REVIEW ARTICLE

Resolution to Inflammation: Its Role in Reducing Fibrosis and Tissue Repair

Anna Meiliana[1,2,3,*], Andi Wijaya[2,3]

[1]Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Jl. Raya Bandung-Sumedang Km 21, Jatinangor 45363, Indonesia
[2]Prodia Clinical Laboratory, Jl. Supratman No 43, Bandung 40114, Indonesia
[3]Prodia Education and Research Institute, Jl. Kramat Raya No. 150, Jakarta, 10430, Indonesia

*Corresponding author. E-mail: anna.meiliana@prodia.co.id

Received date: Dec 19, 2022; Revised date: Jan 30, 2023; Accepted date: Feb 6, 2023

Abstract

BACKGROUND: Many chronic disorders, including vascular diseases, metabolic syndrome, and neurological diseases, are known to share a common factor of excessive inflammation. It takes a lot of energy to heal damaged tissue, which is a complicated process. The outcome is often suboptimal, with some degree of fibrosis, depending on the tissue's ability to regenerate and the strength of the inflammatory response. We may get new insights into disease causation and therapeutic strategies by better understanding endogenous regulatory points within the inflammatory response.

CONTENT: Despite of the benefit in raising an inflammatory response, it also have unfavourable effects. Unresolved inflammation can over accumulate collagenous connective tissue and induce fibrosis, promote tissue dysfunction, and finally organ failure. Currently, the resolution of inflammation was described in terms of contemporary molecules as a different mechanisms from anti-inflammatory, since in resolution, the pathogen and apoptotic cells crumbs will be cleared and the macrophages will set back the tissue homeostasis. An active transition in the mediators that predominate in exudates occurs in conjunction with the remission of inflammation. These groups of inborn pro-resolution named resolvins, maresins, and protectins work to reduce inflammation by triggering certain pathways that support homeostasis rather than by suppressing the immune system.

SUMMARY: The resolution of inflammation, once believed to be a passive process, is now understood to entail active biochemical programs that allow inflamed tissues to regain equilibrium. In this review, we spotlight the resolution to inflammation as a strategy to prevent tissue fibrosis and hinder the organ damage.

KEYWORDS: inflammation, resolution, fibrosis, wound healing, specialized pro-resolving mediators

Indones Biomed J. 2023; 15(2): 106-23

Introduction

Twenty years ago, four cardinal indications of inflammation have ben described as calor (heat), dolor (pain), rubor (redness), and tumor (swelling). Currently, many studies found the link of some diseases linked to chronic inflammation, including rheumatoid diseases, atherosclerosis (1), neurological disorders (2), and so many more, were driven by ongoing pro-inflammatory processes as well as dysregulated resolution, and that therapy based on correcting these defects will aid in directing ongoing inflammation down a pro-resolution pathway. Pro-resolution solutions naturally provide more flexibility than traditional anti-inflammatory methods, but despite our growing understanding of resolution biology, there are still some very evident limits. Pharmacologically, it is difficult to treat the Virchow's 5th cardinal sign functio laesa (loss of tissue function). Similar to how inflammation may develop in a variety of ways, resolution mechanisms are also varied,

and data to far points to the likelihood that they are tissue- and stimulus-specific. It is therefore unknown if there is any one proresolution regimen will function as a cure-all for various disease states, despite the possibility of elucidating core cellular and molecular mediators.

When an injury or infection occurs, the microcirculation's defensive response is inflammation. Inflammatory reactions, both local and systemic, work to reduce the stimulus that triggered them, aid in tissue repair and healing, and, in the case of infections, create immunological memory so that the host will mount a quicker and more focused response in the future.(3) In reaction to a trigger or injury, an organ may develop fibrosis, which is the excessive deposition of connective tissue components. Proteins from the extracellular matrix (ECM) was accumulated and often disturb the physiological architecture, cause organ dysfunction. Most diseases caused by chronic inflammation cannot be totally healed without leaving a scar, even in active regenerating organs such as liver. Almost all organ systems may be impacted by fibrotic tissue remodelling such as the remodeling of the myocardium in heart failure, the remodeling of the arteries in atherosclerosis, the remodeling of tumors' epithelial-mesenchymal transition and desmoplastic responses, and the remodeling of airways in chronic obstructive pulmonary disease (COPD) and asthma. Even though the disorder isn't frequently linked to fibrosis, fibrotic tissue responses frequently play a significant role in disease outcomes and total morbidity.(4) In fact, fibrotic tissue reactions have been predicted to be responsible for up to 45% of all fatalities in the developed world.(5) In general, fibrosis incidence and the cost on healthcare systems are rising globally, and as a result, fibrosis is more and more acknowledged as one of the biggest healthcare concerns of our day.(5,6)

Monocytes and macrophages may have different functions in tissue repair. Recruited monocytes frequently causing collateral tissue damage (7), while the tissue-resident macrophage population seems to have more advantageous traits by displaying pro-resolving, anti-inflammatory, and pro-regenerative activities (8). Recent research have concentrated on unraveling the mechanisms that permit these various activation states since it is thought that the conversion of proinflammatory monocytes and macrophages to the pro-resolving phenotype is essential for optimal wound healing and reducing fibrosis.(9) Conventional anti-inflammatory therapy acts by inhibit inflammatory factors and antagonize proinflammation signals or in other word only treat the symptoms, but not resolving completely. While pro-resolution factors will not only enhance the pathogens removal but also setting back the local tissue into homeostasis. Even many studies showed the failure of current therapies due to a relative resolution deficiency.(10-12). In fact, integrating pro-resolution with anti-inflammatory technologies may prove to be a more effective technique than current methods. We hope that this review can open a new paradigm for a better strategy in treating chronic inflammatory diseases and fibrosis before they progress into some organ damage.

Inflammation: An Overview

Inflammation is the main host's defence mechanism against infection. The inflammatory response comprises interactions between several cell types, by releasing numerous chemical mediators, as well as reactions to those mediators. Inflammatory response started when there is tissue damage or infection. Soluble mediators will be released to the area of injury, so the blood flow vascular wall permeability is increased to allow the bigger molecules to penetrate the endothelium. Chemoattractant were released from the site of inflammation and the overexpression of adhesion molecules on the endothelium both encourage leukocyte migration from the blood stream into the surrounding tissue. At the location of the inflammation, these freshly arriving and activated leukocytes subsequently release chemical mediators. Depending on the type of cell involved, the nature of the inflammatory stimulus, the involved anatomical site, and other factors, there are different mediators released including cytokines, chemokines, platelet activating factor (PAF), prostaglandins (PGs), leukotrienes (LTs), endocannabinoids, reactive oxygen species (ROS), and/or amino acid derivatives. The presence of inflammatory mediators brought about by this influx of cells into the area of inflammation as well as the cardinal symptoms of inflammation, including redness, swelling, heat, pain, and loss of function, are created.(13)

Localized acute inflammation is a common event of the host's defense against tissue damage and infection brought on by invasive microbial invaders.(14) Although the initial goal of this inflammatory response is to protect the host, somehow when it left without proper control, it can lead to a variety of acute, chronic, and systemic inflammatory illnesses. In fact, excessive, uncontrollable, or chronic inflammation is a contributing factor in a number of the most prevalent and challenging to treat conditions, including cardiovascular disease (CVD), diabetes, inflammatory bowel disease (IBD), rheumatoid arthritis (RA), periodontal

disease, asthma, age-related macular degeneration (AMD), and some neurological conditions like Alzheimer's disease. (14-16) Although it is widely recognized that inflammatory pathways play a role in the development of each of these illnesses, it is not entirely clear how exactly inflammation contributes to their etiology. Inflammation resolution is an active process (17–20), which has led to new understandings and treatment paradigms for various disorders (21).

