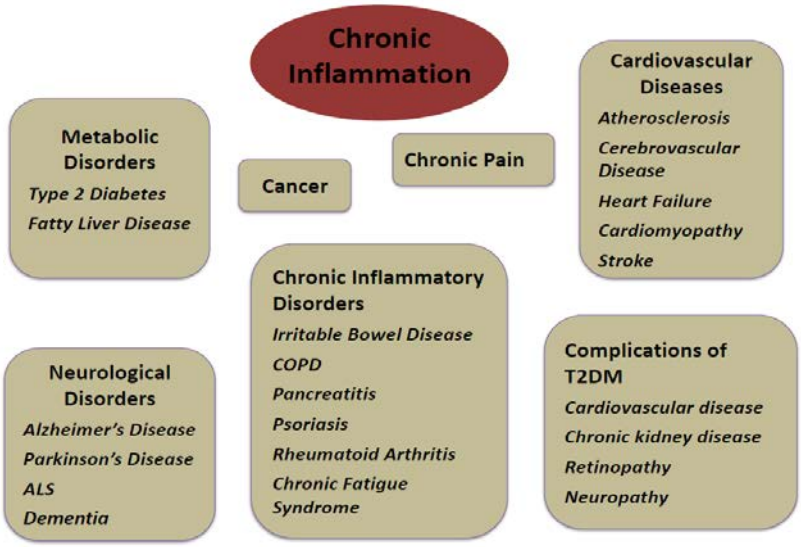
The Role of Specialized Pro-Resolving Mediators (SPM) on Inflammation

Introduction

In 2000, Harvard researcher Charles Serhan PhD discovered new lipid molecules class, called specialized pro-resolving mediators (SPMs) that are an integral component of the resolution of inflammation pathway. That breakthrough revolutionized our beliefs about the resolution of inflammation.[1] Surprisingly, inflammation does not just fade away, but is a tightly orchestrated process requiring many cellular and molecular players.[1,2] The SPMs are now understood to play key roles in resolving inflammation and returning tissue to a healthy state or homeostasis. Leading scientists now have compelling evidence that the resolution of inflammation is an active process and that chronic inflammatory disease arises partly due to failure of the biological pathways of resolution.

Inflammation plays a key role in many common chronic diseases and conditions.[3] In atherosclerotic plaques, for example, inflammatory cytokines and immune cells, including dead and dying macrophages, form a ”necrotic” center that may cause the lesion to rupture.[4] In pulmonary diseases such as asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis, chronic inflammation damages the airway epithelium and alters both lung function and immune responsiveness.[5] Other common, chronic diseases that involve inflammation include arthritis, type 2 diabetes, cancer, osteoporosis, obesity and metabolic syndrome, and depression (Figure 1).[6] Even aging is associated with a mild pro-inflammatory state termed “inflammaging.”[7]

Figure 1. Partial list of diseases associated with chronic inflammation.[6]



In fact, chronic diseases associated with inflammation are the leading cause of death and disability in the United States.[8] Together, cardiovascular disease and cancer account for nearly one-half of all deaths each year.[8] As of 2012, one-half of all adults in the United States, about 117 million people, had one or more chronic health conditions.[8] And chronic diseases tend to cluster.[9,10] Of the ten most common chronic diseases, national data from 2012 revealed that 24.3% of patients had one chronic disease, 13.8% had two diseases, and 11.7%, or nearly 14 million people, had three chronic diseases.[9] Perhaps not surprisingly, quality of life is inversely related to the number of chronic conditions, and the presence of even a single chronic condition significantly affects quality of life.[11-13] Chronic disease is also expensive.[13] The direct and indirect costs alone of the five major diseases total nearly $1 trillion annually. Indeed, chronic inflammation may be the single largest contributor to the medical burden in industrialized societies.[14]

