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REVIEW ARTICLE

Formyl peptide receptor 2 as a potential therapeutic target for inflammatory bowel disease

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Inflammatory bowel disease (IBD) is a global health burden whose existing treatment is largely dependent on anti-inflammatory agents. Despite showing some therapeutic actions, their clinical efficacy and adverse events are unacceptable. Resolution as an active and orchestrated phase of inflammation involves improper inflammatory response with three key triggers, specialized pro-resolving mediators (SPMs), neutrophils and phagocyte efferocytosis. The formyl peptide receptor 2 (FPR2/ALX) is a human G protein-coupled receptor capable of binding SPMs and participates in the resolution process. This receptor has been implicated in several inflammatory diseases and its association with mouse model of IBD was established in some resolution-related studies. Here, we give an overview of three reported FPR2/ALX agonists highlighting their respective roles in pro-resolving strategies.

Keywords: resolution; inflammation; FPR2/ALX; SPM; IBD; pro-resolving

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INTRODUCTION

Inflammation plays a dual role in human health. Proper inflammatory response contributes to the clearance of pathogens, whereas excessive or incontrollable inflammation could lead to diseases. Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), is a group of idiopathic colorectal inflammatory disorders with a progressive and unpredictable course, impairing the quality of life among patients [1]. The incidence and prevalence of IBD begin to increase markedly at the turn of this century [2]. It has become a major health burden worldwide [3]. Currently, treatment strategies for IBD make use of anti-inflammatory agents such as aminosalicylates, corticosteroids, small-molecule immunosuppressants, and therapeutic antibodies. Some patients eventually need surgery to remove intestinal lesions [4, 5]. However, these existing drugs have limited clinical efficacy, significant adverse events and an unwanted therapeutic ceiling [6].

Approximately 30% of IBD patients develop drug resistance and allergic reactions during long-term therapy with anti-tumor necrosis factor-α (TNF-α) antibody, although it gives relief to patients with refractory IBD [7]. In patients with moderate to severe IBD, the rate of mucosal healing was only about 50% despite intensive anti-inflammatory treatment [8]. In addition, more than 50% of patients with IBD were at risk of experiencing a suboptimal response to anti-TNF-α therapy in a 2-year trial [9]. These results reveal an unmet medical demand and a therapeutic ceiling associated with anti-inflammatory approaches.

Resolution of inflammation is an active process initiated after the onset of acute inflammatory response. Some studies suggest that promoting resolution was beneficial to mucosal healing of chronic diseases like IBD [10]. Despite the goal of complete mucosal healing is difficult to achieve, gastroenterologists have turned their attention from colitis symptom control to mucosal healing and pro-resolution of inflammation in an effort to treat IBD and deal with the therapeutic ceiling [11]. Furthermore, recent reports highlight the role of FPR2/ALX [combining nomenclature of formyl peptide receptor 2 (FPR2) and receptor for aspirin-triggered-lipoxins (ALX)], a human G protein-coupled receptor (GPCR), in resolution mechanisms [12]. Some FPR2/ALX agonists exhibited pro-resolving effects and therapeutic potential in mouse models of IBD [13].

KEY TRIGGERS OF INFLAMMATION AND RESOLUTION

Four phases of inflammation development

Inflammation as a protective host response, manifesting as pathophysiological tissue dysfunction or homeostasis damage, occurs when a variety of infections, toxins or trauma activate the immune system. These harmful triggers are subsequently neutralized in a coordinated and active process of resolution that repairs and restores tissue integrity and function [14, 15]. Classical symptoms associated with this process include pain, fever, redness, swelling, dysfunction and organ damage [16]. At molecular and cellular levels, a series of inflammatory responses lead to increased blood flow, telangiectasia, leukocyte infiltration

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and release of chemical mediators. This course can be divided into four phases: (i) acute or chronic injury and barrier defect; (ii) onset of acute inflammation; (iii) triggering resolution mechanisms; and (iv) chronic inflammation [10]. Several reports described that these four phases do not progress sequentially but rather overlap; in other words, the activation and resolution of inflammation can occur simultaneously [17]. As a rapid and self-limiting process, acute inflammation lasts for a few days generally, and once harmful factors are eliminated, it resolves without causing major damage to the body. Properly controlling inflammation prevents the spread of infection or injury, followed by resolution in which the affected tissue returns to its original structural and functional state [18]. However, inadequate resolution may cause intractable injury and persistent inflammation leading to chronic inflammation [10].

