ANNUAL REVIEWS

Annual Review of Pharmacology and Toxicology

Resolution Pharmacology: Focus on Pro-Resolving Annexin A1 and Lipid Mediators for Therapeutic Innovation in Inflammation

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Annu. Rev. Pharmacol. Toxicol. 2023. 63:449–69

First published as a Review in Advance on September 23, 2022

The *Annual Review of Pharmacology and Toxicology* is online at pharmtox.annualreviews.org

https://doi.org/10.1146/annurev-pharmtox-051821-042743

Keywords

therapeutic innovation, resolution of inflammation, specialized pro-resolving lipid mediators, annexin A1 peptides

Abstract

Chronic diseases that affect our society are made more complex by comorbidities and are poorly managed by the current pharmacology. While all present inflammatory etiopathogeneses, there is an unmet need for better clinical management of these diseases and their multiple symptoms. We discuss here an innovative approach based on the biology of the resolution of inflammation. Studying endogenous pro-resolving peptide and lipid mediators, how they are formed, and which target they interact with, can offer innovative options through augmenting the expression or function of pro-resolving pathways or mimicking their actions with novel targeted molecules. In all cases, resolution offers innovation for the treatment of the primary cause of a given disease and/or for the management of its comorbidities, ultimately improving patient quality of life. By implementing resolution pharmacology, we harness the whole physiology of inflammation, with the potential to bring a marked change in the management of inflammatory conditions.

INTRODUCTION

Inflammation and Therapies

The quest to limit the inflammation associated with disease propagation and chronicity has been at the center of medicinal studies for centuries (1). From the beginning, it was appreciated that inflammation is in essence a protective process. However, in disease, this life-saving process, for reasons that even today are incompletely understood, goes awry, leading to organ and tissue damage and, in extreme circumstances, even death. Efforts to develop therapeutics to treat patients that present with exuberant inflammation have primarily focused on inhibiting factors or processes that contribute to the propagation of inflammation. This approach is predicated on the paradigm that such exuberant inflammation results from the unabated production of proinflammatory factors and/or the activation of pathways that propagate inflammation. These therapeutics have been successful in the treatment of many conditions and have significantly improved the quality of life of many people around the globe. Unfortunately, however, their effectiveness is not universal. Indeed, many of the therapies in current use for the clinical management of chronic diseases present with a variety of side effects that range from mild to severe and potentially even life-threatening. Furthermore, they are sufficiently effective only in a proportion of patients. As a consequence, patients are exposed to adverse effects of these drugs. Furthermore, in patients where they are ineffective, this approach results in disease progression, with a reduction in patient quality of life. These limitations, and many others associated with current therapeutics, have spurred the search for novel treatments (2).

The Resolution of Inflammation

Studies conducted by many laboratories over the last three decades have challenged the paradigm that inflammatory disorders arise solely from the exuberant production of activating molecules and/or the engagement of pathways that propagate inflammation. Indeed, it is now increasingly recognized that disruptions in the production and activities of factors that govern the resolution phase of acute inflammation, to terminate it in a timely fashion, are a central component in the onset and/or progression of many conditions characterized by overzealous inflammation (3–9).

Systematic studies evaluating the cellular and molecular mechanisms that are engaged during acute self-limited inflammation demonstrated that the formation of autacoids in experimental inflammatory exudates coincided with the turning off of inflammation and the initiation of reparative mechanisms (10). Soon it emerged that, in line with the multitude of proinflammatory mediators (lipid mediators, proteins, peptides, and autacoids), the resolution phase of inflammation was also governed by distinct pro-resolving mediators, including proteins such as annexin A1 (AnxA1), lipid mediators such as lipoxin A_4 (LXA_4), and autacoids such as nitric oxide and adenosine (8, 11–14). The list of pro-resolving mediators has grown over time, expanding nearly as much as the large group of proinflammatory mediators (see, e.g., 8, 11–14). This offers several opportunities for innovative pharmacology and guidance in the development of novel drugs.

Importantly, studies evaluating the mechanism of action of these endogenous protective molecules in experimental disease settings demonstrated that, in contrast to anti-inflammatory drugs, these molecules did not completely block the formation of inflammatory mediators by immune and stromal cells and the trafficking of leukocytes to the site of inflammation. Pro-resolving mediators and their mimetics—such as stable analogs or peptides—modulated the inflammatory reaction and impacted, for instance, on the production of cytokines to an intermediate degree (e.g., reductions of ~30–40%), never abrogating the intensity of the inflammatory phase. Similarly, leukocyte trafficking was modulated, and inhibition of neutrophil migration was coupled with

the nonphlogistic recruitment of monocytes (15, 16). These monocytes mature to macrophages and clear cellular debris and bacteria from the inflamed tissue site to promote resolution. More recently, studies have shown that pro-resolving mediators can afford long-lasting effects by reprogramming immune cells toward a host-protective phenotype that confers both potent antimicrobial and tissue-protective activities (17, 18).

Prototypes of Pro-Resolving Peptide and Lipid Mediators

The appreciation that specific classes of lipid molecules terminated inflammation and restored organ function led to naming the novel mediators specialized pro-resolving mediators (SPMs) (8, 19). The observation that SPMs limit inflammation and enhance the ability of phagocytes and stromal cells to clear pathogens is particularly intriguing.

