

From Inflammation to Resolution: Therapeutic Insights into Chronic Disease Management

Anastasia Vladimirovna Poznyak^{1*}, Nikita Aleksandrovich Mitkin², Daria Dmitryevna Borodko³, Alexander Nikolaevich Orekhov¹

¹Institute for Atherosclerosis Research, 4-1-207, Osennaya Street, 121609 Moscow, Russia

²Laboratory of Cellular and Molecular Pathology of Cardiovascular System, Research Institute of Human Morphology, Petrovsky Russian National Center of Surgery, 2, Abrikosovsky Lane, 119991 Moscow, Russia

³Laboratory of Molecular Genetic Modeling of Inflammation, Institute of General Pathology and Pathophysiology, 8, Baltiyskaya Street, 125315 Moscow, Russia

*Corresponding Author: Anastasia Vladimirovna Poznyak, Institute for Atherosclerosis Research, 4-1-207, Osennaya Street, 121609 Moscow, Russia
Email: tehhy_85@mail.ru

ABSTRACT

Inflammation is a fundamental biological process implicated in various physiological and neurological disorders, including cardiovascular diseases, cancer, diabetes, and neurodegenerative conditions. Chronic inflammation is linked to significant health challenges and mortality worldwide, emphasizing the importance of understanding its mechanisms and resolution. This review elucidates inflammatory processes as essential components of the immune response, highlighting pharmacological interventions for promoting timely inflammation resolution. We explore the dual phases of inflammation—acute and chronic—detailing the complex cellular interactions and signaling pathways that govern the inflammatory response to pathogens and tissue injury. In particular, we emphasize specialized pro-resolving mediators (SPMs), such as lipoxins and resolvins, which play crucial roles in transitioning inflammation from a detrimental to a healing state. Additionally, we discuss innovative therapeutic approaches, including tissue engineering, cellular therapies, and the utilization of SPMs, aimed at enhancing inflammation resolution. The roles of gaseous mediators and peptide/protein mediators in modulating inflammation are also examined. Through this comprehensive analysis, we advocate for the development of pro-resolving treatments to improve outcomes for patients with chronic inflammatory disorders. By understanding the intricate dynamics of inflammation and its resolution, new avenues for targeted therapy emerge, offering promise for mitigating the impacts of chronic inflammatory diseases and enhancing patient quality of life.

Keywords: Inflammation, chronic inflammation, chronic inflammatory disorders, therapeutic strategies, specialized pro-resolving mediators, inflammation resolution

How to cite this article: Anastasia Vladimirovna Poznyak, Nikita Aleksandrovich Mitkin, Daria Dmitryevna Borodko, Alexander Nikolaevich Orekhov. From Inflammation to Resolution: Therapeutic Insights into Chronic Disease Management. *Int J Drug Deliv Technol.* 2026;16(88s):9-26. DOI: 10.25258/ijddt.16.88s.2.

Introduction

Inflammation is a complex biological response triggered by harmful stimuli, such as pathogens, damaged cells, or irritants, and plays a critical role in protecting the body. This process is essential for maintaining homeostasis, facilitating tissue repair, and initiating the immune response. However, when inflammation becomes chronic, it can lead to a range of serious health issues, including cardiovascular diseases, diabetes, cancer, neurodegenerative disorders, and mental health conditions such as depression and schizophrenia. Chronic inflammation is intricately linked to the pathogenesis of these disorders, resulting in significant morbidity and mortality worldwide [1,2].

Understanding the mechanisms of inflammation and its resolution is vital for developing effective therapeutic strategies. This review aims to elucidate the inflammatory processes inherent to the immune response while emphasizing the importance of pharmacological interventions that promote the resolution of inflammation. We will explore how these processes not only contribute to healing but also, when dysregulated, give rise to chronic inflammatory conditions that require targeted treatment approaches [3,4].

Throughout this review, we will discuss specialized pro-resolving mediators (SPMs) and their pivotal roles

in regulating inflammation resolution. We will also examine innovative therapeutic strategies, such as tissue engineering and cellular therapies, that aim to enhance these natural mechanisms. Additionally, we will consider the influence of gaseous mediators on inflammation resolution, shedding light on their potential for therapeutic applications. By synthesizing current knowledge on inflammation and its resolution, this review provides insights into novel avenues for treating chronic inflammatory diseases. Understanding the mechanisms of inflammation and its resolution is crucial for developing effective therapeutic strategies.

Inflammation

Inflammation is a crucial component of the immune response, initiated in response to tissue injury or pathogen invasion. It can be broadly categorized into two main stages: acute inflammation and chronic inflammation. Understanding these stages is vital for recognizing how inflammation contributes to various physiological processes and diseases.

Acute Inflammation is characterized by a rapid onset and short duration, typically lasting from a few hours to a few days. This process consists of two pivotal stages: initiation and resolution [5,6]. The first stage involves the activation of the immune system in response to injury or infection, leading to a cascade of

biological events designed to eliminate the offending agents. Key mechanisms involved during this phase include endothelial activation and leukocyte infiltration.