Inflammation

Normally, inflammation acts as a protective host defense that arises and subsides.[15] It eliminates and foreign organisms or environmental toxins, repairs tissues, and establishes immune memory.[15] An insult, such as a splinter or infection, recruits resident macrophages and mast cells to release cytokines and pro-inflammatory lipid mediators that carry signals between different types of immune cells and other cell types.[15,16] As inflammation begins, cytokines and lipid mediators influence surrounding cells to increase the permeability of blood vessels and attract immune cells to the area.[15] Arriving neutrophils engulf foreign microorganisms in a process called “phagocytosis.” Phagocytosis signals the end of inflammation and the start of resolution.[16] Since, even under normal circumstances inflammation may occur naturally several times a day, limiting this potentially harmful process is essential.[14]

Causes of Chronic Inflammation

What causes chronic inflammation? A common cause is the recurrent initiation of acute inflammation through persistent infection, such as by tuberculosis and H. pylori.[14] Other causes include environmental stimuli (air pollution, food allergens), aging, persistent injuries, and lifestyle factors (cigarette smoke, inactivity, poor diet).[14]

Obesity also triggers inflammation.[14] First, adipocytes (or fat cells) and cells that line blood vessels (vascular smooth muscle and endothelial cells) produce reactive oxygen species in response to over-nutrition.[14] They are locally harmful to tissue but may also circulate and injure tissues in distant locations.[14] Second, engorged adipocytes become dysfunctional and may die, which can initiate inflammation. Consequently, adipose tissue contains activated macrophages that secrete cytokines, inflammatory molecules that enter the bloodstream and affect other tissues such as the vasculature and brain. Inflammation also contributes to the link between obesity and diabetes.[6,14] Lifestyle modifications, such as increasing physical activity, quitting smoking, and healthy eating, can reduce or even halt chronic inflammation.[14]

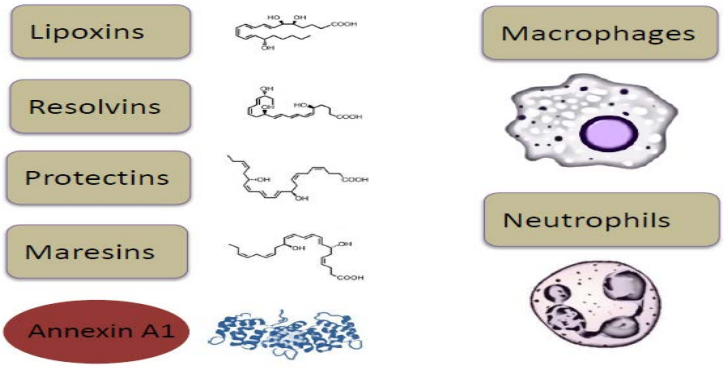
Aging is inevitable, but perhaps inflammation is not.[17] The aging process is associated with a mild pro-inflammatory state, term “inflammaging”.[6] Other evidence indicates that while the risk of chronic inflammatory disease increases with age, there are mitigating factors that can improve health[14] and the quality of life. In this view, aging is not a disease but an accumulation of

inefficient metabolic systems that in some cases can be avoided or ameliorated by lifestyle choices.[18]