Formation of essential fatty acid–derived SPMs is tightly regulated in the cells of origin. Evidence to date highlights a central role for lipoxygenase and cyclooxygenase enzymes in the initiation of SPM biosynthetic pathways. Intriguingly, these enzymes also catalyze the formation of classic eicosanoids such as the prostaglandins and leukotrienes, thus suggesting that the cell, during the resolution phase of inflammation, can switch its activity from producing inflammation-initiating mediators to SPMs (10, 17, 20–23). Furthermore, mounting evidence indicates that even the formation of specific SPMs is differentially regulated, with levels of distinct mediators increasing at different intervals during acute self-resolving inflammation. For example, in murine peritonitis, the level of resolvin (Rv)D2 peaks before that of RvD3 (24). In human experimental inflammation, lipoxin B_4 (LXB_4) concentrations reach a maximum early in the course of the inflammatory response, and Maresin (MaR1) and LXA_4 levels peak in the resolution phase (25). These observations suggest that enzyme activity is also regulated to favor the formation of one SPM over other products of the same enzyme. While the mechanisms that regulate this switch in enzyme activity are poorly described at present, recent studies suggest that post-translational mechanisms may play a key role in this process. Fredman et al. (26) demonstrated that phosphorylation of ALOX5 leads to a switch in the product profile of this enzyme from producing LXA_4 to producing LTB_4. This switch is linked with the translocation of the enzyme from the cytosol to the nuclear envelope. Intriguingly, this phosphorylation event was reversible upon application of RvD1, restoring the ability of macrophages to produce LXA_4, suggesting that one SPM may also activate feed-forward loops and upregulate the formation of other SPMs (26). Recent studies have suggested that this translocation mechanism may also contribute to a switch in activity for ALOX15 (21), although the mechanism(s) contributing to this biology has not yet been identified.

Examples of pro-resolving proteins and peptides include the glucocorticoid-inducible protein AnxA1, galectin-1, the melanocortin peptide systems, and angiotensin 1–7 (Ang1–7). AnxA1 is a 37-kDa protein and is one of the targets that are upregulated, rather than suppressed, by glucocorticoids. As such, AnxA1 pairs with glucocorticoid-induced leucine zipper (GILZ) and phosphatases, to name a few, as downstream effectors of the pharmacology of glucocorticoids, since they all limit inflammatory cell activation and the duration of the inflammatory reaction (27). Of note, low-dose steroids are sufficient to upregulate AnxA1, which stands in contrast to the large doses required and used for immunosuppression (28). Human and rodent myeloid cells are abundant in their expression of AnxA1; however, this protein is also expressed by epithelial and endothelial cells as well as, to a lower extent, by T lymphocytes. On these cellular sources, AnxA1 levels are increased not only by low-to-moderate concentrations of glucocorticoids but also by cytokines such as IL-6 (29). Moreover, expression of AnxA1 is modulated by the inflammatory process itself, and, for instance, cell migration increases its expression through de novo synthesis, as seen in experimental peritonitis (30). Therefore, regulatory circuits exist to modulate AnxA1

expression during the course of an inflammatory reaction through soluble factors as well as mechanical inputs. Such tight and multipronged control of AnxA1 expression and localization supports the concept that this mediator is of importance.

Over the last two decades, the nonredundant role of AnxA1 in several settings of experimental inflammatory diseases has been demonstrated through the use of transgenic mice. There are several studies conducted with AnxA1$^{-/-}$ animals that reported aberrant, protracted inflammation in the absence of the regulatory tone exerted by endogenous AnxA1. Initially reported in the context of acute inflammation, the first evidence that demonstrated lack of resolution in these animals came from Asma Nusrat's lab (31): Induction of dextran sulfate sodium colitis in AnxA1$^{-/-}$ mice did not have much of an impact on the onset-to-peak phase of the gut inflammatory response; however, while the experimental disease lasted 7 days in wild-type animals, it did not resolve in the absence of AnxA1. Since then, exacerbation of inflammation, a higher degree of cell recruitment, and higher production of inflammatory mediators have been reported by a large number of studies with AnxA1$^{-/-}$ mice in different settings, spanning experimental arthritis (32) to sepsis (33), asthma to allergic responses (34), and stroke (35) to infarct (36). Two further comments are due.

Initial studies also assessed the intermediatory role of endogenous AnxA1 in the anti-inflammatory actions of glucocorticoids, which in many cases lost efficacy when administered to AnxA1$^{-/-}$ mice, especially if administered at anti-inflammatory and not immunosuppressive doses. Further, the profound phenotypes displayed by AnxA1$^{-/-}$ mice in many models of disease strongly indicate that this mediator has fundamental modulatory properties. In fact, as reviewed recently, virtually all mechanisms of the resolution of inflammation are promoted by AnxA1: (*a*) inhibition of granulocyte recruitment (37), (*b*) nonphlogistic migration of monocytes (38), (*c*) activation of neutrophil apoptosis (39, 40), (*d*) promotion of macrophage phagocytosis (41) and efferocytosis (42), (*e*) regulation of macrophage and dendritic cells switching to a pro-resolving phenotype (38, 43), and (*e*) instruction of stromal cells to signal the return to homeostasis (or allostasis when referring to chronic diseases). Such a broad pro-resolving portfolio of activities by AnxA1 is also due to the downstream induction of other pro-resolving mediators such as IL-10 (44, 45) and GILZ (46). Similarly, the SPM LXA_4 can engage endogenous AnxA1 in human neutrophils (47) as well as in complex settings of metabolic inflammation in the mouse (48). Such interconnections have been discussed recently (6) and represent an added value for targeting the resolution of inflammation to activate positive circuits at the molecular and cellular levels, maximizing, in our view, the potential for the pharmacological efficacy of novel therapeutics that are developed based on this science.