Despite being created to harm infections, the cellular processes involved in the inflammatory response and the chemical mediators they produce can harm host tissues. The activation of negative feedback mechanisms, such as the release of anti-inflammatory cytokines or pro-resolving lipid mediators, the inhibition of pro-inflammatory signaling cascades, the loss of inflammatory mediator receptors, and the activation of regulatory cells, causes inflammation to typically be self-limiting and resolve, frequently quickly. Loss of these regulatory mechanisms can lead to excessive, inappropriate, or persistent inflammation, which can harm host tissues permanently. As a result, illness and pathological inflammation may both develop, such as RA, Crohn's disease, ulcerative colitis, lupus, lupus, type-1 diabetes, as well as acute cardiovascular events. In some conditions, like RA, IBD, and asthma, the central role of inflammation in the pathology is well understood as elevated inflammatory mediators infiltrates in specific organ such as joints, lungs, intestinal mucosa, *etc*. These conditions usually treated with anti-inflammatory agents. The significance of inflammation has just lately been apparent in other conditions, such as atherosclerosis and obesity, and its contribution to the pathology in combination with the many other components at play is less evident.(13)

Normally, the healing process consists of two separate phases: the regenerative phase, in which damaged cells are replaced by cells of the same kind, erasing all traces of the injury; and the fibroplasia or fibrosis phase, in which connective tissue replaces healthy parenchymal tissue. Although initially advantageous, the healing process can become pathogenic if it is improperly managed by leading to significant ECM component deposition where normal tissue is replaced with permanent scar tissue.(22) Extensive tissue remodeling and fibrosis can ultimately result in organ failure and mortality in several conditions, including idiopathic pulmonary fibrosis (IPF), liver cirrhosis, cardiovascular fibrosis, systemic sclerosis, and nephritis.(5)

It is the uncontrolled prolonged inflammation induce fibrosis, due to excessive tissue remodeling and repair for months. Most fibrosis share the characteristic of persistent production of growth factors, angiogenic factors, proteolytic enzymes, and fibrogenic cytokines. These factors gradually alter and destuct normal tissue structure, despite having distinct aetiological and clinical manifestations.(23-25)

Resolution of Inflammation

Acute inflammatory responses are self-limited in normal condition, just as surgically produced tissue damage, in that they go away on their own and are often divided into initiation and resolution phases.(14) The first response of inflammation is the edema formation, continue with polymorphonuclear neutrophils (PMN) infiltration. After that, monocytes and macrophages follows to clear the PMN, and start the inflammation resolution (Figure 1).

As of now, we see beginning chemical mediator gradients as a temporal escalation to resolution and declining of acute inflammation.(26) Resolution is characterized by an active host response (26) as opposed to a merely passive dilution of proinflammatory mediators (27), allowing tissues to regain function (14). Figure 2 describes the ideal clearance of an inflammatory event.(28) In the first phase, as acute inflammation happens with four inflammatory characteristics, PMNs was increased marking the neutrophil infiltration to eliminate the pathogens, either from injury, aggression, or infection, with help of monocytes and M1 macrophages. After the pathogens were eliminate, lipoxins, resolvins, protectins and maresins (the Specialized pro-resolving Mediator (SPM)) will take over and induce the removal of inflammatory debris, while the M1 macrophages switch into M2. By that, the homeostasis was set back. (18,29) The pro-resolution process is clearly not the same as the anti-inflammatory process.(30)

The sn-2 position of phospholipids is a crucial part of membrane phospholipids where n-6 and n-3 polyunsaturated fatty acids (PUFAs) were frequently seen.(31) Common membranes components including linoleic acid, Dihomo-γ-linolenic acid (DGLA), arachidonic acid (ARA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) can be available depend on some factors such as diet, metabolic processes, the particular cell-/tissue type, and the type of phospholipids present. Different phospholipids was composed by different fatty acid.

ARA is most frequent found the PUFA in the majority of cell types and has a direct relationship with inflammation status. The eicosanoid family of mediators was produced from ARA which act as the substrate for the enzymes cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450. Eicosanoids, which comprise PGs,

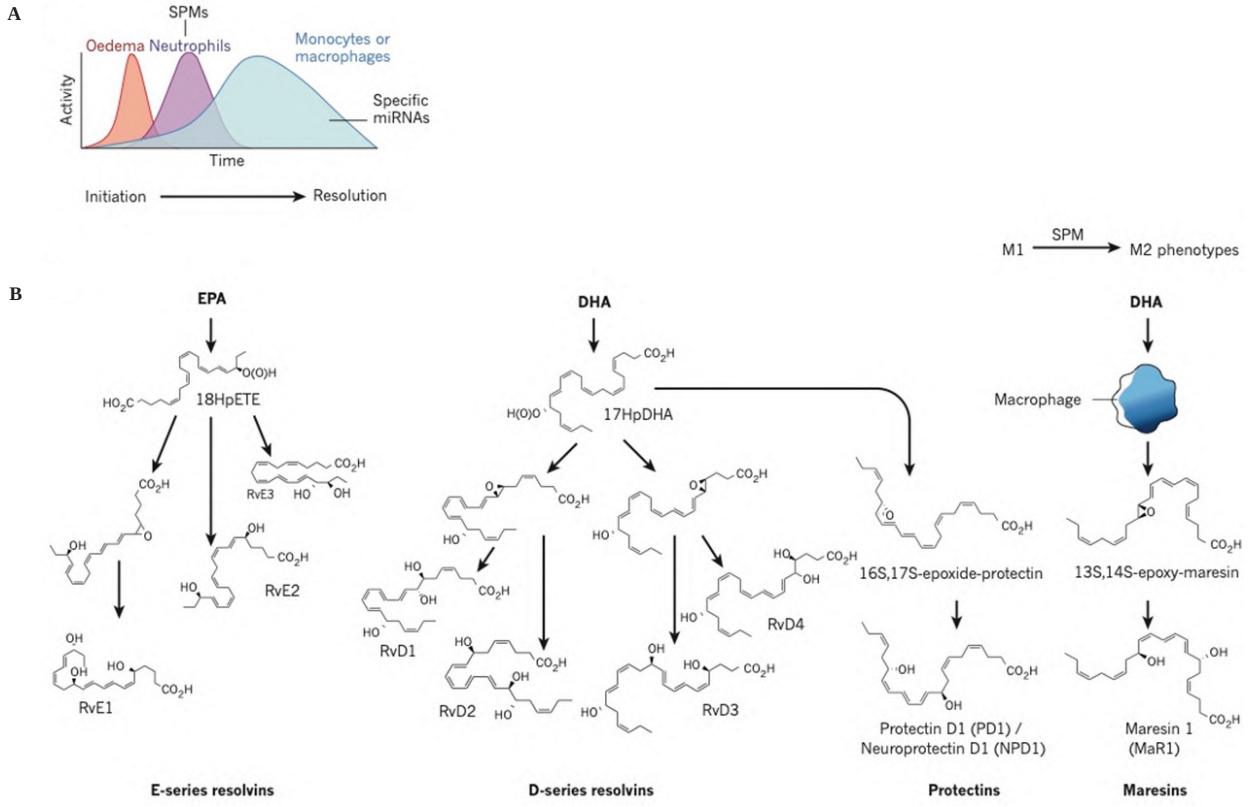

Figure 1. Production of specialized pro-resolving mediators in resolving inflammatoryexudates.(26) (Adapted with permission from Macmillan Publishers Limited).