During the initiation stage, the endothelial cells lining blood vessels undergo a phenotypic change, a process known as endothelial activation [7-9]. This alteration enhances vascular permeability and promotes a pro-coagulant state, facilitating the adhesion and infiltration of leukocytes into the affected tissues. Specifically, the endothelium expresses cell adhesion molecules (CAMs) that mediate the adherence of leukocytes, which are further activated upon recognizing pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) through pattern recognition receptors (PRRs). This inflammatory signaling cascade culminates in the activation of NF- κ B, leading to increased expression of CAMs and further recruitment of immune cells to the site of injury [10-12].

Following the initial defense, the resolution stage of acute inflammation is characterized by the clearance of immune cells, particularly neutrophils, and restoration of normal tissue function. This resolution phase involves a reduction of neutrophil infiltration by approximately fifty percent, clearance of the inflamed tissue, and the generation of specialized pro-resolving mediators (SPMs) primarily synthesized by macrophages and neutrophils [13,14]. These mediators not only promote the apoptosis of excess leukocytes but also stimulate tissue regeneration and repair [15-18]. Normally, if the underlying cause of inflammation is resolved, this response concludes successfully, leading to the restoration of homeostasis. However, when the cause of inflammation is persistent or unresolved, the process can transition into chronic inflammation. This prolonged inflammatory state may arise from ongoing infections, autoimmune disorders, or sustained exposure to irritants, leading to tissue damage and contributing to various chronic diseases. Recent research has highlighted the significant role of chronic inflammation in the progression of conditions such as neurodegenerative diseases, asthma, diabetes mellitus, cancer, cardiovascular diseases, atherosclerosis, inflammatory bowel diseases, and rheumatoid disorders [19-21]. Chronic inflammation is associated with continuous immune cell activation, increased production of pro-inflammatory cytokines, and the potential for tissue fibrosis and degeneration, ultimately resulting in debilitating health consequences.

In summary, inflammation is a double-edged sword: while the acute inflammatory response is essential for protecting and healing the body, its persistence can lead to chronic inflammation and a myriad of associated diseases. A comprehensive understanding of these processes is vital for developing therapeutic interventions aimed at managing inflammation-related conditions. In summary, inflammation is a double-edged sword: while the acute inflammatory response is essential for protecting and healing the body, its persistence can lead to chronic inflammation and a myriad of associated diseases.

Biological Mechanisms Linking Inflammation to Chronic Diseases

Chronic inflammation has been increasingly recognized as a central contributor to the development and progression of various chronic diseases, including cardiovascular disorders, diabetes, cancer, and neurodegenerative diseases. Understanding the biological mechanisms that link inflammation to these conditions is essential for developing effective therapeutic strategies [22-24].

At the heart of the inflammation process is the interplay between immune cells and inflammatory mediators. Acute inflammation is characterized by an initial recruitment of leukocytes, primarily neutrophils, to the site of injury or infection [25,26]. This is followed by the activation of pro-inflammatory cytokines, such as tumor necrosis factor (TNF) and interleukin-1 (IL-1), which further amplify the inflammatory response. However, if this acute phase is not resolved properly, it can transition into chronic inflammation, where immune cells, including macrophages and T lymphocytes, persistently infiltrate tissues [27,28].

The specific role of SPMs in resolving inflammation highlights their therapeutic potential. These lipid mediators, such as lipoxins, resolvins, and protectins, are generated from essential fatty acids and participate in complex signaling pathways that promote resolution and tissue repair [29,30]. For instance, lipoxin A4 (LXA4) enhances the clearance of apoptotic neutrophils via efferocytosis, effectively terminating the inflammatory response and preventing tissue damage [31]. LXA4 and its receptors, especially formyl peptide receptor 2 (FPR2), mediate signaling pathways that lead to suppression of pro-inflammatory cytokine production and promote macrophage polarization towards a reparative phenotype [1,2].

Resolvin E1 (RvE1), another SPM, has also been shown to actively mediate the resolution of inflammation. It engages with its receptor, ChemR23, which induces a signaling cascade that downregulates inflammatory gene expression in macrophages, thereby facilitating tissue healing [3]. RvD1, a member of the resolvins, similarly promotes the clearance of neutrophils and enhances the migration of macrophages to areas of inflammation, further underscoring the importance of these mediators in controlling chronic inflammatory processes [32,33].

Importantly, the interaction of these mediators with their receptors extends beyond just resolving inflammation—it also influences cellular communication and tissue homeostasis. For example, during the resolution phase, SPMs can trigger the production of anti-inflammatory cytokines, such as IL-10, which helps to establish a balanced immune response and prevents the phenomena of chronic inflammation that underlies many diseases [4,5].