In summary, identification of pro-resolving molecules and elucidation of their pharmacology via reprogramming target cell phenotype and function have led to a paradigm shift in our understanding of endogenous mechanisms that contribute to diseases associated with unabated inflammation. This in turn has opened exciting novel opportunities to harness these endogenous mechanisms by developing novel agonists and mimetics that carry the protective activities of these molecules. The present review discusses the evidence underpinning the exciting opportunities that resolution pharmacology presents, together with the future challenges that would need to be overcome to enable the exploitation of this novel therapeutic paradigm (**Figure 1**).

SPECIALIZED PRO-RESOLVING MEDIATORS

Mounting evidence supports the protective roles of essential fatty acid–derived SPMs in multiple experimental systems ranging from neuronal inflammation to vascular disease and adipose inflammation. For example, in the central nervous system, MaR1 was recently observed to reduce inflammation in the spinal cord of mice during experimental autoimmune encephalomyelitis, a model

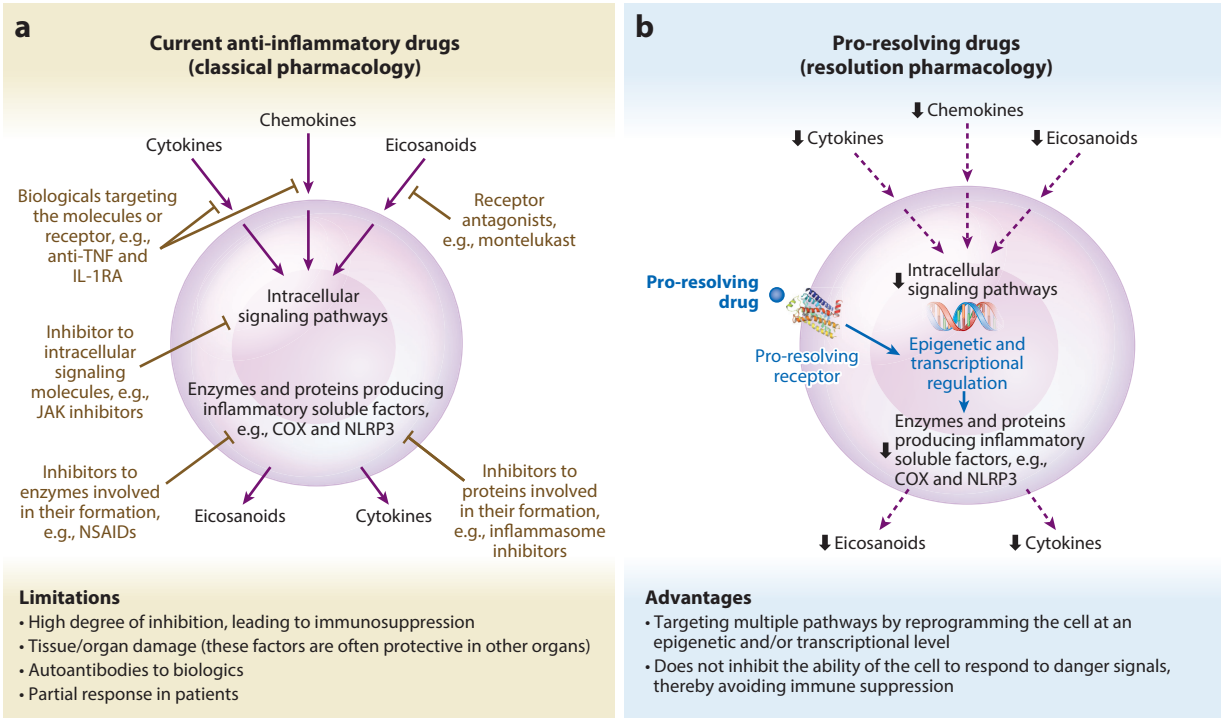

Figure 1

Resolution pharmacology offers a novel therapeutic approach compared to classical pharmacology. (*a*) The schematic shows the current approach to anti-inflammatory therapies—what is referred to as classical pharmacology. These therapies have been developed through blockade of the synthesis of specific proinflammatory mediators or through antagonizing their receptors that convey proinflammatory signals and promote proinflammatory mechanisms. Limitations associated with classical anti-inflammatory therapies include the risk of immunosuppression (due to the inability of physiological inflammation to take place), damage to specific organs (which would be protected by the mediator targeted by the therapy, e.g., NSAIDs on gastric mucosa), the development of autoantibodies (with reduced efficacy over time), and the fact that there is variability in the patient response. (*b*) The schematic shows the novel approach, which harnesses the biology of the resolution of inflammation. This approach requires activation of specific pro-resolving pathways or pro-resolving receptors. This positive and agonistic approach will lead to long-lasting effects with a switch in the phenotype of target cells through epigenetic and transcriptional regulation. The end point will be moderate reduction in several proinflammatory mechanisms and mediators, while avoiding the risk of immunosuppression. Development and validation of pro-resolving drugs can establish a distinct branch of pharmacology we refer to as resolution pharmacology. Abbreviations: COX, cyclooxygenase; NLRP3, NLR family pyrin domain containing 3; NSAID, nonsteroidal anti-inflammatory drug.

of multiple sclerosis. These changes were also linked with an improvement in clinical signs of the disease, including enhanced neurological outcomes and protection from demyelination (49). In separate studies, $PD1_{n\text{-}3\ DPA}$ was found to be protective in experimental epileptogenesis, whereby administration of this mediator reduced the expression of inflammatory cytokines, including tumor necrosis factor (TNF)-α and IL-6, in the hippocampus of mice during experimental epileptogenesis. These changes were linked with a marked improvement in mouse weight recovery, rescue of cognitive deficit, and a marked reduction in spontaneous seizures (50). The ability of $PD1_{n\text{-}3\ DPA}$ to reduce spontaneous seizures was recently linked with its ability to increase the inhibitory drive on the perisomatic region of pyramidal neurons. These studies demonstrated that $PD1_{n\text{-}3\ DPA}$ acts directly on inhibitory transmission, most likely at the presynaptic site of inhibitory synapses (51). In cardiovascular diseases, RvE1 reduced experimental pulmonary artery hypertension via activation of its cognate receptor ChemR23 and modulation of wingless-type MMTV (or