thromboxanes and LTs play crucial role in mediating and controlling inflammatory processes.(32-34) High levels of ARA, indeed will activate phospholipase A2 and trigger the increase of eicosanoid molecules production. Numerous anti-inflammatory medications, including as non-steroidal anti-inflammatory medicines (NSAIDs) and COX inhibitors, target ARA metabolism, demonstrating the close connection between ARA metabolism and inflammatory processes.(35)

After acute challenges, leukocytes within seconds to minutes will biosynthesize lipid mediators such as PGs and LTs for their pro-inflammatory properties.(36,37) As inflammation progresses, neutrophils in congealed exudates stop releasing chemoattractants and begin to produce protective lipoxins within hours, acting as agonists to actively inhibit inflammation and encourage resolution. (17,18,38) Both PGE and 2-PGD2 have pro-inflammatory activities (36), but both of them can promote lipid-mediator class switching, *i.e*., the temporal switch of biosynthetic enzymes expression via neutrophils infiltration, to change their phenotype into a pro-resolution.(18,39) The loss of neutrophils from the local inflamed sites marked a success resolution, followed by its clearance by macrophages, continue with phagocyte exit from the exudate via the lymphatics (Figure 3).

The n-6 polyunsaturated fatty acid ARA is released from membrane phospholipids intracellularly by a number of phospholipase A2 enzymes (PLA2s), particularly cytosolic PLA2 (cPLA2), and used to make LTs.(40) 5-LOX, the key enzyme in cellular LT production, is aided by the accessory proteins 5-lipoxygenase-activating protein (FLAP) and coactosin-like protein (CLP), which are required for complete function.(41,42)

A temporal lipid mediator class switch occurs if PGE2 produced by cyclooxygenase precedes lipoxin production. (11) Human PMNs treated to PGE2 or PGD2 produced 15-LOX, a PMN stop signal that prevents future recruitment by converting LTB4 production to lipoxin synthesis.(18) Because lipoxin A4 (LXA4) also induces macrophage efferocytosis, which involves the phagocytosis of apoptotic PMNs and debris, this PMN phenotypic flip denotes the resolution phase.(26,43-45) There are three families of lipid-mediators, dubbed protectins, resolvins (resolution phase interaction products), and maresins (macrophage mediators in resolving inflammation).(17,20,46,47) Each is structurally unique and is produced by biosynthesis from EPA), n-3DPA, or DHA.(20,26,48,49)

Although the crucial role that inflammatory processes play in both health and illness has long been understood (14), the specific molecular mechanisms and biological

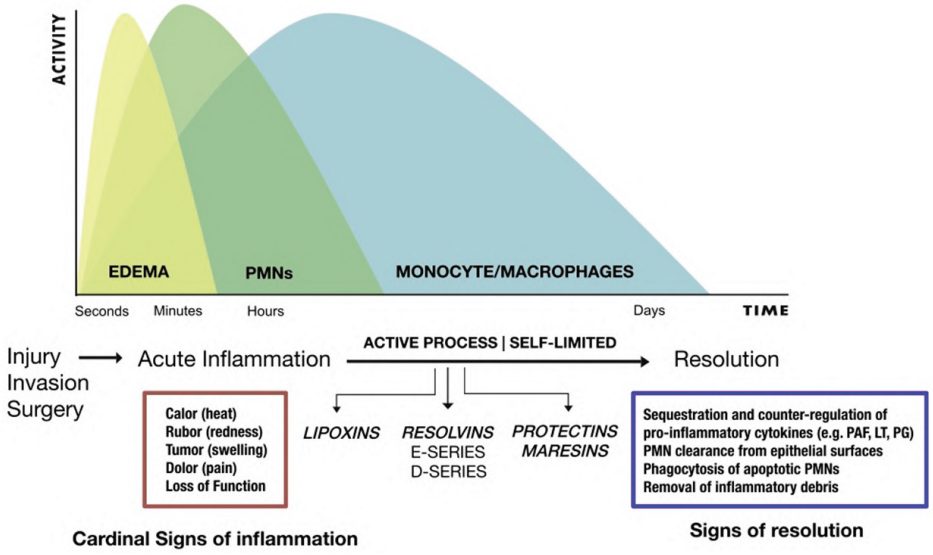

Figure 2. The ideal outcome of inflammation: complete systems approach to mapping resolution. (28) (Adapted with permission from Elsevier).

processes that control how inflammation develops and resolves continue to be of interest. Recent studies have shown compelling evidence that inflammation resolution is not a passive process as previously thought.(17,20,50) Resolution, on the other hand, is a biosynthetically active process that is controlled by pharmacological mediators, receptor-signaling pathways, and SPMs.(26)

SPMs are exceptional because they have pro-resolving and anti-inflammatory actions without reducing the immune response.(51,52) Contrary to traditional anti-inflammatory treatments like corticosteroids and NSAIDs, SPMs are produced endogenously by numerous cells and have powerful effects in the nanomolar to picomolar range, thus they offer great therapeutic potential because they are frequently thought to be nontoxic and are probably well tolerated when provided exogenously.(53)

Chronic Inflammatory Diseases

The world prevalence of cardiovascular diseases (CVD) has been rising despite the availability of safe and effective LDL-lowering medication.(54) Most of cardiovascular impairment triggered by inflammatory exacerbations and/or unresolved harmful stimuli after acute episodes, including atherosclerosis, aneurysm disease, and venous thrombosis. The innate and adaptive immune systems of the host are both activated chronic inflammatory disease.(55)

In atherosclerosis, loss of endothelial integrity and damage to the underlying vascular smooth muscle cells (VSMCs) cause acute vascular injury, which prompts a quick response of platelets, coagulation factors, and leukocytes, especially neutrophils and monocytes.(56-59) These substances adhere to and infiltrate the vascular wall, producing a variety of growth factors, proteases, cytokines, and vasoactive compounds that trigger subsequent proinflammatory gene cascades in the VSMCs and adventitial cells that survive. These signals work together to increase early leukocyte recruitment and trigger cellular repair processes. Vascular healing and the creation of neointima are caused by the substantial phenotypic transition that VSMCs go through to become activated, migratory, and proliferative. Monocyte-derived macrophages (MDMs) in the vascular wall have an M1 phenotype early after damage and produce chemokines like MCP-1 that encourage more cellular recruitment. Neointimal hyperplasia is caused when

