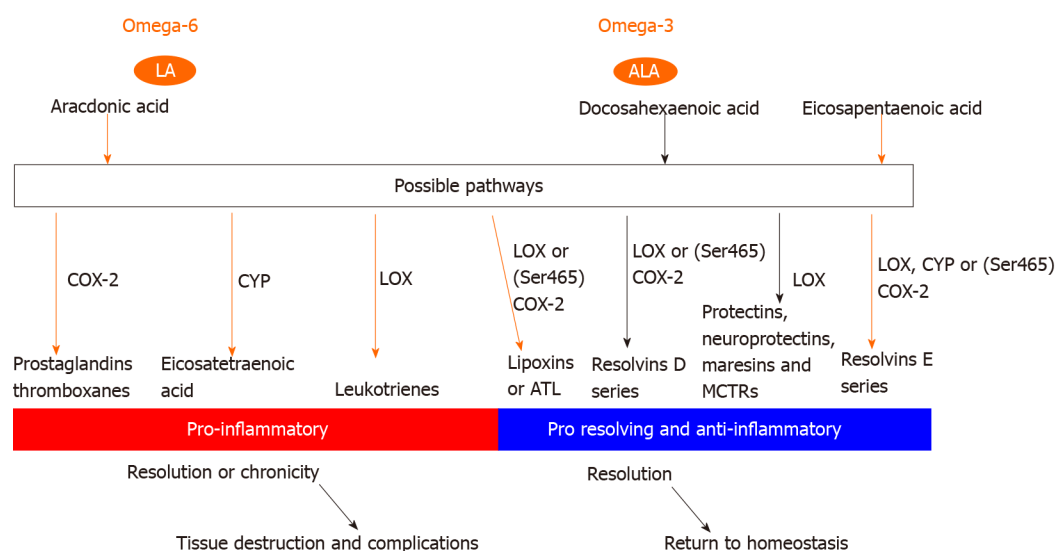
A new genus of pro-resolving lipid mediators was uncovered from studies into the mechanisms in resolution of self-limited inflammation. These substances were termed SPMs, such as LXs, resolvins, protectins, and MaRs. These lipid mediators are each temporally produced by resolving-exudates with distinct actions for return to homeostasis[1,3,9].

SPMs have potent anti-inflammatory and novel pro-resolving mechanisms that enhance microbial clearance. They bind to different receptors and share among themselves the ability to modulate the expression of pro-inflammatory cytokines, pathways associated with cyclooxygenase-2 (COX-2) and nuclear factor kappa B (NF- $\kappa$ B), and cell adhesion molecules; limit the flow of neutrophils to the inflamed site and induce apoptosis of those present there; increase the recruitment of monocytes; stimulate phagocytosis of apoptotic cells and cellular debris; encourage the return of cells present in inflammatory exudate to blood and/or lymphatic vessels; and induce tissue repair, returning to tissue homeostasis, without expressing immunosuppressive activity at any time and with potential action manifested in doses from picograms to nanograms[10,20-23].

The effects of these immunomodulatory substances have been made evident on the microbial defense, pain, organ protection and tissue regeneration, wound healing, cancer, reproduction, and neurobiology-cognition[14-16]. This topic will address the functions of SPMs in resolution physiology.

**LXs:** LXs were the first pro-resolution mediators to be identified. They originate from ascorbic acid (AA), an n-6 PUFA, extracted from cell membranes, through the action of phospholipase enzyme A2 (cPLA2), during the inflammatory process. AA serves as a precursor for both the formation of leukotrienes and prostaglandins, as well as for LXs, depending on the inflammation stage[19,24]. The synthesis of LXA4 and LXB4 occurs from the oxidation of AA, under stimuli of cell-cell interactions that provide the enzymes necessary for the conversion of fatty acid through two main pathways: (1) Oxygenation of AA by 15-lipoxygenase 15-LOX (present in epithelial cells, eosinophils, and monocytes) followed by conversion by 5-LOX (present in neutrophils), with formation of compounds that will be hydrolyzed by LXA4 or LXB4 hydrolase to generate bioactive LXs; or (2) Through the interaction between leukocytes and platelets, acting on 5-LOX and 12-LOX[25,26]. Furthermore, LXs can be synthesized in the presence of aspirin, which acetylates serine residue of COX-2 and inhibits the formation of thromboxanes and prostaglandins, thus facilitating the conversion of AA into an intermediate compound (15R-HETE) that, in turn, undergoes the action of 5-LOX, producing bioactive epimers of LXs, called aspirin-activated LXs ([Figure 1](#))[26-29]. LXs act mainly through their interaction with the membrane G-protein coupled