Wnt) integration site family member 7a/β-catenin signaling in pulmonary artery smooth muscle cells (52). RvD1 is thought to limit human atherosclerotic carotids vulnerable to rupture given that this mediator was reduced in human vulnerable plaques compared to stable plaques. Furthermore, administration of this mediator to atherosclerotic mice promotes plaque stability, including decreased lesional oxidative stress and necrosis, improved lesional efferocytosis, and a thicker fibrous cap (53). Recent studies also demonstrated that RvD1 promotes the clearance of necroptotic cells, which are key contributors to the formation of vulnerable plaques, in experimental settings by reprogramming macrophage metabolism (54).

In addition to regulating the biology of terminally differentiated immune cells, recent studies have uncovered a role for these mediators in directing the differentiation of immune cells to confer protective functions, whereby the n-3 DPA–derived protectins are involved in the differentiation of both human and mouse monocytes to macrophages regulating the phenotype of the differentiated macrophage as well as its ability to clear apoptotic cells in vitro and in vivo (55). RvD3 and $RvD5_{n\text{-}3\ DPA}$ confer regulatory functions to human and mouse $CD4^+$ T cells by promoting or supporting their differentiation to regulatory T cells (56). Readers are directed to the following articles for further discussions on the biological activities of SPMs (57–62).

ANNEXIN A1 AND ITS PEPTIDES

Based on the control exerted by endogenous AnxA1, as assessed in several models of inflammation and disease, one predictable way to harness this knowledge has been to identity AnxA1 mimetics. The starting point here was the notion that the N-terminal region of AnxA1 is unique, with little similarity to the other annexins (63). Since AnxA1, and not the others annexins, was involved with inflammation and glucocorticoid pharmacology, fragments of its N-terminal region were tested. The first peptide to be studied was peptide Ac2-26, which reproduced the effects of the whole protein on neutrophil trafficking (37, 64). This tool has been studied extensively and used, together with *AnxA1*$^{-/-}$ mice, to provide proof-of-concept for the pathopharmacology of this system in experimental models of disease. **Table 1** presents a nonexhaustive list of in vivo models where AnxA1 deficiency or administration of peptide Ac2-26 produced pharmacological efficacy. From a pharmacological perspective, the most important contribution of peptide Ac2-26 to this field has been its use in identifying formyl-peptide receptors (FPRs) as its main molecular targets. From the laboratory of Volker Gerke (65) emerged the original observation that FPR1 was activated by peptide Ac2-26 to inhibit neutrophil activation and chemotaxis, which soon extended to FPR2/ALX and FPR3, the receptor types that respond to peptide Ac2-26 (66, 67). Intriguingly, full-length AnxA1 displayed a higher affinity for FPR2/ALX, whereas peptide Ac2-26 was equipotent to all three receptors of the family, with an apparent EC_{50} around 1 μM (68). In contrast, AnxA1 bound to FPR2/ALX with an EC_{50} of approximately 10 nM. Even more intriguing was the observation that AnxA1 shares this receptor target with LXA_4 (69), so that the receptor is often referred to as FPR2/ALX; this is another example of resolution networks. We can summarize a large body of work here by stating that, by and large, the bio-actions of AnxA1 and peptide Ac2-26 on myeloid cells are mediated through FPR2/ALX, whereas peptide Ac2-26 engagement with nonmyeloid cells such as epithelial cells and fibroblasts is often mediated by FPR1, as shown in experimental models (70, 71). The reason behind this peculiar difference between the whole protein and the short peptide remains unsolved and may be linked to the engagement of distinct receptor domains (72) and/or the higher flexibility of the short peptide. Irrespective of this, the discovery of Gerke and colleagues was fundamental to explaining the biology of AnxA1 and its peptide mimetics and offered a novel platform on which to build resolution pharmacology, that is, by developing agonists of FPR2/ALX.

Table 1 Nonexhaustive list of diseases treated by delivery of peptide acetyl (Ac)2-26 and endogenous annexin-A1