Resolution of Inflammation

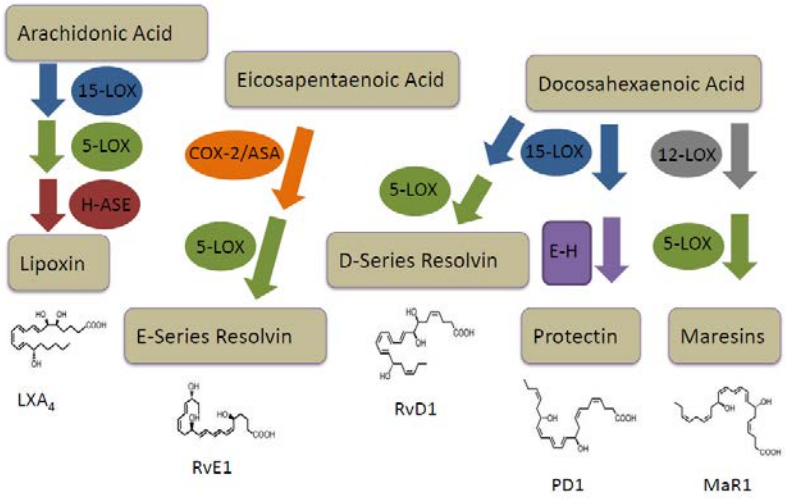
The breakthrough understanding that resolution is an active process led Professor Serhan to a superfamily of naturally occurring lipid mediators, the SPMs.[1] While SPMs function to resolve inflammation and expedite a complete return to normal structure and function, they do not block the initial inflammation.[16] Achieving resolution requires stopping further immune recruitment to the site and clearing inflammatory cells–a tightly regulated process akin to a carefully orchestrated symphonic pathway that involves many skilled artists with defined roles (Figure 2).[19] First, SPMs signal for the activated immune cells to be killed through a process called apoptosis. Next, SPMs signal macrophages to engulf those dead cells, after which further SPM signaling promotes a molecular switch to change the role of the macrophages to a resolving role. Clearance of dead cells also leads to production of additional SPMs that suppress further immune recruitment and promote tissue repair.[5] Resolution is a fundamental process in all organs and prevents unintended tissue injury that may occur from excess or chronic inflammation.[5]

Figure 2. Partial list of cells and molecules involved in the resolution of inflammation.[19]



Discovering the SPMs filled a long-standing gap in our understanding of inflammation and corrected a misconception regarding the anti-inflammatory actions of the omega-3 fatty acids. Researchers had known that fish oil provided considerable health benefits related to EPA and DHA, two of the omega-3 essential fatty acids, but no one had identified beneficial compounds produced from EPA or DHA that promoted the resolution of inflammation Instead, the beneficial effects of omega-3 fatty acids were attributed to competition with omega-6 fatty acids, which resulted in decreased synthesis of pro-inflammatory intermediates.[1] SPMs, derived from EPA and DHA, and arachidonic acid (AA; Figure 3), regulate inflammation through binding to specific cellular receptors which modifies cell behavior to promote resolution.[16]

Figure 3. Specialized pro-resolving mediators are synthesized from polyunsaturated fatty acids through a series of enzymatic reactions.[2]



Abbreviations: Resolvins: LXA_4, lipoxin-A_4; RvE1, resolvin E1; RvD1, resolvin D1; PD1, protectin D1; MaR1, maresin R1; Enzymes: 15-LOX, arachidonate 15-lipoxygenase; 5-LOX, arachidonate 5-lipoxygenase, H-ASE, hydrolase; COX-2/ASA, acetylsalicylic acid acetylated cyclooxygenase-2; 12-LOX, arachidonate 12-lipoxygenase, E-H, epoxidation hydrolysis.

SPM Mode of Action

SPMs appear to act primarily through specific cellular receptors that initiate intracellular signaling cascades ultimately leading to cell actions, such as microbial phagocytosis and clearance.[2] Most of the SPM receptors identified to date are a type of receptor known as a "G-protein coupled receptor."[2] These receptors span the cell membrane and mediate events between the outside and inside of the cell. Receptor binding causes specific cell behaviors. SPMs and their receptors form a complex system that can be finely tuned to achieve various specific cell behaviors (Table 1).[2]

Table 1. Selected biological actions mediated by SPMs.[16]

Cell Behaviors Mediated by SPMs	Tissue-Level Outcomes of SPM Actions
• Inhibit neutrophil recruitment • Reduce vascular permeability • Reduce endothelial cell proliferation and migration (limit revascularization---is this really the case?) • Promote lymphocyte removal of phagocytic cells (efferocytosis or phagocytosis) • Reduce leukocyte infiltration • Reduce cytokine levels	Halt of inflammation Promote tissue repair Regenerate original structure and function and return to homeostasis