**Figure 1 Schematic illustration of biosynthesis and action of lipid mediators involved in inflammatory response.** AA: Arachidonic acid; DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid; COX-2: Cyclooxygenase-2; CYP: Cytochrome P450 enzymes; LOX: Lipoxygenase; Ser465: Serine residue 465; ATL: Aspirin-activated lipoxins; LA: Linoleic acid; ALA:  $\alpha$ -Linolenic acid.

formyl peptide receptor 2 (ALX/FPR2), but can also exert their action by binding with protein receptor G32 (GPR32), cysteinyl leukotriene receptors, aryl hydrocarbon receptor, and growth factor receptors[28-31]. A result of the interaction with these receptors is that LXs are able to act on numerous tissues, highlighting their action under monocytes/macrophages, T lymphocytes, neutrophils, epithelial cells, and fibroblasts[30,31]. In general, LXs stimulate chemotactic activity on PMNs, interrupting the recruitment, activation, and diapedesis of these cells; modulate the action of myeloperoxidase which functions as a potent suppressor of apoptosis, allowing neutrophils to be redirected to programmed death; and activate pathways, such as ERK/NRF2 and PI3K/Akt, which postpone the death of macrophages, and stimulate the internalization of ALX/FPR2, favoring a rearrangement of the cytoskeleton and facilitates phagocytosis, thus providing an optimization of the depurative activity of these leukocytes. Moreover, LXs counter-regulate the expression of pro-inflammatory cytokines, such as TNF- $\alpha$  and IL-8, and transcription factors such as NF- $\kappa$ B and activating protein-1 (closely associated with the control of various inflammatory genes) and peroxisome proliferator-activated receptor gamma (related to the reduction of the inflammatory process); compete antagonistically with leukotriene receptors, and decrease the expression of adhering molecules and the production of superoxide; and modulate the production of metalloproteinases by fibroblasts and the performance of growth factors such as platelet-derived growth factor, epidermal growth factor, vascular endothelial-derived growth factor, and connective tissue growth factor, slowing various proliferation processes, including angiogenesis[27,30-33]. The beneficial effect of LXs and similar substances has been demonstrated in several studies related to inflammatory diseases, including asthma[34], atherosclerosis[35], rheumatoid arthritis[36], obesity[37], and chronic obstructive pulmonary disease[38].

**Resolvins:** Resolvins are lipid mediators biosynthesized from n-3 PUFAs by the action of cPLA2. Currently, resolving E series (RvEs) and D series (RvDs) are recognized, derived from eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), respectively. RvD1-RvD6 have their biosynthesis mediated by 15-LOX or COX-2/aspirin, which converts DHA into an intermediate compound, which is modified by 5-LOX (present in neutrophils) to generate direct precursors of RvDs; RvEs, in turn, have their biosynthetic cascade initiated with the conversion of EPA by the COX-2/aspirin or cytochrome P450 pathways, resulting in an intermediate compound that can undergo action of 5-LOX to form RvE1, or 12/15-LOX in the case of RvE3, or can be changed by 5-LOX and reduced to RvE2[20,39]. RvE1 and RvE2, less powerfully, act by binding to the leukotriene B(4) receptor 1 (BLT1) and mainly to the ChemR23 receptor, widely expressed in antigen-presenting cells (APCs). The RvE1-BLT1 binding is antagonistic to the effects of leukotriene B4 (LTB4), which results in the suppression of the NF- $\kappa$ B pathway and cessation of signals of survival of PMNs. In addition, the

interaction with ChemR23 induces apoptosis and leads to increased PMN phagocytosis, from the activation of PI3K and/or mitogen-activated protein kinases (MAPK) pathways and inactivation of Akt and ERK signaling, which also results in reduced expression of TNF- $\alpha$ , IFN- $\gamma$ , and IL-6, and hinders the diapedesis process of new leukocytes to the site of inflammation and the fibroblast activity[28,31,39,40].

