Specialized Pro-resolving Mediators (SPMs)

Brief Research Review

Executive Summary

- Inflammation is an immune response to insults such as injuries (cuts, wounds, etc.) infections (bacterial, viral, or fungal), or unhealthy dietary patterns.
- Although acute inflammation is a normal, protective response, it can give rise to chronic inflammation if left unresolved.
- Groundbreaking research has discovered that SPMs are produced at the inflamed site after the initial inflammatory response, and function as “resolution agonists,” orchestrating resolution to facilitate the return to homeostasis and tissue healing.
- An important key to controlling/resolving inflammation and subsequently preventing chronic inflammatory conditions lies in SPMs and their pro-resolving properties.
- SPMs are produced from long-chain polyunsaturated fatty acids—especially EPA and DHA—illustrating the importance of appropriate nutrition in the body's resolution of inflammation.
- Although EPA and DHA are metabolic precursors of SPMs, SPMs are directly responsible for resolution activities whereas EPA and DHA are involved in other beneficial biological activities. Therefore, SPM supplementation may represent an effective approach in supporting resolution.

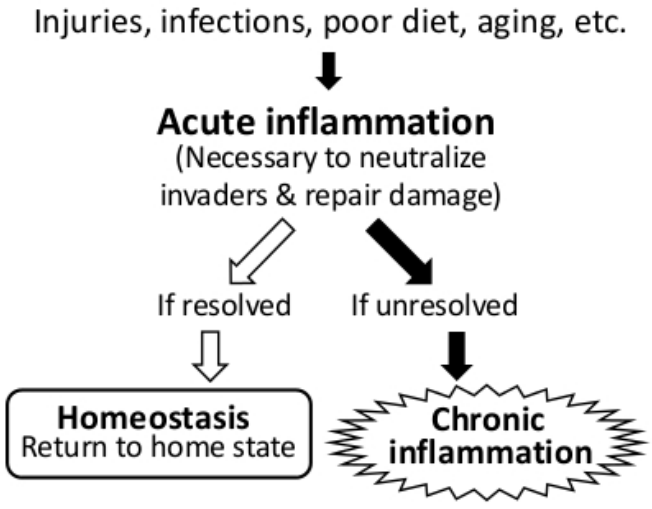
Specialized Pro-resolving Mediators (SPMs), a Novel Nutritional Approach to Resolve Inflammation

IS INFLAMMATION HARMFUL OR HELPFUL TO YOUR HEALTH?

Acute inflammation is a localized, protective immune response of the host in attempt to immediately eliminate invading pathogens and/or repair injured tissue.[1] Unhealthy dietary patterns have also been linked to inflammation.[2] Ideally, an acute inflammatory response is a self-limited process, leading to resolution that enables tissue healing and a return to homeostasis (restoration to the previous normal condition; **Figure 1**).[3]

Acute inflammation, if left unresolved or uncontrolled, can give rise to a prolonged state of chronic inflammation that causes damage to the host, resulting in pain and/or dysfunction (**Figure 1**). Many chronic diseases such as cardiovascular disease, arthritis, diabetes, metabolic syndrome, inflammatory bowel disease, periodontal disease, asthma, and age-related macular degeneration, as well as some neurological disorders, have been linked to chronic inflammation.[4-9] Furthermore, aging may be associated with a mild pro-inflammatory state that has been termed "inflammaging."[10]

Figure 1. Whether the acute inflammation is resolved will determine its biological effect.



Key point: Acute inflammation is a normal defense response. How effectively it resolves determines whether inflammation becomes harmful or helpful to health. The ideal outcome is complete resolution.

A REVELATION IN INFLAMMATION RESOLUTION

An acute inflammatory response begins within seconds to minutes following the presence of harmful stimuli such as pathogens, injuries, or irritants. The initiation phase is orchestrated by pro-inflammatory eicosanoids, cytokines, chemokines, and other chemical messengers.[11,12] Among the first responders are neutrophils—the most abundant type of white blood cells—that travel from the blood stream into the inflamed site (forming exudates, whitish creamy pus) to engulf the stimuli.[3,13] This devouring is termed ***phagocytosis***. What follows is the resolution phase.[14] Scientists have traditionally believed resolution to be a *passive* process that occurs when harmful stimuli are eradicated and the pro-inflammatory signals dissipated. Then came a discovery that potentially offers a new direction for innovative nutritional therapies.