Studies utilizing animal models have shed light on the intricate roles of these mediators. In experimental models of rheumatoid arthritis, administration of resolvins has demonstrated a reduction in joint inflammation and bone erosion, highlighting their therapeutic potential in preventing the progression of

inflammatory diseases [6]. Similar observations have been made in models of cardiovascular diseases, where SPMs have been shown to inhibit monocyte adhesion to endothelial cells and reduce vascular inflammation [34].

By exploring the complex interactions at the molecular level, it becomes evident that SPMs are not merely passive contributors to inflammation resolution; they actively coordinate and modulate the immune response, guiding it towards a more regulated state that mitigates tissue damage and promotes healing [35,36]. This understanding aids in identifying potential targets for therapeutic interventions aimed at enhancing the actions of these mediators, offering hope for patients suffering from chronic inflammatory disorders.

Key Specialized Pro-Resolving Mediators (SPMs) and Their Functions

In this section, we will outline the various specialized pro-resolving mediators involved in inflammation resolution. In Table 1, we briefly summarized some key features of different SPMs and their functions, highlighting the clinical significance.

Table 1. Brief overview of key SPMs.

Type of Mediator	Examples	Biosynthetic Enzymes	Functions	Clinical Significance
Lipoxins (LXs)	Lipoxin A4	Lipoxygenase (5-LOX, 15-LOX)	Inhibit neutrophil recruitment, promote macrophage apoptosis	Potential therapeutic targets in arthritis and IBD
Resolvins (Rvs)	Resolvin D1, Resolvin E1	Lipoxygenase (5-LOX, 12-LOX)	Reduce inflammation, enhance phagocytosis	Improvement in chronic inflammatory conditions
Protectins	Protectin D1	Lipoxygenase (15-LOX)	Support neurons, protect tissues from oxidative stress	Neuroprotection in neurodegenerative diseases

Type of Mediator	Examples	Biosynthetic Enzymes	Functions	Clinical Significance
Maresins (MaR1)	Maresin 1	Lipoxygenase (12-LOX)	Promote resolution of inflammation	Role in cardiovascular health and tissue repair

Autacoids

Specialized proresolving mediators

Pro-resolving mediator lipoxin A4 is a biologically active mediator. It is generated via interplay of 2 groups of LOX enzymes. If the synthesis takes place in leukocytes, 5LOX and 15LOX are involved, and if it takes place in platelets and leukocytes, it is 5LOX and 12LOX. Rvs, MaR1s and protectins were lately identified as biologically active proresolving lipid mediators (LMs). They are also generated via coordinated activities of cell-dependent LOXs and COXs [37,38]. SPMs include all these mediators. SPMs have multilateral functions to stimulate protective mechanisms and induce activation of resolution via related receptors. Provided that the mediators are biologically active in femto-molar and nano-molar range, and autacoids themselves are temporal, their recognition and quantitative assessment need methods that are different from methods that are usually applied in metabolomics and lipidomics [39-41]. Serhan laboratory was first to use methods that involve solid-phase extractive (SPE) approach, liquid chromatography (LC) – MS/MS and organic chemistry to determine standards for every biologically active mediator, pathway biomarker, precursor and metabolite, that guarantee clear recognition of every pro-resolving mediator and contents of the metabolomes [42-44]. Furthermore, existing standards allow interlaboratory approach validation. Applying these methods, a number of laboratories have found SPMs in significant concentrations in human plasma, urine, synovial fluid and breast milk. Finding of SPMs, e.g., Rvs, that are obtained from ω -3 FAs demonstrates a mechanism for positive influence of fish oil supplements in subjects with arthritis [45,46]. Studies in murine model of 12/15LOX function deficit in leukocytes or FPR2 show worsened gravity of the disorder and tissue injury in inflammation arthritis (IA). Studies in 5-LOX-null murine model showed aggravated long-term infectious arthritis. Cyclooxygenase-2 blockade holds resolution of RA caused by collagen. Although, that phenotype can be saved by PGE-2-mediated synthesis of lipoxin A4 [47-49]. These discoveries highlight the huge role of enzymes and their products in curbing experimental arthritis. In context of joints, enzymes of bio-synthetic pathways for SPMs and pro-resolving receptors are released in stromal cells and leukocytes in synovia. 5LOX are released by neutrophils, mast

cells and macrophages in synovial membrane and sublining. 15LOX type I is found mostly in membrane macrophages, sublining ECs, fibroblasts, and articular chondrocytes [48-50]. In subjects with rheumatoid arthritis, synovial tissues show increased 5LOX, 15LOX type I and prostaglandin E2 messenger RNA in comparison to subjects with OA (osteoarthritis) [51,52]. Thus, certain pro-resolving effectors and pathways may become enhanced in affected tissues to regulate inflammation; however, in chronic conditions, these efforts are often ineffective, allowing the disorder to persist [53,54].