RvDs act essentially from binding to three types of G protein-coupled receptors (GPCRs): ALX/FRP2 - RvD1 and RvD3; GPR32 - RvD1, RvD3 and RvD5; GPR18 - RvD2. RvD4 and RvD6 have not yet had their receptors identified[40,41]. To date, the main studies related to resolvins are concentrated in RvD1 and RvD2[28]. In general, the activation of the ALX/FRP2 receptor by resolvins promotes the inhibition of the MAPK pathway, hindering the process of leukocyte transmigration and expression of inflammatory cytokines, similar to the action of LXA4. In addition, under the action of the GPR32 receptor, resolvins potentiate the phagocytic activity of macrophages and modulate the differentiation of T lymphocytes, stimulating the formation of Treg and inhibiting Th1 and Th17, which reduces the transcription of TNF- $\alpha$  and IFN- $\gamma$  and inactivates the NF- $\kappa$ B pathway. Finally, the RvD2-GPR18 axis acts by improving the non-flogistic phagocytosis of PMNs - partly due to the increase in signal transducer and activator of transcription (STAT)3 phosphorylation, STAT5, ERK1/2, Akt, and ribosomal protein S6 - and limiting neutrophil traffic and the expression of inflammatory mediators, such as TNF- $\alpha$  and IL-1 $\beta$ , besides inducing macrophage polarization to the pro-resolving phenotype (M2)[28,41-44]. Specifically, published data has suggested that the induction of macrophage transformation towards the M2 phenotype could become a potential therapeutic intervention for sepsis and other inflammatory conditions[41,43]. Furthermore, some studies show that resolvins have part of their action performed by their ability to modulate the expression of microRNAs, such as miR-21, miR-219, miR-146b, and miR-208a[40,42].

Additionally, an analgesic capacity of resolvins has also been reported. This probably originates from the inhibition of transient receptor potential (TRP) channels, which are related to the constitution of inflammatory pain[42,45]. The pro-resolution actions of resolvins have also been reported in several studies associated with the attenuation of inflammatory processes, such as in chronic kidney disease[46], periodontitis[47], Alzheimer's disease[48] obesity[49], and cancer[50].

**Protectins and MaRs:** Protectins and MaRs are two structurally distinct families of potent local mediators, which are also biosynthesized from DHA. The formation of protectins is mediated by 15-LOX, generating intermediate metabolites that are later converted into protectin D1 (PD1) or neuroprotectin D1 (when this phenomenon occurs in neural tissue). MaRs, in turn, are produced by macrophages under the action of 12-LOX from intermediate compounds, resulting in MaR1, MaR2, and a new class of macrophage-derived molecules - MaR conjugates in tissue regeneration[20,51,52]. PD1 is capable of preventing the migration of PMNs and favoring their phagocytosis, modulating the expression of CC chemokine receptor 5. In addition, PD1 inhibits the secretion of TNF- $\alpha$  and IFN- $\gamma$  by T cells and stimulates the apoptosis of these cells through cell signaling associated with lipid rafts present in the plasma membrane[9,19,52]. MaRs present an inhibiting action on PMN flow and incitement of eferocytosis of cells present in the inflammatory exudate. Furthermore, they accelerate tissue repair, inhibit painful stimuli (through the blockade of TRP vanilloid 1, which is an essential nociceptive integrator in primary afferent neurons), deplete the production of LTB4, counter-regulate the production of inflammatory cytokines (IL-1 $\beta$ , IL-6, and TNF- $\alpha$ ), and inhibit the activity of transcription factors such as NF- $\kappa$ B[19,53-55]. Concerning the other SPMs, the identification and structural elucidation of these new families of bioactive resolution mediators have opened the possibility of diverse pathophysiologic actions in several processes including infection, inflammatory pain, tissue regeneration, neuroprotection, neurodegenerative disorders, wound healing, and others[53-55].

## IMPORTANCE OF RATIO OF N-6/N-3 ESSENTIAL FATTY ACIDS AND NUTRITIONAL IMPLICATIONS

There are two classes of essential fatty acids, n-6 and n-3. The distinction between n-6 and n-3 PUFAs is based on the location of the first double bond, counting from the methyl end of the fatty acid molecule[56]. These fatty acids participate in the formation of membrane phospholipids and are considered essential because humans, like all



mammals, cannot synthesize them due to the lack of delta-12 and -15 desaturases enzymes. Therefore, they must obtain n-6 and n-3 PUFAs from their diet. Consequently, feeding and/or supplementation are the main source of linoleic acid [(LA): C18:2 n-6] and  $\alpha$ -LA [(ALA): C18:3 n-3], which are later used as substrates to obtain other n-6 and n-3 series by cellular machinery[56,57]. LA is plentiful in nature and found in most of the seeds. ALA, however, is found in the chloroplasts of green leafy vegetables, in the seeds of flax, rape, chia, and perilla, and in walnuts. Diets based on fish, fish oil, beef, and lamb can also supply LA and ALA. It is important to mention that wild fishes contain more n-3 PUFAs than cultivated ones, because marine fishes feed on phytoplankton and zooplankton that are abundant in n-3 PUFAs whereas farmed fishes consume feed made of cereal and vegetable oils that contain higher proportions of n-6. Similarly, cold-water fishes accumulate higher proportions of n-3 PUFAs that help them to adapt to cold environment than warm-water fishes. Both essential fatty acids are metabolized to longer-chain fatty acids of 20 and 22 carbon atoms[56].