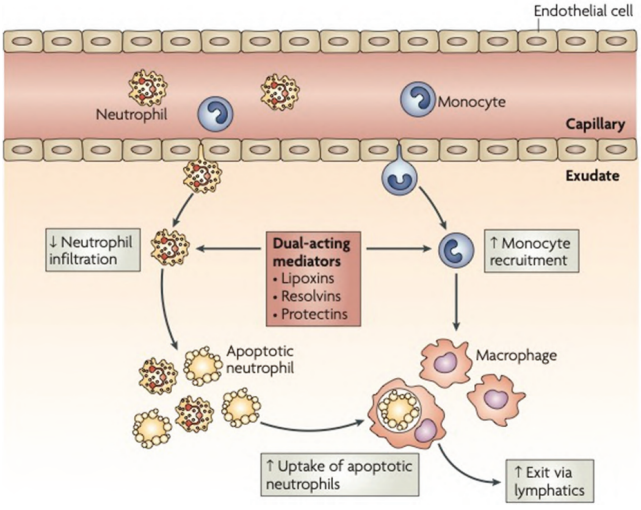

Figure 3. Dual anti-inflammatory and pro-resolution actions of specific lipoxins, resolvins and protectins.(39) (Adapted with permission from Nature Publishing Group).

local inflammation and VSMC phenotypic alterations are prolonged; this may result in a reduction in ultimate lumen diameter. Acute inflammation has developed as a natural host defensive mechanism against pathogens that are both microbial and sterile.(60)

Chronic inflammation arises when acute inflammation is not under control or cured, which may lead to organ damage (61), like CVD, diabetes, obesity, Alzheimer's disease, asthma, and autoimmune diseases (62-66). Two important stages of the acute inflammatory response are commencement and resolution. Chemical messengers such as cytokines, chemokines, and mediators produced from lipids, such as PGs and LTs, attract immune cells to the site of damage during the initiation phase of the immune response.(67) First to arrive, PMNs start to phagocytose and destroy infections. Immediately after being drawn to the location of inflammation, monocytes undergo differentiation into macrophages that aid in furthering the removal of pathogens and start to plan the next phase, the resolution of inflammation.(68) This stage is marked by efferocytosis, the phagocytic elimination of apoptotic cells, and the repair of injured tissue. The inflammatory response is quenched while pathogen clearance continues. Resolution is characterized by a shift in the synthesis of lipid mediators from LTs, a proinflammatory mediator, to SPMs, such as resolvins and lipoxins, an SPM.(20,50,69) Current knowledge direct on the incomplete of inflammation resolution as a significant contributing component of chronic inflammation.(62,70-72)

RA is another example of chronic inflammatory disease, with persistent synovitis that causes joint degeneration, increasing disability, and hastened cardiovascular disease that risk in mortality.(73) The failure of resolution responses may contribute to the persistence of chronic inflammatory illnesses like arthritis.(74) Therefore, to prevent joint damage, current RA treatments try to act early and continuously reduce inflammation (75), such as the use of methotrexate and disease-modifying antirheumatic drugs which significantly improved patients' prognosis. Despite this, only 50% of patients who have had treatment will show a decline in disease activity from a high to a sustained level of low or, less frequently, remission.(76) In addition, therapy prevents joint deterioration but rarely restores it (77), and patients receiving biologic medicines have a higher chance of developing opportunistic infections. (76,78) New treatment strategies are thus needed to combat disease chronicity and preserve joint integrity.(79)

According to clinical and epidemiological data, many diseases including malignancies is significantly promoted by chronic inflammation. People who have chronic hepatitis B infection, *Helicobacter pylori* infection, or autoimmune diseases like IBD, for instance, have a higher lifetime chance of developing liver cancer, gastric cancer (GC), or colorectal cancer (CRC). Also known as tumor-induced inflammation, solid tumors themselves display some hallmarks of inflamed tissues. Proinflammatory mediators such cytokines, chemokines, and lipids are elevated in chronic inflammatory disorders and solid tumors, and unregulated immune cells are heavily infiltrated as well as endothelial cells and fibroblasts are recruited.(80-82) The finding that NSAIDs decrease the occurrence, metastasis, and death of many solid tumors, including gastrointestinal cancer (83-89), lends credence to the idea that chronic inflammation encourages tumor initiation, development, and progression.

COX-2 gene is overexpressed immediately at the sites of inflammation in several malignancies, including those that develop in the gastrointestinal tract. While COX-1 was known to supply basal levels of prostanoids including PGs, thromboxanes, and prostacyclins in most tissues, and is important for platelet and tissue homeostasis. For instance, about 50% of colorectal adenomas and 85% of adenocarcinomas have increased COX-2 expression. (90-92) Patients with CRC and esophageal cancer who have higher COX-2 expression had lower overall survival times.(93,94) However, inconsistent findings regarding the relationship between COX-2 expression and survival in GC patients have been published.(95) ARA is transformed by COX enzymes into an intermediate endoperoxide that may then be further converted to prostanoids, including PGs like PGE2, PGD2, PGF2, PGI2, and thromboxane A2 (TxA2). Additionally, prostanoids interact with G protein-coupled receptors on cell surfaces to carry out their biological actions. The PGE2 receptors are named EP (EP1, EP2, EP3, and EP4), the PGD2 receptor is designated DP1 and DP2, the PGF2 receptor is labeled FP, the PGI2 receptor is designated IP, and the TxA2 receptor is designated TP.

The level of prostanoids increased rapidly in acute inflammation, even before leucocyte infiltration. This shows their important role in inflammatory process. PGE2 and PGI2 are prostanoids that have been demonstrated to cause acute inflammation in most animal models.(33) PGD2, on the other hand, has been demonstrated in animal models to decrease acute inflammation by binding to its DP receptors and through the enzymatically independent production of 15-deoxy-12,14-PGJ2 (15d-PGJ2).(96) The NF-κB signaling pathway is directly inhibited by 15d-PGJ2, which mostly binds to PPAR.(97,98) PGE2 and PGI2 contribute

significantly in a similar way to arthritis and IBD which is by enhancing chronic inflammation.(99,100) The setting affects PGD2's function in chronic inflammation. On the one hand, adjuvant-induced arthritis is inhibited *in vivo* by PGD2-derived 15d-PGJ2.(26) PGD2, however, promotes allergic inflammation (100), whilePGF2 and TxA2 have uncertain functions in inflammation (101).