Disease area	Model	Details	Pharmacological effect(s)	Reference
Uveitis	Endotoxin-induced uveitis	Ac2-26 200 μg	Reduction of leukocytes, inflammatory mediators, and COX-2 expression	122
Allergic conjunctivitis	Ovalbumin sensitization and challenge	Ac2-26 10 mg/kg	Reduced chemosis, conjunctival hyperemia, lid edema, and tearing	123
Arthritis	Carrageenan-induced acute arthritis	Ac2-26 1 mg/kg	Reduced synovial lavage leukocyte count	124
Diabetic nephropathy	High-fat-fed streptozotocin-induced diabetic mice	Ac2-26 (*AnxA1*$^{-/-}$ mice)	Reduced lipotoxicity (lipid droplet size) and renal injury	125
	db/db mice and diabetic *Anxa1* knockout mice	Ac2-26 (*AnxA1*$^{-/-}$ mice)	Reduced renal injury, tubule-interstitial lesions, and fibrosis	126
Stroke	Endotoxin-induced microcerebrovascular thrombosis and sickle transgenic mice	Ac2-26 100 μg	Reduced thrombosis and platelet activation	127
	Middle cerebral artery occlusion and reperfusion	Ac2-26 100 μg (*AnxA1*$^{-/-}$ mice)	Reduced brain necrosis and neurological symptoms	35
Atherosclerosis	*Apoe*$^{-/-}$ mice on a high-fat diet	Ac2-26 50 μg (*AnxA1*$^{-/-}$ mice)	Reduced atherogenesis and arterial myeloid recruitment	128
	Ldlr$^{-/-}$ mice on a high-fat diet	Ac2-26 nanoparticles	Higher collagen layer, reduced oxidative stress, and plaque necrosis	129
Transplantation	Heterologous skin transplantation	Topical Ac2-26 (*AnxA1*$^{-/-}$ mice)	Improved the take of the implant, angiogenesis	130
Myocardial infarct	Coronary artery occlusion/ reperfusion	Ac2-26 1 mg/kg	Reduced myocardial necrosis	131
Pleurisy	Endotoxin-induced pleural inflammation	Ac2-26 100 μg	Augmented neutrophil apoptosis	40
Silicosis	Silica particle–induced lung injury	Ac2-26 200 μg intranasal (*AnxA1*$^{-/-}$ mice)	Reduced collagen deposition and granuloma formation	71
Pulmonary allergy	House dust mite sensitization and challenge	Ac2-26 200 μg intranasal (*AnxA1*$^{-/-}$ mice)	Reduced lung inflammation in house dust mite allergic reactions	34
Pneumonia	*Streptococcus pneumoniae*	Ac2-26 (*AnxA1*$^{-/-}$ mice)	Maintained lung barrier integrity and reduced neutrophil activation	132
Meningitis	*Streptococcus pneumoniae*–induced meningitis	Ac-26 1 mg/kg intravenous	Reduced neutrophil counts and glial activation	133
Gastric ulcers	Indomethacin-induced gastric lesions	Ac2-26 100 μg/kg (*AnxA1*$^{-/-}$ mice)	Enhanced gastric ulcer healing	134

(*Continued*)

Table 1 (*Continued*)

Disease area	Model	Details	Pharmacological effect(s)	Reference
Intestinal anastomosis	Dextran sulphate sodium perioperative colitis and surgery	Ac2-26 nanoparticles (*AnxA1*$^{-/-}$ mice)	Improved postoperative recovery and anastomotic healing	135
Renal protection	Cyclosporine-induced renal injury	Ac2-26 1 mg/kg	Reduced hemodynamic changes, tubular injury, and macrophage infiltration	136
Bladder obstruction	Bladder outlet obstruction–induced inflammation	Ac2-26 1 mg/kg	Reduced bladder weight	137

"(*AnxA1*$^{-/-}$ mice)" indicates a study where mice that had been nullified for the pro-resolving protein were used, eliciting opposite results compared to those of peptide acetyl (Ac)2-26.

RESOLUTION PHARMACOLOGY

We propose that new therapeutics will be developed this decade by exploiting the science of resolution. To this end, resolution pharmacology can be achieved in different ways, as discussed below, noting that these elements are mainly representative and do not provide an exhaustive list of therapies and approaches under development or, in our opinion, suitable for development.

Increasing Endogenous Resolution Pathways

Since several inflammatory conditions are linked with a disruption in SPM formation, investigations have evaluated potential avenues for boosting endogenous formation. Given that omega-3 fatty acids are substrates for the production of SPMs, and supplementation of experimental animals and humans is linked with beneficial effects in certain inflammatory settings, recent studies have evaluated the potential that some of the protective activities of these supplements could be mediated via the formation of SPMs (73, 74). Indeed, in healthy volunteers we observed that a single-bolus administration of an omega-3 supplement led to a rapid, dose-dependent, and transient upregulation of human peripheral blood SPM levels (75). This increase in SPMs correlated with the regulation of diurnal changes in peripheral blood phagocyte responses (75). Similar findings were also made in patients with peripheral artery diseases, where supplementation led to an increase in peripheral blood SPM concentrations, which was linked with a shift in peripheral blood monocyte and monocyte-derived macrophage phenotype and function (76).

Intriguingly, the ability of omega-3 supplements to upregulate SPMs is not a universal function and confers protective actions on immune cells. In recent studies, we observed that different commercially available supplements were converted to SPMs to different extents and that this differential conversion to SPMs reflected the ability of such substrates to regulate human monocyte-derived macrophage phenotype and function (77). These observations suggest that the form of the essential fatty acid (e.g., triglyceride versus phospholipid, and so forth), as well as other potential components found with the substrate, has a marked impact on both the conversion of the fatty acids to SPMs and the ability of such substrates to confer protection in inflammation.

Mounting evidence indicates that commonly utilized drugs also regulate SPM formation. Aspirin was the first drug found to upregulate the formation of these autacoids, whereby the acylation of cyclooxygenase type 2 (COX-2) by aspirin switches its catalytic activity from the production of prostaglandins to that of epimeric forms of resolvins, protectins, and lipoxins, termed aspirin-triggered SPMs (23, 78). These molecules display enhanced resistance to metabolic inactivation while retaining the same affinity to the cognate receptors for the lipoxygenase-derived SPMs. We

recently reported that these molecules are also involved in mediating the immune-directed protective activities of aspirin in inflammation-associated colorectal cancer in mice by regulating the phenotype and function of macrophages and $CD8^+$ T cells, among others (79).