Key Differences between SPM Mode of Action and Other Actions of EPA/DHA

EPA and DHA influence inflammation through a number of mechanisms, including via SPMs.[21,22] First, as cell membrane components, they affect membrane fluidity, cell-signaling, and even gene expression.[22] Second, intracellular fatty acids can mediate cell behaviors by interacting with specific cell receptors. These free fatty acid receptors, including G-protein coupled receptor protein 120 (GPR120), are active in many tissues of the body and influence diverse processes, from inflammation to glucose metabolism.[23] Third, EPA and DHA are substrates for the synthesis of eicosanoids: prostaglandins, thromboxanes, and leukotrienes. These bioactive molecules modulate the intensity and duration of inflammatory processes.[22] Finally, the SPMs, derived from AA, EPA, and DHA, act through mechanisms and pathways that are distinct from the free fatty acid receptor- or eicosanoid pathways. They drive the resolution of inflammation.[16,22] SPM synthesis from EPA and DHA may be limited, however, and in some cases, as in asthma, SPM biosynthesis is decreased, suggesting that individuals with asthma may derive benefit from exogenous SPMs to support the resolution pathway.[5]

SPMs: Resolution of Inflammation for Potential Clinical Applications and Aging

Failed resolution can lead to chronic disease through various mechanisms.[21] For instance, continuous production of angiogenic molecules during inflammation may stimulate cancer growth.[14] In lung, chronic exposure to a toxin, such as cigarette smoke, may lead to tissue injury leading to chronic inflammation and autoimmunity.[14] As we have seen, a long list of common diseases is attributable to inflammation and, in many cases, people have more than one inflammation-related disease.[9] Current research, described in this section, seeks to discover whether SPMs are involved in the development of atherosclerosis, Alzheimer's disease (AD), lung diseases, and others.[14,21] Inflammation's role in aging is another active area of research.[24]

Aging is associated with increased chronic low-grade inflammation, called inflammaging.[24] In inflammaging, elevated systemic cytokine levels contribute to disease pathogenesis and also affect many body systems sub-clinically.[7] For instance, inflammaging contributes to cognitive decline, and also worsens neurodegenerative diseases such as AD and Parkinson's disease.[25] In community dwelling adults with AD, even mild inflammation worsens symptoms and hastens disease progression.[25] Inflammaging also predisposes people to reduced function and frailty.[7] Related to frailty, chronic inflammation contributes to the loss of muscle mass in older people.[26] In fact, gait speed in older people is linked to specific patterns of inflammatory cytokines, suggesting that particular patterns of inflammation are more detrimental to function.[27] These effects of inflammation on muscle derive partly from the accumulated effects of inefficient tissue repair due to unresolved inflammation. Rapid and effective repair of muscle requires a tightly controlled inflammatory response. Systemic inflammation and ineffective repair leads to long-term deterioration of muscle mass and function.[26] Similar findings have been observed in the tissues of joints where inflammaging contributes to age-related degradation of articular cartilage, bone, and other tissues.[28] Increased background inflammation contributes to disease burden and increases vulnerability for reduced function and frailty.[7,29]

Decades of research pinpointing the details of lesion formation and the inflammatory process in atherosclerosis have not led to a cure, and existing therapy focuses on risk factor reduction. With the advent of SPMs and the understanding of resolution, it is conceivable that SPMs may be able to alter the course of vascular inflammation and lead to resolution. SPM pathways

operate in vascular injury, and have direct effects on vascular cells. In cell culture experiments, SPMs inhibit smooth muscle cell migration, reduce monocyte adhesion, and decrease the effects of inflammatory cytokines.[30] Overall, systemic SPM treatment resulted in reduced vessel hyperplasia (Table 2), and raised the possibility that SPMs could be used to prevent vessel inflammation following vascular surgery or stent insertion.[19,30] SPMs may someday be used in anti-platelet therapy (Table 2).[31]