In recent decades, the pattern of consumption of these acids has become the focus of several studies because of their connection to the evolution of inflammatory conditions. The beneficial health effects of n-3 fatty acids EPA and DHA were described first in the Greenland Eskimos who consumed a high seafood diet and had low rates of coronary heart disease, asthma, type 1 diabetes mellitus, and multiple sclerosis[58]. Since that observation was made, the beneficial health effects of n-3 fatty acids have been extended to include advantages related to cancer, IBD, rheumatoid arthritis, and psoriasis[58-60].

A change of n-6/n-3 ratio in the food supply of Western societies has occurred over the last 150 years. A balance existed between n-6 and n-3 for millions of years during the long evolutionary history, and genetic changes occurred partly in response to these dietary influences. In this sense, some authors highlight an increase in n-6 intake and a reduction of n-3, especially in countries that adopt a "Western diet" - with prevalence of consumption of industrialized foods, meat from terrestrial animals, and fast food to the detriment of vegetables and fish meat and other seafood[59-61].

In light of this reality, studies indicate that the n-6/n-3 ratio offered in the current Western human diet varies between 10:1 and 20:1, reaching values 50 times higher than n-6 in relation to n-3. This proportion is extremely high when compared to that present in the primitive diet, where it remained between 1:1 and 2:1[62,63]. This significant change in the food profile has raised a number of questions over the last 150 years. Although an ideal constant has not yet been established, diets with a high n-6 content have been related to the maintenance of the inflammatory response, hemodynamic changes, and the development of chronic diseases, while the increase in n-3 intake would be able to bar and reverse these pathological processes[60,63,64]. Supporting this data, a cross-sectional study found significantly lower levels of systemic inflammation, manifested by reduced measurements of c-reactive protein (an acute inflammatory protein) and F2-isprostane (a marker of lipid peroxidation), in 646 subjects who had a diet based on fish, vegetables, and fruits compared with other types of diets[65].

To better understand the impact of these fatty acids, it is important to remember some factors that influence the actions and conversions of these fatty acids because they explain part of the controversial results in the literature on the use of PUFAs. Humans can convert LA to AA and ALA to EPA and DHA, but the effects of these fatty acids result essentially from the action of their metabolites in the body. When ingested, these fatty acids can generate other fatty acids of the same family, and are then incorporated into cell membranes. The conversion of ALA to EPA and DHA depends on several dietary and genetic factors, including ratio of LA and ALA in the diet, deficiency of other nutrients, gender difference, and polymorphisms in desaturases and elongases. For conversion into new compounds, LA and ALA compete for the same enzymatic group (desaturases and elongases) and can generate, respectively, AA or EPA and DHA[56,66]. The conversion efficiency to generate DHA from ALA is greater in young women compared to that in men due to the estrogen effect[67].

Thus, after biosynthesis and conversion, these new fatty acids, when requested, are available from the plasma membrane by phospholipase A2 and act as substrates for the production of different bioactive agents; among these are the eicosanoids and SPMs[64-68], as detailed in the previous topic and illustrated in Figure 1.

Many studies suggest that the increase of n-3 PUFAs in the diet is able to alter the composition of cell membranes, in order to make available a higher concentration of EPA/DHA and to lower the availability of AA. Consequently, the production of eicosanoids with pro-inflammatory properties would decrease, because of the lower

substrate supply and the enzymatic competition between EPA and AA due to the COX and LOX pathways. This would result in a reduction of pro-inflammatory mediators [57,66,69]. In addition, n-3 PUFAs would also be able to act on the inflammatory pathway through the synthesis of SPMs, such as resolvins, protectins, and MaRs, which act together to allow the restoration of local homeostasis [23,70].

In this context, several studies have evaluated the effect of intake of n-3 PUFAs on inflammatory diseases. Regarding IBD, several studies suggest the change in the dietary pattern as a relevant risk factor in the pathogenesis of the disease [70-73] and relate the increasing incidence of IBD worldwide to the change of n-6/n-3 ratio in the diet of modern societies [74], including long-term prospective studies [75].