While bio-synthetic mechanisms for SPMs are found in synovial fluid, the SPMs are detected in synovia as well, as expected. Using LM profiling, we detected resolvin D1, resolvin D3, and the LX pathway biomarker 5S, 15S-dihydroxy eicosatrienoic acid in the synovia of patients with rheumatoid arthritis [55,56]. Moreover, Giera et al. have found resolvin D5, MaR1 and lipoxin A4 in synovia [57]. It is yet to be investigated if there is a deficiency of SPM synthesis in joints in acute stages of the disorder. Although, we suggest that profiling of LMs might be helpful with grouping of subjects with rheumatoid arthritis, with determination of profiles related to particular subject groups. Such profiling can be applied to choose the treatment approach. 17R resolvin D1 is an epimer of resolvin D1. It seems to exert arthroprotective function, as was detected in a murine model of K/B×N arthritis [58,59]. It decreased leukocyte infiltrate in joints and alleviated gravity of the disease, wasting syndrome and paw edema. Moreover, new defense activities of 17R resolvin D1 have been discovered. Among them are promotion of chondrocyte ECM genesis and defense against degrading of cartilage. 17R resolvin D1 showed arthroprotective function in case of pain syndrome caused by CFA injection into paws [60,61]. It reduced concentrations of tumor necrosis factor and interleukin 1 beta and alleviated hyperalgesia. These findings additionally confirm that synthesis of SPMs could be crucial for joint defense and that a disruption of those pathways can facilitate the disease pathogenesis. Subsequently, approaches based on SPMs could lead to development of new therapeutic approaches [62,63].

Adenosine

Adenosine is a compound with significant biochemical activity. It is crucial for adenosine diphosphate and adenosine triphosphate for which it serves as a precursor. It is also biosynthetically related to the cyclic adenosine monophosphate [64,65]. Cronstein et al. discovered that an anti-rheumatic agent methotrexate elevates concentrations of adenosine, that decreases aggregation and activity of leukocytes at inflamed regions [66]. Consequently, Tregs' capacity of adenosine synthesis was proved to be predictive of the response to this drug. Methotrexate is commonly applied for treatment of rheumatoid disorders such as rheumatoid arthritis, psoriasis or vasculitis. This implies that this autacoid has vital physiologic characteristics. Adenosine pro-resolving characteristics are mediated by particular

receptors among which types A-2a, A-2b and A-3 are especially relevant in inflammatory and auto-immune disorders [67,68]. Apart from classic antiphlogistic activity, e.g., suppression of cytokine expression from macrophages and DCs, adenosine can also stimulate efferocytosis of macrophages. It is a mechanism of clearance of cells which have undergone apoptosis or necrosis. In context of tissue repairment and homeostasis reconstitution, the A-2a receptor can protect in case of experimental arthritis in murine model [69-71]. Administration of a pro-drug to increase adenosine concentrations in tissues decreased arthritis by modulating reactivity of neutrophils and inflammatory monocytes. Regarding bones and joints, A-2a activation mediated a decrease in the resorption of bone tissue caused by wear particles. This result was connected to a significant elevation of interleukin 10 concentrations (and simultaneous reduction of interleukin 1 beta and tumor necrosis factor) in murine model after therapy with selective A-2a agonists [72,73].

Gaseous mediators

There are 3 major soluble gases with physiologic activity. They are nitric oxide (NO), carbon monoxide (CO), and hydrogen sulphide (H₂S). In the recent years, their antiphlogistic characteristics were identified. Regarding the resolution of inflammatory processes, NO was the first to be found to suppress recruitment of neutrophils to post-capillary venules by modulating guanylate cyclase function in ECs [74,75]. These strong suppressive effects have also been detected for H₂S. Elevation concentrations of H₂S suppressed recruitment of neutrophils into inflamed regions, while suppressing of its genesis aggravated cell response. It is noteworthy that H₂S was found to promote annexin A1 expression from cellular sources [76,77]. That decreased interplay of neutrophils and endothelium. In murine model of deficiency of this protein this effect was not observed. In case of arthritis, H₂S donor NaHS reduces reactivity of chondrocytes and fibroblasts in synovia after administration of interleukin 1 beta or interleukin 6. In a model of inflammatory process and pain syndrome in joints caused by zymosan, H₂S showed protective and antinociceptive effect as well as defended against cartilage injury. A connection has been found between CO and the synthesis of SPMs in regulating acute inflammatory processes and secondary organ injury during ischemia-reperfusion injury (IRI) [78,79]. At lower dose, CO increased concentrations of 15LOX type I, resulting in an elevation of SPMs concentrations and a decrease in inflammatory process. SPMs, such as resolvin D1, PD-1 and resolvin E1, elevate heme oxygenase 1, leading to heme catabolic processes and elevated CO genesis, hereby facilitating protection [80].

Peptides and proteins

Melanocortins

Placebo-controlled studies of adrenocorticotrophin in subjects with serious gout arthritis have demonstrated the arthroprotective activity of this compound. Adrenocorticotrophin has already demonstrated effectiveness in rheumatoid arthritis.