Cellular and Molecular Mechanisms of Fibrosis

Fibrosis is characterized by an excessive deposition of connective tissue components. Fibrosis is a reparative or reactive process and may affect almost every organ system, including the skin, lungs, liver, and kidney. In different organ affected, there will be different changes and alterations which in the end will lead to organ failure (Figure 4).(102) Fibrotic tissue remodelling is frequently associated with significant morbidity and mortality and frequently results in organ dysfunction. The production and deposition of excessive fibrous connective tissue leads to gradual architectural remodeling.(4) Fibrogenic reactions have many of the same underlying mechanical components with the typical wound healing response. However, due to tissue damage from scarring, the corresponding processes are aggravated. Therefore, persistent fibrogenesis causes a change from a supportive "good" fibrotic tissue to a milieu where ECM-producing cells multiply or become overactive, culminating in the production of a significant amount of scar tissue and the loss of normal organ architecture.(103)

Physiologic and pathologic fibrotic responses have the potential to have an impact on nearly all organs in the human body. These responses, which are self-limited under homeostatic conditions, are significant reparative processes that try to restore the functional integrity of damaged tissues through a convoluted chain of activities known as normal tissue repair. In pathologic conditions, however, regular tissue repair mechanism become uncontrolled leading to excessive fibrotic tissue accumulation ultimately results in organ failure.(5,104,105)

It is challenging to assess the entire incidence of fibrotic illnesses due to their extensive and multi-organ occurrence, however it has been estimated that they may account for up to 45% of mortality in Western industrialized countries.(5) It is well recognized that myofibroblasts are the cells ultimately accountable for the pathologic fibrotic process in the fibrotic diseases at the cellular level.(106-111) Myofibroblasts are an unique subpopulation of mesenchymal cells that express smooth muscle actin (α-SMA), produce fibrillar collagens (types I, III, V, and VI) and other ECM macromolecules significantly more often, and produce more tissue inhibitor of metalloproteinase (TIMP), which inhibits the activity of ECM-degrading enzymes.(112-115) Additionally, myofibroblasts cause changes in the biomechanical characteristics of the impacted tissues, resulting in a gradual rise in tissue stiffness, a recently identified incredibly effective profibrotic stimulation.(116-120)

According to the damaged organ and the specific fibrotic response, the origin of myofibroblasts might different.(108,109,121) There are several precursor cells such as fibrocytes from bone marrow; transdifferentiation from totally different cells such as epithelial, adipocytes, endothelial cells; or activation and proliferation of dormant tissue-resident fibroblasts.(122)

There are significant similarities between fibrotic disorders and normal wound healing (Figure 5).(123) An initial injury sets off a series of reparative mechanisms in damaged tissues to restore organ integrity in both situations. Leukocyte infiltration, activation, and accumulation in damaged tissues are the results of the reparative cascade, which begins with an early inflammatory reaction to the starting trigger.(5) Although fibrotic situation can be different, but all exhibit a common trait of polarization towards a T helper 2 (TH2) cell-M2 macrophage-mediated

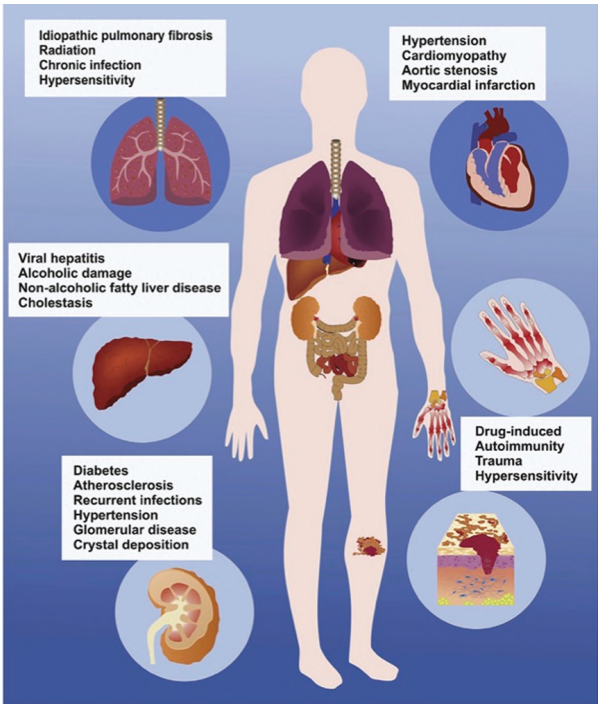

Figure 4. Major causes of organ fibrosis.(102) (Adapted with permission from Elsevier).

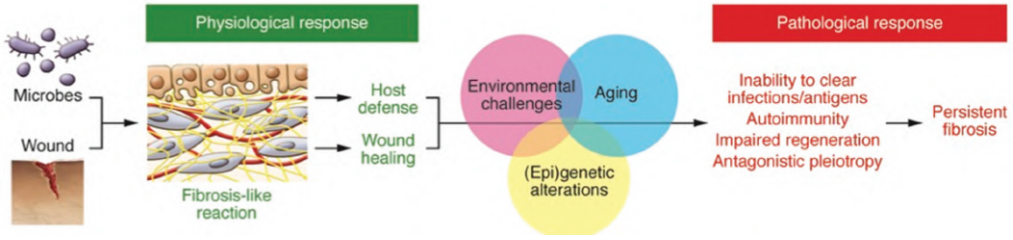

Figure 5. Evolution of fibrosis.(123) (Adapted with permission from American Society for Clinical Investigation).

response, and expression of profibrotic mediators.(5) Myofibroblast activation and accumulation are facilitated by these mediators. A diverse group of cells known as myofibroblasts are distinguished by the production of contractile proteins and the profuse release of ECM proteins. Many different cell types, including resident fibroblasts and various vascular wall cells, such as pericytes, endothelial cells, and smooth muscle cells, can develop at least a partial myofibroblast phenotype. Another contributors to ECM protein release including epithelial cells, bone marrow-derived fibrocytes, and bone marrow-derived progenitor cell populations.(108)

Myofibroblasts go through apoptosis during typical wound healing, and the reparative responses end after the damage has been fixed.(124) However, in some condition the intrinsic or extrinsic trigger is persistence, including genetic or epigenetic alterations, or aging process. This can lead to chronic immune respond, where tissue remodeling and fibroblast activation continue as an unchecked, ongoing process in fibrotic diseases (Figure 6).(125) Therefore, fibrotic tissue remodeling can be viewed as an accelerated and protracted wound healing response.(126) Therefore, abnormal stimulation of tissue repair responses may not be the sole factor in the development of fibrotic disorders, but also defective termination.

Macrophages play a crucial role in the body's reaction to wound injury. Circulating M1 macrophages generated from monocytes are necessary for the first inflammatory stage of the wound response.(127) In the latter stages, a particular, a population of M2 macrophages which regard as reparative, express CD206 (also known as MRC1) and CD301b (also known as MGL2) replaces these initial macrophages.(128) In inflammatory and fibrotic conditions, separate waves of macrophages with similar characteristics are seen.(129)

In cutaneous, pulmonary, and hepatic fibrosis, interleukin (IL)-13 and M2 macrophages play important roles. The liver and lung fibrosis and inflammation that IL-13 causes are mediated by macrophages in a slightly different way (130), while in the lung it depend on the activation of transforming growth factor (TGF)-β1, the liver operates in the independent way (131,132). Liver fibrosis resolution can be slow down by selective deletion of IL-4-IL-13 receptor (IL-4 receptor α-chain) (130), means that macrophages can play a different role in fibrosis development, depend on the phenotype, macrophages origin, affected tissue, and the inflammation stimulus (133,134).