Reifen *et al.* [73] evaluated the *in vivo* and *in vitro* effect of plant-derived n-3 on the development of experimental colitis in two different protocols. This study showed a reduction in the damage caused to the mucosa by the aggressor agent, accompanied by a negative regulation in the mRNA expression of pro-inflammatory factors. A similar result was found by another group, which identified a reduction of IL-6, TNF- $\alpha$ , LTB<sub>4</sub>, and nitric oxide (NO) in animals supplemented with n-3 for 4 wk and with experimental colitis induced by 2,4,6-trinitrobenzene sulfonic acid (TNBS) [76]. Positive effects concerning the progression of experimental colitis were also observed in protocols that treated animals with SPMs. This suggests an important role of these substances in the improvement of IBD patients supplemented with n-3 PUFAs [77-80].

Nevertheless, clinical trials evaluating the impact of supplementation and n-3-rich diets on the development of IBD are still quite controversial and conflicting, especially in Crohn's disease (CD), due to the lack of standardization of cohorts, choice of placebos, and therapies (dosages and duration) adopted. In general, they show a discreet beneficial association between the use of n-3 PUFAs and the development of IBD, with reduced disease activity and improvement of quality of life [73,81-83].

Thus, there is evidence in the literature of the potential relevance of PUFAs in the inflammatory signaling and development of chronic disorders. However, more studies should be encouraged to clarify the beneficial effects of n-3 PUFAs, in order to identify novel dietary strategies for maintenance of clinical remission and anti-inflammatory/pro-resolution therapeutic approaches for inflammatory diseases, in particular, IBD.