Adrenocorticotrophin is a thirty-nine aminoacid peptide which is produced by the POMC gene-encoded polypeptide cleavage. Alpha-melanocyte-stimulating hormone comprises the first thirteen amino acids of adrenocorticotrophin, but it undergoes amidation on C-terminus [81]. It has long been believed for a long time that adrenocorticotrophin exerted antiphlogistic function only by promoting the cortisol expression by adrenal glands as well as that alpha-melanocyte-stimulating hormone carried out mediation of tanning only via melanin [82]. Although, in 1990 five MCRs were cloned, which increased the probability of wider activity of adrenocorticotrophin and alpha-melanocyte-stimulating hormone. More receptors besides melanocortin-2 and melanocortin-1 showed potential for being implicated by natural melanocortins (MCs) [83,84]. Macrophage melanocortin 3 receptor was proved to be a new effector of pro-resolving characteristics of MCs, regulating cytokine expression and stimulating pro-resolving activities such as efferocytosis and phagocytosis of macrophages [85,86]. Adrenocorticotrophin was found to be efficient in experimental gout. It remained effective in a rat model of adrenalectomy, thus excluding a possibility of adrenal glucocorticosteroids (GCSs) being involved, and when administered in human knee joint, thus preventing elevation of GCSs in bloodstream [87].

An agonist of MC receptor demonstrated arthroprotective function in arthritis associated with inflammation, however, to a smaller degree than GCS dexamethasone. Although, the agonist of MC receptor showed bone tissue preserving effect, while dexamethasone worsened the bone resorption [88,89]. Hereby, these findings imply that agonists of MC receptor might be a new category of antiarthritic drugs with potent pharmacological characteristics. These results add to the existing data on physiologic role of melanocortin 3 receptor. Studies in a melanocortin 3 receptor-null murine model showed higher speed of bone resorption related to aging, which implies that regulation of bone metabolism is an important function of that pathway [90]. This agrees with the fact that elevated osteoclast count was detected in joints in melanocortin 3 receptor-null murine model of inflammation-associated arthritis. That effect is possibly secondary to the suppressive activity of that receptor on osteoclast synthesis signaling pathways. Based on these findings, novel therapeutic strategies may emerge using the pro-resolving characteristics of adrenocorticotrophin and other MCs [91,92]. It is also noteworthy that alpha-melanocyte-stimulating hormone shows a cartilageprotective function. It counteracts the catabolism of interleukin 1 and tumor necrosis factor on chondrocytes. It also protects cartilage from injury. Such protection patterns have been observed in skin repairment, where tissue alpha-melanocyte-stimulating hormone and melanocortin 1 receptor expression is enhanced in repair and resolving stage in burn wounds and scars [93,94].

Lipocortin I

Protein lipocortin I, also known as annexin A1, is a vital proresolving mediator regulated by GCS. Annexin A1 is involved in signaling through N-formyl peptide receptor 2. Trials in genetically modified murine model with annexin A1 deficiency or after treatment with this protein showed that annexin A1 contributes to modulation of neutrophil transport. In vitro and in vivo studies demonstrated that annexin A1 is mediating HDAC suppressants capacity of stimulating apoptotic processes and efferocytosis in neutrophils [95,96]. Endogenous annexin A1 is implicated in regulation of M-1–M-2 switch of macrophages in the course of hepatic fibrosis. Similar protection function was observed in AS. Studies in annexin A1-null murine model revealed aggravated inflammation in the joints in arthritis caused by antigens. Although, that effect was not detected when serum-transfer arthritis model was used on annexin A1-null murine model [97-99]. This result implies that this mediator is model specific or that its regulation activity is exerted only when the joint disorder is low-grade. Notably, in both annexin A1-null models dexamethasone effectiveness against arthritis was decreased considerably. Dexamethasone turned out to be not capable of regulating cytokine release and cartilage injury prevention. It is noteworthy that GCSs are the typical example of endogenous proresolving effector, which reflects a key component of stress response. Notwithstanding their impact on CV and metabolic systems, their regulation function must not be underestimated [100].

Galectins

Galectins are a class of proteins which bind to CHs. They are capable of modulation of numerous mechanisms, some of them show pro-resolving activity. Galectins are synthesized by immune cells, and their release is the highest at the peak of the inflammation response. Galectin 1 was detected in resolution exudate in murine model of peritoneum inflammation caused by zymosan [101-103]. It was reported to be suppressed by lidocaine, which can delay the resolution of inflammation. This protein family is believed to serve as a connection between innate immunity and acquired immunity. In an environment rich in galectin 1, differentiated DCs display elevated regulation activity and are able to inhibit development of auto-immune disorders and decrease inflammatory processes when applied at early stages in MS mice [104,105]. Galectin 1 delays migration of immunogenic DCs through ECs in lymph nodes. In context of arthritis, galectin 3 exerts proinflammatory function and can induce arthritis, while galectin 1 and galectin 9 protect against inflammation in experimental models. The arthroprotective activity of galectin 1 in those models appears to come from its capacity of elevating the sensibility of pro-arthritis T lymphocytes to apoptotic process caused by antigens and of stimulating the shifting from Th1 to Th2 response [106-108]. Galectin 9 exerts its protection function in models of arthritis caused by collagen by contemporaneously downregulating Th17 and upregulating regulatory T