In many organs, one of the typical master switches that activates the fibrotic program throughout the chronic stages of inflammatory disorders is TGF-β. Connective tissue growth factor (CTGF) and PDGF family of growth factors are additional significant soluble pro-fibrogenic mediators. While CTGF is believed to bind to TGF-β and enhance its binding to membrane-bound receptors, members of the PDGF family are potent mitogens and chemoattractants for fibrogenic cells in most organs, encouraging their recruitment and proliferation at sites of tissue injury. (135,136) These frequent mediators boost myofibroblast activity and quantity, which speeds up matrix synthesis and promotes a wide range of diseases that impact many organs, including the skin, lung, liver, kidney, pancreas, and heart.

Fibrosis may be seen as a part of the innate and adaptive immune response to certain infections in numerous ways. In fact, fibrotic illnesses exhibit a number of the cells and mediators that make up the traditional host responses to infections.(137) Thus, a broader understanding of innate and adaptive immunity includes the idea that, besides the macrophages activity of killing the pathogen, further pathogen invasion and spreading were prevented by the scar forming. When seen in this light, cells like fibroblasts and myofibroblasts, which are crucial to the development of fibrosis, take part in host defense by confining pathogens to kill them more effectively or as a fail-safe to stop their spread if killing doesn't entirely eradicate them. As described in Figure 6, apparently wound healing and fibrotic diseases share a common mechanism. Both at initial stages trigger leucocytes infiltration, T helper 2 (TH2) polarization, cell M2 macrophage-mediated response and abundant release of profibrotic mediators. Somehow, in normal wound healing, after the damage has been repaired, the reparative process

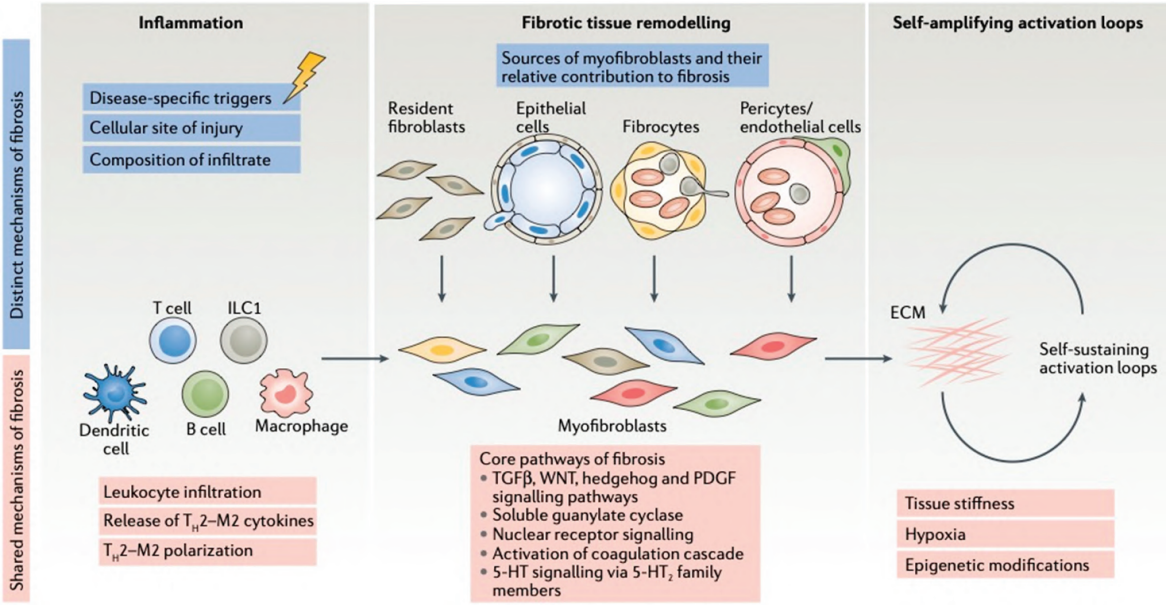

Figure 6. Common and distinct mechanisms in different stages of fibrotic tissue remodelling.(125) (Adapted with permission from Springer Nature).

terminated and the myofibroblast undergo apoptosis. If this process was uncontrolled, scar was formed by fibroblast activation.

In short, fibrosis can be induced by persistent or chronic inflammation. The prolonged inflammation were associated with a higher pro-inflammatory cytokines such as MCP-1, IL-6 and TNF-α, as well as more M1 type macrophages in the "injury site". Together with TGF-β this will alter the cells not to go to apoptosis and lead to over production of ECM, promote a significant amount of scar tissue and the loss of normal organ architecture and induce the production and deposition of excessive fibrous connective tissue leads to gradual architectural remodelling.

Somehow, the development of a fibrotic scar can be seen as the effort to increase the survival likelihood through a number of mechanisms, such as limiting excessive blood loss, acting as a barrier against the entry of microbes, and creating a temporary matrix to aid in the regeneration of damaged epithelium. Almost usually, inadequate or unsuccessful regeneration is accompanied by persistent fibrosis in several species.(138) According to the evolutionary theory presented above, a fibrotic response can be persistent and become pathologic because of a persistent pathogen or antigen (which is not identified yet), an altered immune response such as autoimmune, or a defect regenerative response, either due to aging, genetic or epigenetic problem, or pleiotropic effect of specific genes involved in development and wound healing. The first two are related to physiological fibrosis' host defense mechanism, while the last two are to wound healing.(123) Some key regulators to identify fibrosis regulation including acute phase proteins (SAP), caspases, angiogenic factors (VEGF), growth factors (PDGF), peroxisome proliferator-activated receptors (PPARs), cytokines (IL-13, IL-21, TGF-1) and chemokines (MCP-1, MIP-1), as well as elements of the renin-angiotensin-aldosterone system (ANG II), which now become potential targets for antifibrotic drugs.

Human Fibrotic Diseases

Fibrotic illnesses contribute for 45% of all-cause mortality since fibrosis is a common hallmark of the pathophysiology of a variety of diseases affecting various organ systems (4), there are only few effective treatments available (123). One example of fibrotic disease is a complicated immune-mediated connective tissue condition known as systemic sclerosis (SSc) causes excessive ECM deposition in the skin and numerous internal organs as well as microvascular damage and inflammatory cell infiltration.(139-141) The leading causes of death in SSc include cardiac arrhythmias, heart failure, pulmonary fibrosis, pulmonary arterial hypertension, and other severe organ dysfunctions that develop during the course of the illness.(142) New understanding of the disease pathophysiology had identified the immunological, vasculopathic, and fibrotic pathways involved.(143) The exact etiopathogenesis of SSc is still unknown, but current data found the involvement of

immune cells in disease's onset and progression such as T and B cells, macrophages, TGF-β, dendritic cells (DCs), and various cytokines.(139,140,144)

Some of SSc risk factors include a combination of the ongoing Raynaud's phenomenon, an imbalance in steroid hormones, certain chemicals, thermal or other damage. In genetically predisposed patients, endogenous and/or exogenous environmental risk factors encourage epigenetic processes.(145) In SSc, fibrosis mostly affects the skin but can also spread to visceral organs including the heart and lungs. The stimulation of fibroblasts and excessive ECM deposition that characterize SSc lead to fibrosis. Immune abnormalities are associated with vasculopathy in SSc in addition to fibrosis, with the majority of evidence linking vascular injury to the activation of immune cells.(140)