Resolution is an *Active* Process Orchestrated by SPMs

Researchers have learned that an elaborate system is in place to resolve inflammation.[14] Specialized pro-resolving mediators (SPMs) are produced in tissue exudates during the resolution phase and function as "resolution agonists" to accelerate the return to homeostasis (**Figure 2**).[13,14]

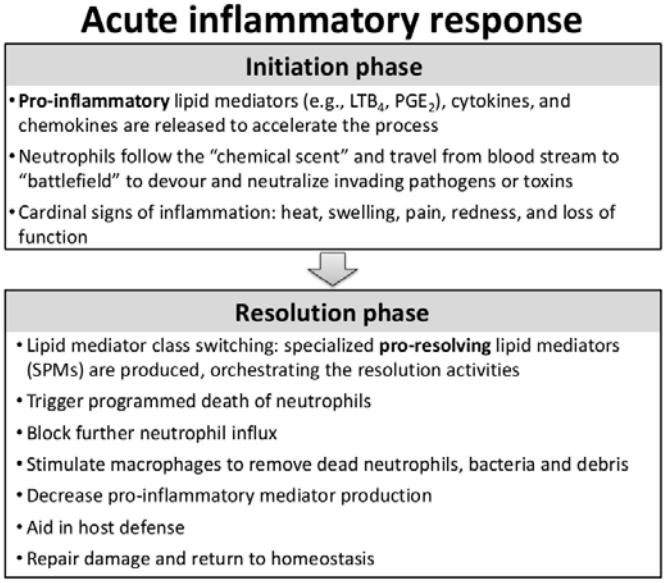


Figure 2. A brief description of the acute inflammatory response.

In order to restore to the previous normal condition, the existing stimulated neutrophils need to be removed from the

inflamed site and additional influx of neutrophils to be stopped, otherwise they would cause collateral tissue damage and persistent inflammation.[15] Extensive experimental research has demonstrated that SPMs block excessive infiltration of neutrophils, regulate a timely apoptosis (programmed cell death) of existing neutrophils, and stimulate macrophages to remove dead neutrophils, debris, and microbes.[16,17] Phagocytosis by macrophages during the resolution phase is also referred to as efferocytosis, literally meaning "burying of dead cells." SPMs may also decrease pro-inflammatory mediator production, enhance efflux of macrophages from inflamed tissues, and promote tissue regeneration.[18-21]

Key point: SPMs are produced during the resolution phase of an acute inflammatory response. They are essential in orchestrating resolution activities, shutting down inflammation, expediting the complete return to homeostasis, and promoting tissue repair.

FAMILIES OF SPMs

In the resolution phase of acute inflammation, long-chain polyunsaturated fatty acids (PUFAs) in tissue exudates are available for the conversion into SPMs.[22-24] Four families of SPMs with distinct chemical structures have been identified; they are resolvins, protectins, maresins, and lipoxins.

The majority of SPMs are biosynthesized from omega-3 fatty acids: eicosapentaenoic acid (EPA) as the substrate for E-series resolvins (RvE1–RvE3), and docosahexaenoic acid (DHA) as the substrate for D-series resolvins (RvD1 – RvD6), protectin D1 (PD1, or NPD1 when formed in neural tissues), and maresin 1 (MaR1) (**Figure 3**).[25]

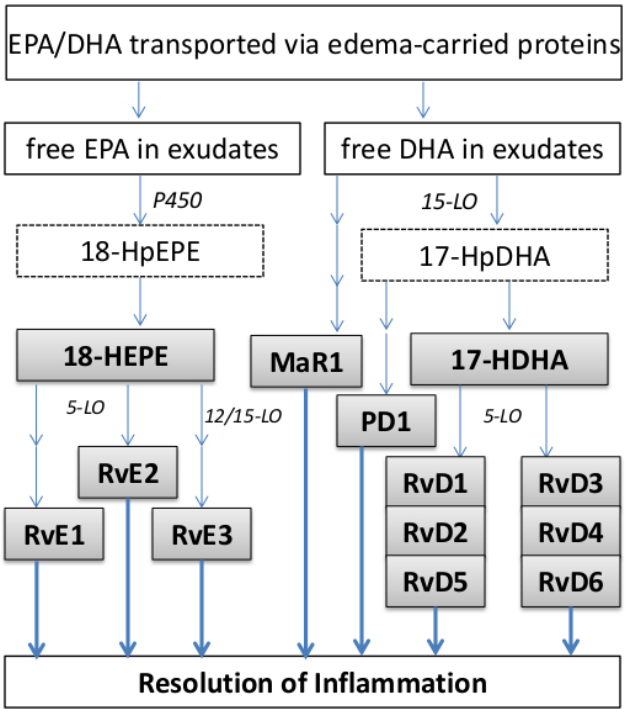


Figure 3. SPMs (grey boxes) that are biosynthesized from omega-3 fatty acids EPA and DHA include E-series and D-series resolvins (Rv), protectins (PD), and maresins (Mar).