cells genesis. Galectin 9 impact is not limited to acquired immunity cells or models of arthritis caused by collagen. Studies in models of arthritis caused by immunity complexes showed that galectin 9 is modulating Fc-gamma receptors expression on macrophages, enhancing the suppressive Fc-gamma RIIB and inhibiting Fc-gamma RIII, dominant Fc receptor, leading to a decrease in the disorder gravity [109-111]. In vitro and in vivo studies showed that galectin 9 is capable of stimulation of apoptotic process of fibroblast-like synoviocytes (FLS). This effect facilitated prevention of joint damage related to those cells. Fibroblasts and other stromal cells appear to regulate the switching from acute to chronic inflammatory process. Galectin 1 concentrations are decreased in synovial tissues on human subjects with JIA and in synovia of rheumatoid arthritis (RA) subjects [112,113]. At the same time, galectin 9 appears to be elevated with higher concentrations found in synovia fluids and cells of rheumatoid arthritis subjects in comparison to OA subjects. It is yet to investigate if this elevation is a result of the body failed attempt to fight joint disorder because of not activated Gal-9 by proteolysis or it is the consequence of decreased target receptor expression, e.g., after shedding in sites of inflammation [114,115]. As we transition into treatment strategies based on these findings, several avenues emerge for enhancing inflammation resolution.

Design of resolving-based treatments

Considering the available data on the inflammatory processes resolving biology, it is possible now to determine the way of using this information for development of new arthroprotective clinical approaches. We suggest at least 3 different strategies that can be utilized to develop treatment based on inflammation resolving [15]. In Table 2, we provided the summary of various pro-resolving therapeutic strategies, which represents in brief the content of the following paragraphs. In Figure 1, we summarized the concept of resolving-based treatments.

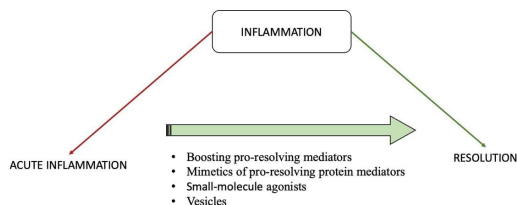


Figure 1. Inflammation-resolution concept.

Boosting pro-resolving mediators

The first strategy depends on elevating concentrations of endogenous pro-resolving mediators. Application of dietary supplement, e.g., fish oil supplementations, suits this strategy. Fish oil supplementation is frequently applied for arthritic subjects as it gives the substrate for synthesis of SPMs and other pro-resolving mediators. Trials have shown that a number of widely used compounds such as atorvastatin and aspirin are able to enhance endogenous synthesis of SPMs [116,117]. Another strategy that may be used implicates suppression of pro-resolving protein mediators' catabolic process, which is responsible for

the sulfasalazine and methotrexate capacity of elevating adenosine by suppressing enzyme that transforms it to inosine – ADA. Inhibition of annexin A1 catabolic process by various serine endopeptidase suppressants was proved to speed up the resolving in case of acute pulmonary inflammatory process [118]. Activated annexin A1 in myeloid cells by HDAC suppressants speeds up cellular apoptotic process and efferocytosis in the course of peritoneum inflammation. It is noteworthy that this connection was detected by analyzing and comparing sets of genes using connectivity map, which is a powerful instrument to establish connections between known compounds and resolving effectors modulating [119-121]. Antigout characteristic of a proteins comprising alpha-1 antitrypsin administered to the Fc site of immunoglobulin G1 can be in accordance with the suppression of catabolic processes, since it is possible for alpha-1 antitrypsin to increase concentrations of endogenous pro-resolving mediators [122,123].

Mimetics of pro-resolving protein mediators

Another strategy involves an attempt to develop pro-resolving protein mediator mimetics. Presently there are several successful examples of such attempts, e.g., lipoxin A4 and Rvs. These compounds exert similar function to their parent mediators, such as binding capacity. It is crucial to evaluate the pro-resolving signaling response of these compounds in HTS and target confirmation tests [124-126]. BDA-RvD-1 is one of these stable agonists which act in a manner similar to SPMs. BDA-RvD-1 triggers activation of G protein-coupled receptor 32 and possibly facilitates inflammatory process resolution. These compounds have more beneficial properties, e.g., their physical features allow mass production. Another path of mimicry of resolving process is expression of dissolved gaseous mediators. There are examples of continuing mimicry-based clinical translation [127,128]. Targeted approaches might be useful here as well, particularly if the mediators are not stable. E.g., in order to allow to transport the compound into the joint without being degraded in blood. Thus, development of MC where protein triggering activation is latent can ameliorate PK and PD, with desirable impact achieved at low dose. These findings are consistent with knowledge on fusion protein of alpha-1 antitrypsin in arthritis uratica [129,130].