The profibrotic macrophage gene expression profile varied between skin and lung, despite of its same immunopathogenesis in both organs, implying that there may still be minute differences in what those roles are. PDGF receptor, FGF receptor, and VEGF receptor tyrosine kinase inhibitor nintedanib recently prevented myofibroblast development and subsequent fibrosis in a mouse model of SSc. It's interesting to note that these nintedanib-mediated anti-fibrotic actions were connected to a decline in M2 macrophage levels.(146)

Another example of fibrotic disease is IPF, a chronic, progressive interstitial lung disease (ILD) in which the interstitium, the lungs' supporting structure, gradually becomes scarred.(147) IPF is commonly characterized as the presence of a radiographic and/or histological pattern of ordinary interstitial pneumonia (UIP). UIP frequently manifests as honeycombing (well-defined subpleural cystic airspaces), traction bronchiectasis, and peripheral alveolar septal thickening. IPF is believed to start at the base and margin of the lungs before progressively spreading to affect all lung tissue. The illness, which can manifest in familial or sporadic forms, is linked to an intensifying cough and dyspnea (shortness of breath), and has a terrible impact on a patient's quality of life (QoL).(148)

IPF's etiology has been linked to a number of risk factors, including smoking, persistent viral infections, the environment, and specific comorbidities. The genetic hazards are thought to account for up to one-third of risk. (149) Age is the biggest demographic risk factor for developing IPF, indicating that "accelerated" lung aging is what causes it to happen.(150) In fact, practically all cellular and molecular signs of aging are accentuated or manifest early in IPF. The most afflicted cells are alveolar epithelial cells, namely alveolar epithelial type 2 cells (AEC2s). AEC2s are progenitor cells for alveolar epithelial type 1 cells (AEC1s), which sustain alveolar epithelial turnover and have vital secretory (surfactant), metabolic, and immune activities. AEC2s exhibit cellular senescence, mitochondrial failure, genomic instability, telomere attrition, epigenetic alterations, proteostasis loss, and disrupted intercellular communication in IPF.(151) IPF is a complicated condition and each person's proportional contribution to each risk factor is likely to vary.(152) Numerous multidirectional interactions between epithelial cells, mesenchymal cells, and the ECM also contribute to the complexity of IPF. Although all individuals with IPF are now thought to have mechanistically similar disease processes, the precise mechanisms by which these risk factors combine to create illness are yet unknown.(147)

Cirrhosis, which is the main cause of more than 1 million deaths annually globally, is caused by chronic liver inflammation.(153) Viral infection, alcoholic liver disease, nonalcoholic steatohepatitis (NASH), and autoimmune illnesses are the cause of this chronic pathologic processes. There are several pathways that might cause immunological responses, depending on the type of underlying liver damage. Hepatic fibrosis is caused by persistent immunological responses. The development of therapies for chronic liver illnesses depends crucially on our understanding of the mechanisms behind inflammation and fibrosis. A typical result of metabolic or toxic stress is hepatic steatosis which may progress to hepatic injury. Toxin can be alcohol, vinyl chloride, chemotherapy agents, and also the comorbidity from insulin resistance (154,155). Injury alters hepatocyte gene expression, increasing the expression of mesenchymal genes including twist and snail as well as TGF-β, IL-1A, hedgehog ligands, and CXCL10. Injury to the steatotic hepatocyte causes fibrosis and inflammation.(156)

Liver fibrosis is caused by hepatic stellate cell activation, ECM production, and deposition in response to hepatocyte damage, inflammation, and innate immune system activation. When hepatic stellate cells differentiate into myofibroblasts, vitamin A levels drop and the cells lose their adipogenic characteristics.(157-159) The primary vitamin A is stored by quiescent hepatic stellate cells (qHSCs), in form of lipid droplets.(160)

In NASH, myofibroblast or activated hepatic stellate cells (aHSC) secrete pro-inflammatory cytokines and form the ECM. As a result of the liver immune cells' inflammatory activity, primarily macrophages, hepatic stellate cells become activated. TGF-β1 produced by macrophages, which is the most potent known fibrogenic agonist, stimulates hepatic stellate cells.(161) The survival

of aHSCs is supported by hepatic macrophages, including Kupffer cells and recruited macrophages, in an NF-κB-dependent manner, which induce furthers liver fibrosis mediated by IL-1β and TNF-α.(162)

Resolution of Inflammation: A New Therapeutic Frontier for Fibrosis

In many different disease conditions, dysregulated inflammation is a key pathogenic mechanism. With varying degrees of success, treatment methods have traditionally attempted to control the pro- or anti-inflammatory limbs of inflammation. The ability to influence these processes pharmacologically has emerged as a result of research into the mechanisms through which inflammation is treated, and this tactic may provide an additional (and maybe superior) treatment method.(3)

The resolution mechanisms play a role not only in terminating inflammation but also in the transition of innate to adaptive immunity. Therefore, it has been crucial to distinguish the meaning of "anti-inflammation" from that of "pro-resolution".(74,163) Many studies have been conducted to explore more about inflammation and resolution, and hope by targeting only resolution, we can "switch off" signaling cascades or cellular interactions that induce inflammation and resolve it.(164-167)

Theoretically, pro-resolution pathways can be a strategy to cure disorders that are characterized by persistent inflammation. In fact, integrating pro-resolution with anti-inflammatory technologies may prove to be a more effective technique than current methods. When it comes to infections in particular, it was once thought that hastening resolution would result in incomplete clearance of the initial trigger. SPMs increase PMN and macrophages which perform bacterial phagocytosis, and by that SPMs not only promote resolution but also diminished the microbes in cells.(168) Therefore, unlike anti-inflammatory strategies, attempts that boost pro-resolution pathways shouldn't inherently make people more susceptible to infection.(3) Figure 7 describes the difference between anti-inflammatory therapies and pro-resolution treatments. Conventional anti-inflammatory therapy acts by inhibit inflammatory factors and antagonize proinflammation signals or in other word only treat the symptoms, and not resolving the cause while pro-resolution in the first phase enhancing essential factors for pathogens removal, which seems like supporting the pro-inflammatory condition. Then after the pathogen was removed, logically the inflammation will be reduced. This process will be

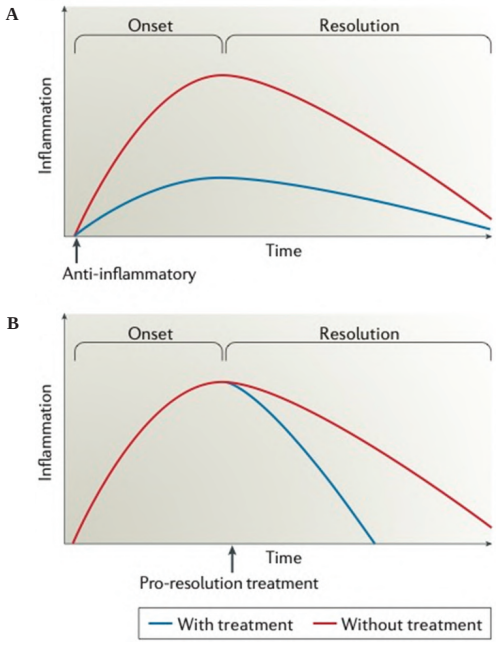

Figure 7. Antiinflammation versus pro-resolution strategies.(3) (Adapted with permission from Macmillan Publishers Limited).

followed by clearance and set the homeostasis back to normal, including the switching M1 macrophages into M2. This is why pro-resolution therapies will not necessarily affect onset but will accelerate resolution.