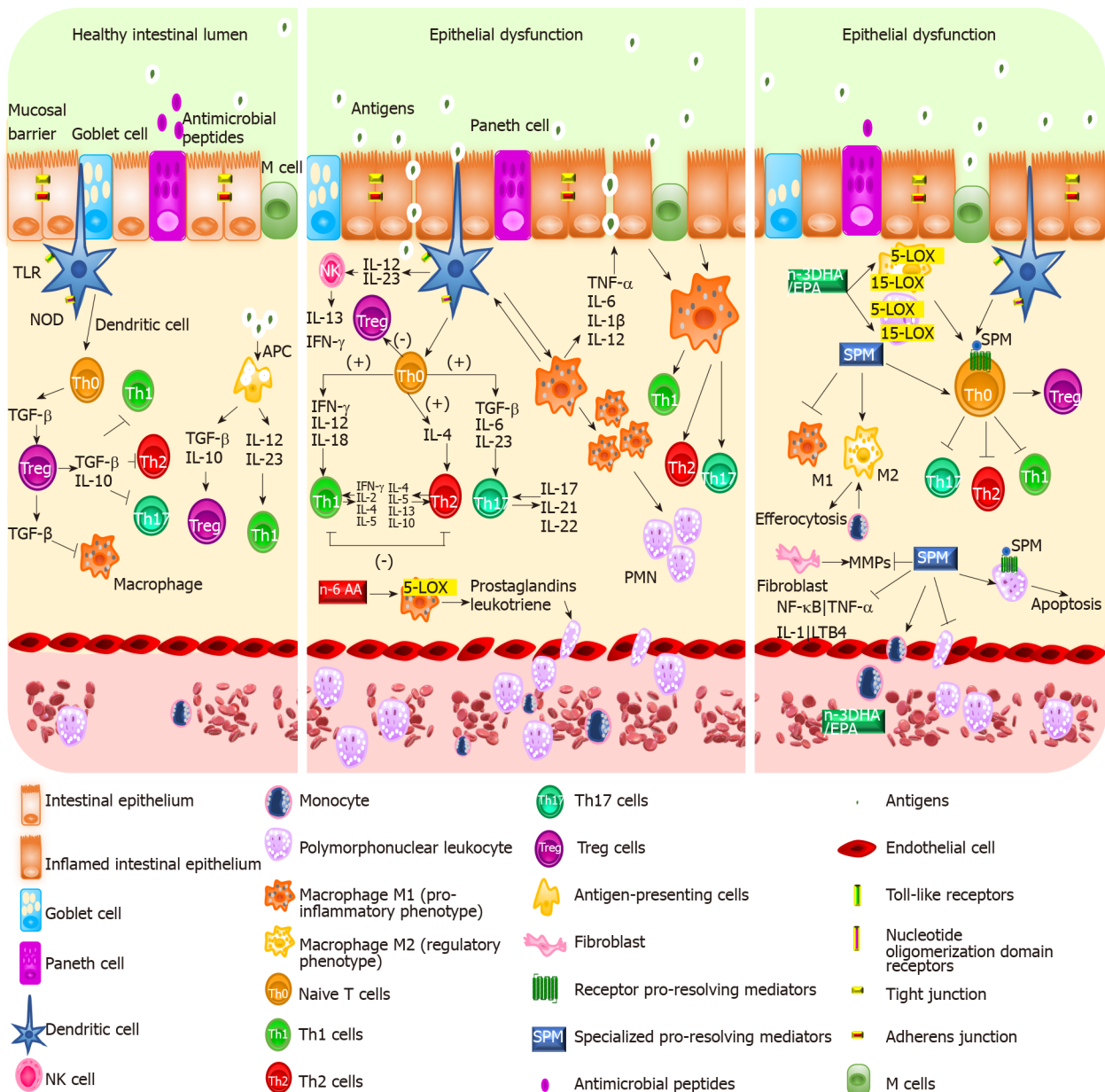
## PARTICULARITIES OF THE INFLAMMATORY RESPONSE PRESENT IN IBD

IBD, which includes CD and ulcerative colitis (UC), seems to involve a shift in the immune system's balance as a pathophysiological component, under the influence of genetic and environmental factors, such as diet and lifestyle. The homeostatic state of the intestinal area is maintained by an interaction between the innate and adaptive immune response in healthy subjects [84]. Studies suggest that changes in this immune balance can cause loss of immune tolerance, leading to a dysregulated immune response, which is associated with the chronic inflammatory mechanism of IBD [85-87].

In this perspective, the immunopathogenesis of IBD is favored by environmental and genetic conditions, and it can be superficially described as the activation of the innate immune response, based on the recognition of luminous antigens by TLRs/NOD type receptors present in specialized cells, due to defects in the intestinal mucosa barrier. Sequentially, the activation of the adaptive immune response with differentiation of T cells and anomalous secretion of pro-inflammatory cytokines, and consequent establishment of chronic inflammation occur [88-90].

The normal intestinal mucosa consists of a layer of epithelial cells covered with mucus secreted by the goblet cells. This mucus, together with other compounds, such as the  $\alpha$ -defensins produced by Paneth cells, plays a role by preventing direct contact between the intestinal epithelium and unknown substances [89,91]. In addition, under normal conditions, this barrier is kept intact through the epithelial cells that are closely linked, with intercellular spaces occluded by the tight junctions [84]. The destruction of the mucus barrier produced by the intestinal epithelium usually occurs in IBD and contributes to exacerbation of the innate immune response.

Paneth cells support the defense of the mucosa through the secretion of antimicrobial peptides (such as  $\alpha$ -defensins), and are related to intestinal inflammation since it has a connection with cellular autophagy. All mediators and cells involved in immunological tolerance, maintenance of the mucous barrier and balance between the inflammatory process, and its resolution are illustrated in Figure 2.



**Figure 2** In the healthy intestinal epithelium, there is preservation of immunological tolerance, and maintenance of the mucous barrier and balance between the inflammatory process and its resolution. In inflammatory bowel disease, there is a loss of intestinal barrier integrity, with consequent activation of innate and adaptive immune responses. There is an intense synthesis of pro-inflammatory mediators, such as leukotrienes and prostaglandins, derived from arachidonic acid, as well as cytokines and chemokines, which lead to the polarization of M1 macrophages, increased influx of polymorphonuclear cells, and differentiation of effector T cells to the detriment of Treg cells. Also, the inflammatory response can be contained from the action of anti-inflammatory factors and specialized pro-resolution lipid mediators (SPMs), which are derived from polyunsaturated fatty acids such as docosahexaenoic acid and eicosapentaenoic acid. SPMs are capable of interfering with the macrophage phenotype, favoring type M2, limiting the traffic of leukocytes, counter-regulating pro-inflammatory mediators, and inducing tissue regeneration. In the absence of SPMs, there may be a failure in the resolution process, leading to chronic inflammation and tissue fibrosis, associated with loss of function. LOX: Lipoxygenase; NOD: Non-obese diabetic; TGF: Transforming growth factor; IFN: Interferon; IL: Interleukin; AA:  $\alpha$ -Linolenic acid; DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid; TLR: Toll-like receptor; SPM: Specialized pro-resolution lipid mediators; NK: Natural killer; TNF: Tumor necrosis factor; PMN: Polymorphonuclear cell.