Statins also upregulate SPM formation. The mechanisms engaged by statins to upregulate the production of these autacoids are tissue dependent; for example, in heart tissues, atorvastatin was observed to upregulate 15-epi-LXA_4 levels via the regulation of COX-2 and ALOX5 expression (80) as well as the phosphorylation status of ALOX5 (81). Whereas in the circulation, atorvastatin regulates the activity of COX-2 via NOS-mediated S-nitrosylation of the enzyme, which leads to an increase in the conversion of n-3 DPA to 13*R*-HDPA. This intermediate is then transferred to the neutrophil, which converts it via lipoxygenase-dependent reactions to 13-series resolvins (RvTs) (20). RvTs are linked with the anti-inflammatory and host-protective actions of atorvastatin in both bacterial infections and inflammatory arthritis, given that inhibiting their formation reverses the protective actions of this statin in these settings. Pravastatin was also observed to upregulate RvT formation, likely via an analogous mechanism to that observed for atorvastatin (82). Furthermore, inhibiting the formation of these autacoids also reversed the anti-inflammatory and joint protective actions of pravastatin in inflammatory arthritis (82).

The glucocorticoid dexamethasone was also recently observed to upregulate SPM formation. In experimental allergic inflammation, dexamethasone upregulated the concentrations of PD1 as well as the RvD precursor 17-HDHA (83). In humans, we also observed that dexamethasone treatment upregulated concentrations of the eicosapentaenoic acid–derived RvE2 and the n-3 DPA–derived $MaR2_{n\text{-}3\ DPA}$ in plasma of patients with COVID-19 (84). Intriguingly, there is evidence that glucocorticoids can also increase expression of FPR2/ALX (85, 86), which is the receptor for AnxA1, RvD1 and LXB_4. In a separate study evaluating the antiemetic activities of dexamethasone after surgery, SPM levels were not changed by dexamethasone administration post-surgery (87). This outcome was also linked with the inability of this drug to significantly reduce pain at the dose administered. This observation suggests that the activity of dexamethasone on upregulating SPM pathways may be context dependent and might reflect its ability to exert its therapeutic activities. Intriguingly, in this study, plasma RvE2 was observed to predict a lower perceived pain score postanesthesia (87).

Mimetics

A direct approach to developing resolution pharmacology is to start from the endogenous mediator of interest and design analogs (for small molecules) or fragments (for protein). These approaches have long been used to design drugs, with classical examples including histamine analogs for peptic ulcer and angiotensin-converting-enzyme type 2 inhibitors such as captopril. Several approaches are used in the quest to harness the protective biological activities of SPMs.

SPM mimetics. One such approach is to develop molecules that are less susceptible to metabolic inactivation, thereby extending their half-life, such as, for example, 19-(p-fluorophenoxy)-RvE1, which limits dehydrogenation at carbon-18 while retaining the potent anti-inflammatory, proresolving, and antinociceptive activities of RvE1 (88, 89). Another consideration is the stabilization of the pharmacophore of the molecule. In this quest, benzo analogs have been developed that insert a rigid structure around the proposed pharmacophore of lipoxins and resolvins. Among these analogs are the quinoxaline-containing synthetic-LXA_4 mimetics (90) and methyl ester-benzo-lipoxin A_4 ($BLXA_4$). The latter was recently reported to protect against gingival inflammation and activate the endogenous production of SPMs present in peripheral blood in patients with periodontal disease (91). **Table 2** presents a nonexhaustive list of stable SPM analogs and their biological activities in relation to the regulation of inflammation.

Table 2 Biological actions of select SPM analogs

Analog	Biological action	Dose	Reference(s)
Lipoxin analogs			
15(*R/S*)-methyl-LXA_4	Inhibits changes in vascular permeability and reduces infiltration of neutrophils	3–130 nM	138
	Stimulates phagocytosis apoptotic neutrophils by macrophages in vivo	2.5–10 μg/kg	139
16-phenoxy-LXA_4	Limits neutrophil infiltration and neutrophil migration toward LTB_4	240 nM	140
15-epi,16-phenoxy-LXA_4	Limits neutrophil migration toward LTB_4	240 nM	140
16-parafluoro-phenoxy-LXA_4	Inhibits neutrophil infiltration	26 nM	138
15-epi,16-para-fluorophenoxy-LXA_4-methyl ester	Reduces neutrophil infiltration following kidney ischemia reperfusion	15 μg per mouse	141
	Protects from airway hyperresponsiveness to methacholine Limits lymphocyte and eosinophil infiltration Protects against vascular injury	10 μg per mouse	142
	Protects from skin inflammation Limits neutrophil chemotaxis	100–1,000 μg/cm^2 0.1 nM–1 μM	143
	Protects from colon inflammation	10 μg/mL (per os)	144
	Inhibits VEGF-induced endothelial cell migration and proliferation	1–100 nM	145
5(*S*)-methyl-LXB_4	Inhibits PMN infiltration	26 nM	138
o-[9,12]-benzo-ω6-epi-lipoxin A_4	Reduces leukocyte infiltration to the temporomandibular joint following CFA administration Reduces neutrophil recruitment in response to zymosan Promotes regeneration of hard and soft tissues irreversibly lost to periodontitis in the Hanford miniature pig	10 ng per mouse 100 ng per mouse 1 μg per site	146 147
D-series resolvin analogs			
7(*R/S*)-RvD1-methyl ester	Reduces expression of MHC II, CD40, and IL-12 following lipopolysaccharide stimulation in dendritic cells Reduces allosensitization during corneal transplant and enhances graft survival and angiogenesis	100 μg per mouse	148
Benzo-diacetylenic-17*R*-RvD1-methyl ester	Accelerates the resolution of *Escherichia coli* peritonitis Reduces second organ injury associated with ischemia reperfusion	100 ng per mouse 1 μg per mouse	149
E-series resolvin analogs			
RX-10045	Decreases corneal opacity after opacity-generating high-correction photorefractive keratectomy	0.01% solution	150
	Improves human dry eye disease symptoms, including dryness, stinging, burning, grittiness, and ocular discomfort	0.05–0.1% nanomicellar solution	151
α-cyclopropane resolvin E_2	Limits exudate leukocyte recruitment in response to *Propionibacterium acnes* infection	300 fg–3 ng per mouse	152
β-cyclopropane resolvin E_2			

Abbreviations: CFA, Complete Freund's Adjuvant; LXA_4, lipoxin A_4; LXB_4, lipoxin B_4; MHC, major histocompatibility complex; SPM, specialized pro-resolving mediator; VEGF, vascular endothelial growth factor.