Many diseases found to be restricted in responding to current treatments due to a relative "resolution deficiency". This raise the possibility of lipid mediator-based monitoring and/or therapeutic options.(10-12) SPMs are particularly intriguing therapeutic possibilities now that it has been shown that they can encourage the resolution of inflammation. Resolution links acute innate inflammation to the emergence of long-lasting, antigen-specific responses and necessitates the collaboration of different cell types. Characterizing the impact of SPMs on adaptive immune responses will prove useful in identifying and treating adaptive immunological abnormalities due to their significance in autoimmune and inflammatory illnesses.(53)

SPMs are made up of at least four different families of powerful lipid mediators: maresins, protectins, resolvins, and lipoxins.(20,46,69,169) They are particularly significant because it established the first molecular basis for the numerous health advantages of the omega-3 fatty acids EPA, DHA, or DPA which are found in abundance in fish and are frequently used as dietary supplements. These essential fatty acids have a long history of being linked to positive effects on human health and the prevention of a number of diseases.(170) A lipid mediator "class switch" occurs when inflammation shifts to resolution. PGs and LTs

as the early proinflammatory were replaced by SPMs, and there are temporary changes in cellular enzymes such the 5- and 15- LOXs expression, location, and activity which affect in eicosanoid profile shifting.(171-173) The M1-M2 phenotypic change in macrophages, which is essential for tissue healing, is promoted by SPMs once they are accessible because they coordinate crosstalk between leukocytes and local cell populations.(174) SPMs also aid in resolution by positively influencing LOX activity and leukocyte SPM receptor expression.(137,172,173)

Polyunsaturated fatty acids, such as ARA, EPA, DHA, and DPA, are released from phospholipids in response to an inflammatory stimulus, and a succession of lipoxygenases, including 5-LOX, 12-LOX, and 15-LOX, catalyze their synthesis to create lipid mediators of inflammation and resolution.(52) LTB4 receptor 1/2 (BLT1/2) and cysteinyl LT receptor 1/2 (CysLT1/2) are two GPCRs that proinflammatory LTs like LTB4 and LTC4 act on. These receptors are activated, which increases the production of inflammatory cytokines like IL-6 and IL-8 as well as inflammatory enzymes like COX-2 and 5-LOX, which in turn promotes the recruitment of neutrophils. Similar to LTs, SPMs bind to and operate on their associated GPCRs, inducing cellular mechanisms that promote resolution.(175) Apoptosis, reduced leukocyte recruitment, efferocytosis, macrophage phenotypic switching from proinflammatory to pro-resolving, and tissue repair mechanisms, such as cell, matrix, and blood and lymph vessel reconstitution are included in these processes.(176,177)

A crucial characteristic of progressive atherosclerosis in human and mouse plaques has recently been discovered as an imbalance of pro-resolving to proinflammatory lipid mediators.(71,72) Resolvin D1 (RvD1), a mediator that promotes resolution, was shown to be present in low levels in areas of human atherosclerotic plaques with large necrotic cores and thin fibrous caps, whereas LTB4 was found to be present in high levels in these same locations.(71) On the other hand, areas of the plaque with less necrosis and thicker fibrous caps showed elevated levels of RvD1 and relatively low levels of LTB4.(71) RvD1 to LTB4 ratio therefore showed a substantial correlation with plaque severity.

Atherosclerotic plaques that are not promptly cleared of apoptotic cells develop secondary necrosis, which causes an increase in inflammation because the necrotic cells emit inflammatory damage-associated molecular patterns (DAMPs).(178-181) Therefore, in chronic non-resolving inflammatory disorders, efferocytosis is an essential stage in the reduction of lesional inflammation. It's interesting to note that SPMs can boost macrophages' ability to efferocytose (20,44,182), and efferocytosis in turn encourages the creation of SPMs by macrophages, including LXA4, RvE1, and PD1 (181,183,184). SPMs, especially lipoxins, operate as chemoattractants to draw in monocytes, which later differentiate into macrophages and increase the efferocytic ability of the body to heal injuries.(44,185,186) Thus, there is a positive resolution feedback cycle involving SPMs and efferocytosis, similar to the scenario with resolving macrophages that was previously stated.(187)

Most diseases caused by chronic inflammation cannot be totally healed without leaving a scar, even in active regenerating organs such as liver. The replacement of non-regenerating parenchymal cells by connective tissues is thus required for the repair of injured tissues, which over time results in considerable fibrosis and scarring. Therefore, a significant technical advance would be the creation of treatment approaches that slow the advancement of fibrosis without impairing the overall healing procedure.(5)

Resolvins can immediately reduce the fibrotic markers such as procollagen type III, collagen type IV, laminin, and hyaluronic acid by lowering proinflammatory and profibrotic cytokines and promoting efferocytosis. For example, collagen type IV and platelet-derived growth factor (PDGF)-BB are powerful fibroblast proliferation promoter via AKT and ERK pathways activation. RvE1 can significantly reduce the accumulation of α-smooth muscle actin (α-SMA) myofibroblasts in interstitial fibrosis. RvE1 protects against the development of hepatic fibrosis brought on by Schistosoma japonicum infection.(188) In the animal model investigation, unilateral ureteric obstruction was used to test RvE1's anti-fibrotic properties. Additionally, in a kidney injury model, RvD1 significantly decreased myofibroblast accumulation and type I and III collagen mRNA levels.(189) Another example, 17(R)-RvD1 therapy exerts anti-inflammatory and anti-fibrotic benefits even when it is given to lung tissue that has already reached a fibrotic state.(190) Additionally, RvD1 reduces the build-up of collagen in cardiac tissue following a myocardial infarction.(191) Various functions of this novel class of lipid mediators, which can inhibit inflammation's progression and chronicity in a number of ways, as well as how they might regulate the onset of fibrotic disorders like SSc.(144)

Conclusion

Inflammation must be reduced in order to maintain tissue homeostasis. A protracted inflammatory response, including an increase in PMNs, excessive generation of

proinflammatory mediators, an increase in the number of apoptotic cells, and incorrect activation of adaptive immune cells, might result from any errors in the resolution phase results in fibrosis. The creation and use of proresolution therapeutic approaches to treat chronic inflammatory pathology may change the treatment of some of the most enduring and widespread diseases that affect people by triggering the stimuli rather than suppressing their beginning and spread. By current knowledge on genomic approach, we can perhaps learn more about the causes of chronic inflammation from various angles and identify new targets for effective customize pharmacological treatments. if we approach such a wide range of illness conditions from the other angle and focus on enhancing clearance of the triggering stimuli rather than suppressing their beginning and spread.

Authors Contribution

AM drafted, wrote, and edited the manuscript. AW proposed the manuscript topic, supervised, and edited the manuscript. All authors had agree with the final manuscript.

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