Small-molecule agonists

The third strategy implicates engineering small molecules to induce tissue repairment and pro-resolving signaling by implicating particular receptors. This activity is the opposite to presently available anti-inflammation treatment which involve antagonists of the receptors, e.g., tumor necrosis factor or interleukin 1 receptor antagonists. It is noteworthy that determination of actual pro-resolving pathways is necessary for this strategy [131,132]. E.g., lipoxin A4 and annexin A1 are stabilizing a homo-dimeric conformation of N-formyl peptide receptor 2, thus triggering activation of a special pathway resulting in phosphorylating of hsp70 and in expression of interleukin 10 in myeloid cells. The 2 agonists of N-formyl peptide receptor 2 impact adds to their

capacity of competition with inflammation signaling as was observed in ECs and macrophages in alveoli [133,134]. Use of biased agonists might be a possible approach to induce signal which has relevance to the needed response, with simultaneous avoidance of postreceptor signaling pathways related to adverse consequences. Resomelagon is a small molecule which is agonizing MC receptors. This drug is able to decrease joint disorder in IA via activation of melanocortin 1 and melanocortin 3 to start signaling via phosphorylation of ERKs and flux of Ca^{2+} , simultaneously preventing cutaneous hyperpigmentation since cAMP production is not triggered [135,136].

Vesicles as a novel treatment strategy

New treatment strategies could be developed based on recent findings related to inflammation resolution. Extracellular vesicles (EVs) are a preserved mechanism of cell-to-cell signaling. They take part in numerous physiologic mechanisms. Upon an elevation of Ca^{2+} within a cell, EVs are budding from cell membrane. Vesicles obtained from neutrophils provide a possibility for a new treatment approach since they facilitate resolution of inflammation [137-140]. EVs may be derived from peripheral blood, then pro-resolving proteins or SPMs are added to them, after which their infusion can trigger inflammation to resolve. EVs with 17R resolvin D1 or benzo-lipoxin A4 accelerated wound healing by recruiting keratinocytes and leukocytes to TMJ in inflammatory process. Interestingly, nano-compounds facilitating resolution enriched with benzo-lipoxin A4 have shown ability to enhance regeneration of tissue in periodontal disease [141,142]. Another useful characteristic of EVs is their capacity of penetration of the cartilage in order to prevent it from being degraded in case of IA. Neutrophils from rheumatoid arthritis synovia were enriched for annexin A1 positive EVs which enhanced restoration of chondrocyte reaction to anti-catabolism or anabolism phenotype. EVs capacity of aggregate annexin A1 and other substances in the lacuna chondrocytes could account for this restoration. There are more nano-compounds with pro-resolving properties that, when enriched with peptides obtained from annexin A1, demonstrated positive effects in AS and IBD. In that research, nano-particles comprised target sequenced which allowed being enriched at regions of vessel and tissue damage [143-145].

Table 2. Novel Therapeutic Strategies to Enhance Inflammation Resolution

Strategy	Description	Mechanism of Action	Examples	Potential Benefits
Pro-Resolving Mediator	Increasing concentrations of SPMs	Enhanced synthesis or reduced degradation	Fish oil supplementation, atorvastatin	Improved resolution of

Strategy	Description	Mechanism of Action	Examples	Potential Benefits
Pro-Resolving Mediator	Increasing concentrations of SPMs	Enhanced synthesis or reduced degradation	Fish oil supplementation, atorvastatin	Improved resolution of
Mimetics of Pro-Resolving Mediators	Developing analogs of SPMs	Mimic natural mediators' effects	BDA-RvD-1, synthetic LXs	Enhanced stability and efficacy in treatment
Small-Molecule Agonists	Targeting specific receptors for SPMs	Induce pro-resolving signaling pathways	Agonists for melanocortin receptors	Reduced joint inflammation and tissue protection
Extracellular Vesicles (EVs)	Utilizing EVs from immune cells	Carry SPMs and proteins to promote resolution	EVs enriched with annexin A1	Targeted delivery of therapeutic agents
Gene Editing Approaches	Modifying gene expression related to SPMs	Enhance endogenous production of protective mediators	CRISPR technologies	Novel treatments for chronic inflammatory diseases

Limitations

Numerous studies have provided evidence for the crucial role of specialized pro-resolving mediators (SPMs) in the resolution of inflammatory processes, suggesting their potential use in treatment. However, there are significant limitations in the application and understanding of these mediators. One major concern is the pharmacokinetics of these substances. For instance, lipoxins (LXs) are synthesized in various

tissues but rapidly undergo degradation by enzymes such as prostaglandin dehydrogenase (PGDH) [146,147] and omega-oxidoreductase. These rapid degradations limit their therapeutic effectiveness. While analogues of epi-lipoxin A4 and epi-lipoxin B4 have been developed to resist these alterations, the stability and biological availability of such compounds remain issues, as they can be sensitive to β -oxidation [148].