During inflammatory activation process, lymphocyte differentiation triggered by specific cytokines occurs, producing mainly Th1, Th2, and Th17 responses. Th1 lymphocytes produce IFN- $\gamma$ , TNF- $\alpha$ , and IL-6, acting in conjunction with macrophages to increase the amount of TNF- $\alpha$ , in order to break the original epithelial cells and promote stroma differentiation into fibroblasts. The fibroblast activation by metallo-proteinases leads to marked tissue degeneration[87,92]. Th2 activation, on the other hand, leads to the production of IL-4, IL-5, IL-9, and IL-13, which act on B cells, promoting specialization, in addition to increasing intestinal mucosa permeability and also inducing cell apoptosis. It is important to emphasize that the disturbance of the Th1/Th2 ratio, in any direction, favors the maintenance of the inflammatory process,

since these cells act in a symbiotic way with negative feedback[2]. Finally, Th17 lymphocytes release IL-17A, which plays an important role in recruiting neutrophils to sites of inflammation, besides releasing IL-21, which also stimulates the production of metalloproteinases that will in turn promote degradation of the extracellular matrix [93]. Moreover, studies highlight that IL-17 induces the expression of pro-inflammatory cytokines, such as IL-6 and TNF- $\alpha$ , chemokines, and metalloproteases, agents that can trigger tissue infiltration and the consequent disrepair of the epithelial tissue of the intestinal mucosa. Other functions attributed to this cytokine are the proliferation, maturation, and chemotaxis of neutrophils to inflammatory sites[86]. The role of IL-21, produced by Th1, Th2, and Th17 in IBD, is due to its different effects on the intestine by inducing pro-inflammatory events, either by inducing the production of Th1 cells or by upregulating the pathways of inflammation mediated by Th1 and Th17. Moreover, it seems to be associated with an increase in the cytotoxicity of natural killer cells[86]. Thus, the main pro-inflammatory effects of these cytokines are characterized by the activation of several cellular targets, such as the endothelium, epithelium, monocytes, fibroblasts, macrophages and neutrophils, that promote the induction of metalloproteinases, IL-1 $\beta$ , TNF- $\alpha$ , and chemokines[93,94].

More specifically, in CD there is a differentiation to Th1 and Th17 pattern, stimulated by IFN- $\gamma$ , IL-12, IL18, and transforming growth factor- $\beta$  and with production of IL-17 and TNF- $\alpha$ , cytokines that feed the inflammatory cycle stimulating APCs and perpetuating mucosal inflammation[2,93,95]. In UC, on the other hand, there is a tendency towards differentiation of Th2, with an immune response abnormally mediated by killer T cells and production of IL-4 and IL-13, factors of cytotoxicity and disruption to the epithelial barrier. In addition, in UC there is participation of Th9 cells, which secrete IL-9, triggering apoptosis of enterocytes and inhibiting mucosal healing[84,95].

## MECHANISM OF ACTION OF LIPID MEDIATORS SPECIALIZED IN PRO-RESOLUTION IN THE CONTEXT OF IBD

As previously described, although the etiology of IBD has not been completely elucidated, it has a characteristic inflammatory response model: Significant tissue infiltration of inflammatory cells - such as neutrophils, APCs, T/B lymphocytes, and macrophages - accompanied by high production of pro-inflammatory cytokines, such as TNF- $\alpha$ , IL-1 $\beta$ , and IL-6. In CD, differentiation to Th1 and Th17 cells is observed, with high secretion of IL-12, IL-17, and IFN- $\gamma$ , while in UC there is a predominance of the Th2 response, with greater production of IL-5 and IL-13[96-98].

Currently, IBD treatment aims to heal the lesions of the inflamed mucosa, with consequent relief of symptoms and improvement in patient's quality of life. The therapeutic goals for IBD evolved from only controlling symptoms, to inducing and maintaining clinical and endoscopic remission, leading to healing of the mucosa. However, current therapies for IBD management have potential side effects and/or lack of response[99]. In the case of immunobiologicals, where are considered the current gold standard for the treatment of these diseases, about 10% to 30% of patients do not respond to therapy[100], showing the need for the study and future adoption of new agents capable of acting by complementary inflammatory pathways to ensure a better prognosis for IBD in the future.

Given this fact, recent research highlights the promising role of SPMs in attenuation and prevention of the inflammatory damage in IBD. Several studies evidenced the action of LXA4 in the attenuation of experimental colitis, through negative modulation of pro-inflammatory mediators, increase of the expression of IL-10, and inhibition of the release of vesicular contents of granulocytes[100,101].