Peptidomimetics. We have described above the focus on the AnxA1-derived peptide Ac2-26 and the reasoning behind it. Similar activities have been directed to other peptides from this protein, including shorter fragments like Ac2-12 (92). At least two other approaches have resulted from the study of AnxA1. One of these approaches similarly focuses on the N-terminal region of the protein with the aim of designing new molecules with longer-lasting effects by modifying sites of cleavage by proteases (93), including neutrophil-derived proteases that abound on inflammatory exudates (94, 95). As such, a 50-amino-acid peptide from the N-terminal region, termed CR-AnxA1$_{2\text{-}50}$ or cleavage-resistant peptide Ac2-50, was shown to possess selectivity for FPR2/ALX, potent anti-inflammatory actions, and thus protection in experimental settings against acute myocardial infarct (96). These effects were mimicked by 48-amino-acid-long sequences, or CR-AnxA1$_{2\text{-}48}$ (97). The protection against mouse heart injury by CR-AnxA1$_{2\text{-}50}$ was also observed in more extreme settings of systemic sepsis with preservation of heart systolic function (98). One of these cleavage-resistant peptides is now being developed by ResoTher Pharma, with compound RTP-026 in a Phase I trial (99) with the aim of future trials in settings of myocardial infarct. Also in the N-terminal region, the tripeptide Ac-QAW protects against cognitive deficiencies and neuroinflammation in experimental settings of postoperative medicine (98, 100).

A second approach, which is based on AnxA1's structure, yielded the antiflammins, peptides initially identified on sequence homology between human AnxA1 and uteroglobin (101). Effective in some disease settings, including experimental uveitis (101) and pulmonary fibrosis (102), antiflammins seem to incite a pharmacology that resonates with that of the whole-length protein as well as peptide Ac2-26 (see **Table 1**). It is unclear whether drug discovery programs have been started based on the experimental data produced with these nonapeptides. It is intriguing that these short sequences also seem to interact with FPR2/ALX (103).

The same strategy used for AnxA1 has been applied to several other proteins and long peptides. In the context of resolution, the work around melanocortin peptides, which mimic the actions of alpha-melanocyte-stimulating hormone and adrenocorticotropin, and angiotensin peptides is relevant. AP214 was designed based on alpha-melanocyte-stimulating hormone and shown to be endowed with pro-resolving properties that include promotion of efferocytosis and acceleration of the resolution phase of experimental peritonitis (104). These pharmacological properties underpinned the efficacy of this synthetic peptide in large animal studies focusing on reperfusion injury after heart surgery (105) and on heart function in systemic sepsis (106). Palatin Technologies developed another class of melanocortin receptor agonists that also control inflammation and offer protection in experimental models of disease, including uveitis (107). The availability of the pan-agonist PL8331 and the selective melanocortin type 1 receptor agonist PL8177 provides valuable pharmacological tools to establish the involvement of distinct receptor targets. Pharmacokinetic studies with PL8177 indicate a favorable half-life in humans after subcutaneous injection, with it being detectable in plasma even after 48 h for the highest dose tested (108). Altogether, these analyses support the further development of PL8177 for pathologies with substantial inflammatory components, one of which could be inflammatory bowel disease (109).

New Chemical Entities

Once the target, often a receptor, for the pro-resolving mediator is identified, a third approach to resolution pharmacology is to then perform high-throughput screening and kick-start drug discovery programs. Clearly, the aim here is to identify and develop agonists at the receptor. In line with the discussion above, we focus here on a very small number of relevant examples. In 2015, we reviewed the state-of-the-art on FPR2/ALX small-molecule agonists under development (110). Since then, compound ACT-389949 was tested by Actelion in Phase 1 studies in healthy volunteers. The published results seem to indicate a relatively rapid tachyphylaxis to the marker being

measured and receptor internalization (111). It is unclear whether this was a compound-specific or class-specific effect. FPR2/ALX internalization has also been reported with some peptide agonists (112), though to a much lesser degree than with the AnxA1 peptide Ac2-26 and LXA_4 (113). Moreover, this study provides evidence for a functional association between FPR2/ALX internalization and phagocytosis, a property that is welcome in the portfolio of pharmacological activities of FPR2/ALX agonists. It remains to be seen whether all FPR2/ALX small-molecule agonists would cause rapid tachyphylaxis or whether this is a feature of ACT-389949 alone. Similarly, whether daily dosage is required and the length of exposure time needed for an FPR2/ALX agonist to produce the desired effect have not yet been evaluated. On a more positive note, Stalder et al. (111) reported that FPR2/ALX agonism with ACT-389949 was safe and well tolerated in all 64 healthy male subjects.

Recently, Bristol Meyers Squibb has also developed a small-molecule-selective FPR2/ALX agonist termed BMS-986235 (110). Recent work has described how the compound was developed and reported the pharmacodynamic properties in settings of experimental heart failure, associating efficacy with the modulation of cardiac macrophage polarization (114). This feature is reminiscent of the study published by Soehnlein and colleagues (36) that discussed AnxA1 and characterized an angiogenic macrophage phenotype in the heart regulated by endogenous AnxA1. BMS-986235 is currently in a Phase I trial, being tested in 128 healthy volunteers of both sexes, in single ascending dose and multiple ascending dose protocols (NCT03335553). No data have been reported as yet. We note how heart failure and heart disease more generally seem to be a reliable target for AnxA1-based therapies as well as for FPR2/ALX small-molecule agonists. The Bristol Meyers Squibb team of García et al. (115) has studied two experimental tools, compound 43 and compound 11, originally described by Amgen (116), and reported the reparative actions of a dual FPR1/FPR2 agonist over a 4-week period; here, the treatment was per os and afforded significant protections against heart injury.