Moreover, traditional methodologies for isolating and quantifying these mediators, such as liquid chromatography-mass spectrometry (LC-MS), require considerable technical expertise and may not be widely accessible, thus limiting their application in clinical settings. The complexity of biological samples can interfere with the accuracy and reproducibility of results, leading to potential biases. Additionally, there is an inherent reliance on animal models to draw conclusions about human inflammation, which can complicate the translation of findings to human physiology.

Inconsistencies in definitions and classifications of mediators further complicate the understanding of their functions. Variations in biosynthetic pathways and the roles of each mediator can differ significantly among studies, making it challenging to draw generalized conclusions. These discrepancies highlight the need for standardized research approaches to provide clearer insights into the efficacy and mechanisms of these mediators.

Future Perspectives

Future research should focus on several critical areas to enhance our understanding and application of pro-resolving mediators. First, elucidating pharmacokinetic characteristics is vital. Conducting longitudinal studies that monitor the dynamic changes of mediators during inflammatory responses and resolution phases in human models will yield valuable insights into their role in these processes. Developing stable analogues of pro-resolving mediators that can resist metabolic degradation without losing bioactivity should be a priority, enabling more effective therapeutic interventions.

Additionally, exploring innovative drug delivery systems, such as nanoparticles or liposomes, could significantly improve the targeting and bioavailability of these compounds in inflamed tissues, enhancing their efficacy. Investigating the pharmacodynamics and potential synergies of combining SPMs with existing anti-inflammatory therapies may yield new treatment protocols that address chronic inflammatory diseases more comprehensively.

Incorporating genomic and proteomic approaches to identify individual genetic variations related to inflammation could pave the way for personalized medicine. Understanding how these variations affect responsiveness to treatment with SPMs will allow for tailored therapeutic strategies that improve outcomes for patients.

By addressing existing limitations in research methodologies and exploring these future directions, we can significantly advance our understanding of inflammation resolution. This endeavor can lead to

innovative treatment strategies that harness the body's intrinsic resolution mechanisms, ultimately improving therapeutic outcomes and the quality of life for patients suffering from chronic inflammatory diseases.

Conclusion

In conclusion, inflammation is a complex biological response pivotal in immune defense and tissue repair, yet when unresolved, it can contribute to the pathogenesis of numerous chronic diseases. This review highlights the vital role of both acute and chronic inflammatory processes in health and disease, emphasizing the importance of timely and effective resolution mechanisms. Specialized pro-resolving mediators (SPMs) and other therapeutic agents demonstrate significant potential to promote inflammation resolution, offering promising strategies for the management of chronic inflammatory conditions such as rheumatoid arthritis, cardiovascular diseases, and neurodegenerative disorders.

Emerging treatment approaches, including the application of tissue engineering, cellular therapies, and the modulation of SPMs, suggest a shift towards more targeted and effective interventions that address not only the symptoms but also the underlying inflammatory processes. By harnessing the body's intrinsic resolution mechanisms, we can improve therapeutic outcomes and enhance the quality of life for patients suffering from chronic inflammatory diseases.

Despite the substantial progress made in understanding the mechanisms underlying inflammation and resolution, there remain significant gaps in the current literature that warrant attention. For instance, while some SPMs have been studied extensively, their pharmacokinetics, stability, and bioavailability are still not thoroughly explored, with many mediators prone to rapid degradation. Therefore, it is essential to conduct longitudinal studies that assess the temporal patterns of SPM production in human cohorts, which could provide valuable insights into the dynamics of the inflammatory response and help identify biomarkers for therapeutic effectiveness. Moreover, future research should also prioritize the development of stable analogues of SPMs that can resist metabolic degradation while retaining bioactivity, as well as innovative drug delivery systems, such as nanoparticles or vesicles, to enhance the targeting of inflamed tissues. Additionally, using genomic and proteomic approaches to identify genetic polymorphisms and protein interactions related to inflammation could reveal new therapeutic targets, allowing for personalized medicine approaches.

Exploring combination therapies that integrate SPMs with existing anti-inflammatory treatments may enhance their efficacy and contribute to the development of more effective protocols for chronic inflammatory diseases. By addressing these gaps and focusing on these research directions, we can significantly advance our understanding of inflammation resolution and promote innovative therapeutic strategies aimed at restoring homeostasis and preventing chronic disease progression. Understanding the intricate interplay between

inflammation and its resolution will be crucial in driving these advancements forward.

Author Contributions: writing—original draft preparation, A.V.P.; writing—review and editing, N.A.O., A.L.R., A.E.K., I.G.L., N.V.E., V.N.S., A.N.O

Funding: This research was funded by Russian Science Foundation, grant number 24-15-00217

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest.

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