Other SPMs, such as RvE1, aspirin-triggered (AT)-RvD1, RvD2, and their intermediate compounds, have demonstrated a potential effect in the control of experimental colitis. Arita *et al*[77] showed that RvE1 protected mice with TNBS-induced colitis, characterized by the improvement of metabolic and histological parameters, reduction of pro-inflammatory factors (TNF- $\alpha$ , IL-1 $\beta$ , IL-12, and NO), and limitation of traffic leukocytes. Other authors have reported that treatment with RvE1 inhibited nuclear translocation of NF- $\kappa$ B and increased the phagocytic activity of macrophages [101]. Bento *et al*[79] investigated the effect of RvD2, AT-RvD1, and 17R-hydroxydocosahexaenoic acid on experimental colitis induced by dextran sodium sulfate (DSS) and TNBS, evidencing the improvement of the clinical profile and histopathological lesions, and cytokine reduction [TNF- $\alpha$ , IL-1 $\beta$ , molecularly imprinting polymers-2, and chemokine (C-X-C motif) ligand (CXCL1)/KC], in addition to decreased expression of



NF- $\kappa$ B and adhesion molecules [vascular cellular adhesion molecule-1, intercellular adhesion molecule (ICAM)-1, and lymphocyte function-associated antigen-1].

Regarding PD1, Masterson *et al*[101] demonstrated that an analog isomer of this mediator was able to inhibit the migration of PMNs and the expression of substances associated with the maintenance of inflammation (TNF- $\alpha$ , IL-1 $\beta$ , IL-6, NO, CXCL1, and CXCL2) in the colon tissue with experimental colitis, highlighting the PD1 activity as a mechanism associated with the protective effect exerted by eosinophils in experimental colitis. Gobbetti *et al*[102] also observed that the administration of PD1 and RvD5 in mice with DSS-induced colitis protected the animals, reducing the levels of pro-inflammatory cytokines and blocking the recruitment of neutrophils. Furthermore, the latter action, being possibly related to the ability of mediators to modulate the expression of adhesion molecules on the surface of neutrophils, hinders the fixation process to the vascular endothelium.

Similarly, Qiu *et al*[103] reported that animals with 5% DSS-induced colitis treated with MaR1 were protected from colitis, with body weight maintenance, reduced disease activity index, and histological lesion protection. In addition, there was an increase in the expression of proteins constituting the intercellular anchorage zone and NFR2 signaling inhibiting macrophage and neutrophil diapedesis, and a reduction in the activation of the TLR4/NF- $\kappa$ B pathway, with a consequent decrease in the production of IL-1 $\beta$  cytokines, IL-6, and TNF- $\alpha$ . A similar result was identified by Marcon *et al*[80] who also observed that MaR1 was able to inhibit the expression of ICAM-1, suggesting a possible mechanism that acts to block leukocyte migration. It was also confirmed, *in vitro*, that MaR1 is able to promote the overexpression of mannose receptor 1 in macrophages, placing then the differentiation of M2 macrophages, as a possible route associated with the positive effects of the administration of MaR1.

Although experimental models of colitis demonstrate the important effects of SPMs on the development of intestinal inflammation, the characterization of the performance of these mediators in IBD in clinical trials is still quite insufficient. In this scenario, altered levels of SPM were identified in human colon biopsies with IBD, accompanied by a positive modulation in the pathway of resolvins and protectins in these samples[102]. Furthermore, it has been noted that patients with UC have little or no LXA4 activity, while patients in remission have elevated levels of this lipid mediator, suggesting a protective capacity of LXA4 by regulating the interaction between leukocytes and enterocytes, inhibiting neutrophil adhesion and diapedesis, suppressing the secretion of cytokines and chemokines by intestinal epithelial cells after an inflammatory stimulus, and stimulating the differentiation and activity of pro-resolving macrophages[9,100,104]. Overall, the results found so far suggest a promising potential of these lipid mediators in IBD. However, further evidence is needed to assess their effectiveness in human patients.

## CONCLUSION

We conclude that the resolution process is indispensable for the contingency of the inflammatory response. This process is governed by a series of SPMs and involves different action fronts, and when they fail, inflammation can establish itself as a chronic process, resulting in a vicious cycle of tissue damage.

Several experimental studies highlight the positive effects of these mediators and their precursors on the attenuation of the exacerbated inflammatory response seen in chronic inflammatory diseases. In the context of IBD, SPMs were able to modulate the secretion of pro-inflammatory cytokines and reduce the recruitment of leukocytes. This demonstrates an important role of these compounds in the development of the inflammatory response, the amelioration of the clinical profile, and the decrease of tissue damage. Regarding the control of chronic intestinal inflammation, different drugs involving anti-inflammatory and immunosuppressive pathways have been studied over the last decades to integrate new drug strategies, but satisfactory results were accompanied by loss of response over time that resulted in recurrences of the disease. In this scenario, although further research is needed to understand the association between IBD and failures in the process of resolution of inflammation, SPMs remain a relevant therapeutic alternative in the context of these diseases, since they are demonstrably able to control inflammation without compromising the host defense mechanism.

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