This section on prototypic synthetic FPR2/ALX agonists cannot be concluded without discussing the Compugen compound TIPMFVPESTSKLQKFTSWFM-amide (or CGEN-855A), which was identified through application of a predictive computational discovery platform screening at FPR2 but was also found to activate human FPR3 (117). CGEN-855A displays efficacy in settings of experimental inflammation and, probably not surprising by now, was also active in inhibiting myocardial infarction (118). It is not clear whether and how this peptide-mimetic agonist at FPR2/ALX was developed any further.

In terms of examples of other pro-resolving therapies developed based on the biology of the resolution of inflammation, we now focus on one small molecule developed to agonize melanocortin receptors, compound AP1189. This molecule acts as a biased agonist at melanocortin receptors, which brings an important added value: It is unable to stimulate melanocytes and thus does not risk causing melanoma with long-term treatment. In fact, AP1189 activates several receptors of this family of G protein–coupled receptors without causing downstream accumulation of cyclic-AMP but rather signaling via phosphorylation of ERK (119). Cyclic AMP synthesis via the adenylate cyclase represents the canonical signaling pathway for all melanocortin receptors, and for a long time it has been thought to be the sole signaling cascade (120). In any case, AP1189 activation of melanocortin receptor type 1 and type 3 (and possibly 5) promotes pro-resolving actions on neutrophils and macrophages and, as a consequence, inhibits the development of inflammatory arthritis in the mouse (119). AP1189 has been tested in rheumatoid arthritis in a Phase IIA trial that was just completed, in which patients received the compound or placebo on top of methotrexate (NCT04004429). A second trial is ongoing in patients with idiopathic membranous nephropathy (NCT04456816).

CONCLUSIONS

Activating pro-resolving targets to temper the overexuberant inflammatory processes that typify several chronic diseases can offer a fresh and effective way for better clinical management, ultimately benefitting the patient. As discussed previously (110), our concept is that resolution pharmacology will be achieved with drugs that are devoid of side effects (especially side effects linked to the pathway/target, as side effects due to the specific chemical molecule, for instance, cannot be excluded nor predicted here). Altogether, this will offer a therapeutic weapon to tackle inflammation that utilizes a fresh approach (i.e., agonists to reprogram immune cells), as presented in **Figure 1**. As pro-resolving therapeutic strategies will rely on active events to occur within the patient's tissue or organ, we could depict resolution pharmacology as an example of patient-tailored therapy or precision medicine. Moreover, we propose that pro-resolving therapeutics such as those discussed here, for example, modelled to mimic resolvins or AnxA1, can offer versatility in their application. For instance, a pro-resolving drug could be administered in combination with or after an aggressive therapeutic treatment. For example, one could envision that, in the treatment of patients with rheumatoid arthritis, anti-TNF therapy would initially be used to bring the flare of the joint under control, and then a pro-resolving drug would be administered for maintenance and potentially to reverse the disease, thereby avoiding the immunosuppression associated with current anti-inflammatory therapies. In addition, pro-resolving therapies can be used to protect secondary organs from the disease or from the canonical drug (the renal protection against cyclosporine presented in **Table 1** is a good example here). In terms of disease, a recent example that aligns with this overview on AnxA1 and SPMs is that of the cardiomyopathy in inflammatory arthritis, where pharmacological administration of the whole protein reduces the echocardiographic changes that accompany the disease in a specific mouse colony (121). It remains to be established whether AnxA1-derived peptides or indeed FPR2/ALX agonists will share this pharmacological effect.

In summary, we have discussed here the current pharmacology of exemplar mediators and pathways that can be harnessed for the development of novel medicines to treat inflammatory diseases or, indeed, the inflammatory components that impact on a large variety of chronic diseases. The underlying proposal is that molecules that coordinate the resolution phase of inflammation carry an untapped potential to guide innovative drug discovery programs. Furthermore, resolution pharmacology will enable innovative therapeutic approaches for the benefit of patients and our society at large.

DISCLOSURE STATEMENT

M.P. is a shareholder of Antibe Therapeutics and ResoTher Pharma ApS; has a directorship of William Harvey Research Limited; is a scientific advisory board member for Antibe Therapeutics and ResoTher Pharma ApS; is a consultant for TXP Pharma AG and Palatin Technologies; and is involved in the following commercial projects: Bristol Myers Squibb, SynAct Pharma AB, and TXP Pharma AG. J.D. is an inventor on patents related to the composition of matter and/or use of pro-resolving mediators, some of which are licensed by Brigham and Women's Hospital or Queen Mary University of London for clinical development. J.D. and M.P. are inventors on a patent related to AnxA1 pro-resolving peptides (European Patent 3533457 B1).

ACKNOWLEDGMENTS

The authors' work relevant to this review has been funded as detailed below. M.P. acknowledges support from the Wellcome Trust (program grant 086867/Z/08/Z), Medical Research Council

UK (MR/K013068/1), the Barts Charity (MGU0489), and The William Harvey Research Foundation. J.D. acknowledges support from the European Research Council under the European Union's Horizon 2020 research and innovation program (grant agreement 677542) and from the Sir Henry Dale Fellowship, which is jointly funded by the Wellcome Trust and the Royal Society (grant 107613/Z/15/Z).

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