Deficits in SPMs are associated with chronic inflammation in asthma, COPD, and cystic fibrosis.[5,33] In severe asthma, levels of the lipoxin are reduced, and levels of leukotriene, a pro-inflammatory lipid mediator, are increased.[5,33] When investigators examined blood levels of lipoxin in people with asthma, they discovered that the ratio of lipoxin to leukotriene correlated with lung function; people with higher proportions of lipoxin had higher lung function.[5] In addition, lipoxin protects patients with asthma from an allergen challenge. Though different pathogenic mechanisms operate in COPD, stable analogs of lipoxin have also successfully reversed inflammation in mouse models of COPD, suggesting a clinical application for SPMs.[35,36] Finally, in cystic fibrosis, inadequate production of lipoxin fosters inflammation and poor repair of the airway surface layer.[33] In primary cultures of lung epithelial cells from a cystic fibrosis patient, lipoxin improved the repair of bronchial epithelia and restored normal airway surface liquid height, a primary requirement for optimal gas exchange.[33] In the lung, resolvins are essential for recovery of function following inflammation and exogenously applied SPMs restore function in several disease models.

Periodontitis, many infections, wound healing, dry eye syndrome, inflammation due to chemical injury, cancer, and chronic pain all involve a chronic inflammatory component that may be improved by using SPMs to resolve inflammation (Table 2).[2,16] SPMs are presently being evaluated for a variety of these conditions and diseases.[19,34] Many of these diseases affect large populations; for example, periodontitis develops in about half of Americans, often resulting in tooth loss.[19] Chronic inflammation is also a hallmark of autoimmune diseases like rheumatoid arthritis and metabolic disorders.[21,34]

Table 2. Potential Clinical applications of SPMs.

Disease/Condition	Results/clinical stage – how is clinical stage highlighted?
Cardiovascular/atherosclerosis[22]	Inhibit smooth muscle cell migration Attenuate leukocyte recruitment and cytokine production
Atherosclerosis[24]	Decrease oxidative stress and necrosis Stimulate fibrous cap formation
Antiplatelet therapy[29]	Altered platelet spreading on fibrinogen Suppressed release of proinflammatory and prothrombic mediators
Vascular inflammation[25-27]	Phase 2b clinical development Decreased homing of neutrophils, macrophages Lowered inflammatory markers Reduced blood pressure
Alzheimer's disease[31,38]	Aβ engulfment increased RvD1 increased Improvement in MMSE score Reduces Aβ cleavage Protects neurons from apoptosis
Stroke[38]	Inhibits leukocyte accumulation Reduces infarct volume
COPD (mouse model)[35,36]	Reduced acute neutrophil inflammation Promoted resolution through M2 macrophages

	Inhibited pro-inflammatory signaling by a common regulatory kinase
Asthma Lung inflammation[5]	Inhibit aberrant neutrophil trafficking and activation Stimulate efferocytosis of apoptotic neutrophils Promote anti-angiogenic, anti-fibrotic, and anti-infective actions In allergic response, facilitate clearance of activated T cells Activate macrophages to remove allergen
Cystic fibrosis[33]	Restores airway surface liquid layer Attenuates inflammatory mediator secretion in CuFi-1 cells Restores phagocytic capacity to alveolar macrophages Improve epithelial integrity/repair
Dry eye syndrome[34,37]	Reduce signs and symptoms Promote tear production Improve corneal epithelium integrity
Periodontitis[34]	Reduce immune cell infiltration Prevent connective tissue and bone loss
Obesity[34]	Reduce adipokines, liver steatosis Decreases inflammatory cytokines Stimulates formation of M2 macrophages Promotes resolution in adipose tissue

Conclusions

Inflammation is a core defect of many common chronic diseases, but existing anti-inflammatory treatments are often ineffective in stopping inflammation and may actually contribute to delay resolution. In fact, inflammation is a natural process that arises and subsides, leaving tissue repaired and functioning as it was prior to injury and inflammatory response. SPMs are bioactive molecules that mediate the resolution of inflammation and maintain inflammatory responses within tightly delineated boundaries, promoting a return to homeostasis. SPMs do not block inflammation, but rather support the natural process of resolution. Understanding the processes of resolution and the role of SPMs in preserving tissue structure and function may lead to innovative therapy for inflammaging and the many common diseases of chronic inflammation.

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