To form E-series resolvins, EPA is first converted via a cytochrome P450 pathway into an intermediate, 18-hydroxyeicosapentaenoic acid (18-HEPE). 18-HEPE undergoes enzymatic reactions to form RvE1, RvE2, or RvE3. To yield D-series resolvins, DHA first undergoes a reaction catalyzed by the enzyme 15-lipoxygenase (15-LO) to an intermediate, 17-hydroxydocosahexaenoic acid (17-HDHA). Through different downstream reactions 17-HDHA is converted to RvD1, RvD2, RvD3, RvD4, RvD5, or RvD6. Alternatively, via other enzymatic pathways DHA is metabolized into PD1 (NPD1) or MaR1 (**Figure 3**).[25]

The omega-6 fatty acid, arachidonic acid (AA), is the substrate for pro-inflammatory prostaglandins (PGE_2 and PGD_2) and leukotrienes (LTB_4 and LTC_4), which have a central role in initiating inflammation.[12] However, research has found that during the resolution phase, AA is the substrate for one SPM family called lipoxins (such as LXA4 and LXB4).[26]

Each SPM exerts distinct, resolution-related activities. Through their combined actions, the resolution of inflammation is completed and homeostasis is achieved.

Key point: The omega-3 fatty acids EPA and DHA are the substrates for 3 families of SPMs: resolvins, protectins, and maresins. The omega-6 fatty acid AA is the substrate for 1 family of SPMs: lipoxins.

SPMs Research in Disease Models

SPMs have been shown to have very potent pro-resolving activity when administered to several inflammation-associated animal models of human disease (**Table 1;** reviewed in[25,27]).

Table 1. Research demonstrating SPMs' properties in inflammation-associated animal models of human disease.

SPM	Disease model
E-series resolvins	Skin indications, oral inflammation, periodontitis, peritonitis, asthma, ocular indications, inflammatory pain, colitis
D-series resolvins	Peritonitis, skin indications, kidney ischemia-reperfusion, ocular indications, peritonitis, sepsis, inflammatory pain, obesity-induced insulin resistance
PD1 (NPD1)	Stroke, peritonitis, asthma, kidney ischemia-reperfusion, ocular indications, Alzheimer's disease, neurodegeneration
MaR1	Peritonitis

EPA and DHA Are Not SPMs

Although EPA and DHA can be converted to resolvins, protectins and maresins, they do not have the properties of SPMs; i.e., blocking and limiting further neutrophil infiltration and stimulating macrophage intake and clearance of apoptotic cells, bacteria, and debris at the inflamed site. SPMs exert their biological effects in the picomolar-nanomolar range via activating specific G-protein coupled receptors (GPCRs), whereas EPA and DHA have no bioactions in that concentration range.[28] Furthermore, because the biological effects of EPA and DHA are subject to multiple downstream metabolic checkpoints (e.g., receptors and enzymatic activities), direct treatment with SPMs or omega-3 intermediate metabolites such as 18-HEPE and 17-HDHA may represent a more targeted, effective approach in promoting resolution than simply increasing intakes of the parent omega-3 PUFAs.

BENEFITS OF RESOLUTION-BASED NUTRITION

For decades, blocking initiation-phase pro-inflammatory mediators (e.g., prostaglandins) or enzymes (e.g., COX-2 enzyme) by pharmacological agents such as nonsteroidal anti-inflammatory drugs (NSAIDs) has been the go-to therapy for many acute and chronic inflammatory conditions. However, **anti-inflammation is not the same as pro-resolution.** Because initiation phase activities are required to "jump start" resolution, traditional COX-2 and lipoxygenase inhibitors may delay resolution activities and undermine the body's attempt to return to homeostasis and tissue healing.[19,29,30] Unresolved inflammation and unhealed tissue can lead to fibrosis that can impair organ function.[1]

Thus, an important key to controlling/resolving inflammation and subsequently preventing chronic inflammatory conditions lies in SPMs and their pro-resolving properties that switch an inflammatory response toward resolution and homeostasis. That SPMs are enzymatically produced from long-chain PUFA (especially EPA and DHA) in tissue exudates indicates the indispensable role of nutrition in regulating inflammation and promoting resolution.

Key point: Anti-inflammation is not synonymous with pro-resolution. SPMs and their pro-resolving properties may represent an important key to promoting the resolution of inflammation without suppressing host immune defenses.

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