Resolution of inflammation is a multi-stage and complex process, characteristics of limitation of blood-borne cells, regulation of chemokines and cytokines, alteration of leukocyte-survive-related pathways, and moderation of macrophage functions [19]. Resolution was once considered a passive process without regulators and a subsequent course that occurred only when pro-inflammatory lipid catabolism and chemokine modification were completed [20, 21]. It was the discovery of specialized pro-resolving mediators (SPMs) that has reshaped our understanding of resolution as an active process of healing or repair [21]. Three key mediators are thought important for resolution: lipids, neutrophils and phagocytes. Failure of one or more resolution steps may result in pathogenesis of long-term inflammation and chronic inflammatory diseases, triggered by continuous activation of the immune system, excessive production of pro-inflammatory cytokines, oxidative stress, tissue damages and dysfunction of homeostasis [19, 22]. In 2015, the concept of "Resolution Pharmacology" was proposed by Perretti and colleagues based on the comparison of pro-resolving vs. standard anti-inflammatory therapies [23]. Pro-resolving approaches were described as suppressing inflammation with fewer unwanted side-effects and better pathogen clearance, tissue repair and function recovery [6, 23].

Lipid mediators associated with resolution

Pro-resolving mediators are endogenous substances that promote resolution actions, including lipids, proteins, gaseous molecules, purines, neuromodulators and reactive oxygen species (ROS). Among them, lipids were demonstrated to act crucially in the inflammation processes starting from onset through progression to resolution [21, 24]. Under physiological conditions, lipid biosynthesis is reprogramed from pro-inflammatory signals to produce SPMs. Derived from polyunsaturated fatty acids (PUFAs), SPMs timely stop tissue damage caused by inflammatory response to avoid lasting impact that may lead to inflammation albeit of a primitive nature [25]. Most of SPMs are metabolites of ω−3 PUFA. It was found that long-term Western diets containing abundant saturated fat and ω−6 PUFA as well as scarce long-chain ω−3 PUFA were associated with an increased risk of IBD [26, 27]. Adherence to the consumption of ω−3 PUFA showed a positive role of evading pathology related to CD [28] and has been strongly recommended for the prevention of IBD [29]. Thus far, attention has been focused on the roles of PUFA-derived SPMs in the transition of inflammation from acute onset to active resolution [19]. Through their biosynthesis in injury tissues and later interactions with GPCRs on infiltrative neutrophils and resident epithelial cells, SPMs trigger three key cellular events at the inflammatory site: (i) weakening activation of epithelial cells; (ii) promoting apoptosis and limiting extravasation of neutrophils; and (iii) inducing M2 phenotype of macrophages and initiating efferocytosis by phagocytes [30]. SPMs additionally exhibit immunomodulatory actions on T and B cells and act on stem cells responsible for tissue repair or wound healing [30].

Regarding the question whether specific SPMs are preferentially secreted by a cell type [31], recent studies on endogenous active lipids revealed a main SPM biosynthesis pathway. Generally, SPMs, including lipoxins (LXs) and aspirin-triggered (AT)-LXs, are synthesized from arachidonic acid (AA) or docosahexaenoic acid (DHA) and catalyzed by 15-lipooxidase (15-LOX). They can be transformed to D series resolvins (RvDs), protectins and maresins. Biosynthesis of E series resolvins (RvEs) comes from eicosapentaenoic acid (EPA) and ω−3 docosapentaenoic acid (DPA) via aspirin acetylation of cyclooxygenase-2 (COX-2-ASA) that can be transformed to T series resolvins (RvTs). Resolvin, protectin and maresin conjugates in tissue regeneration come from their epoxy precursors [19, 31]. LXs are the most typical type of lipid mediators that exhibit pro-resolving properties and can be generated by transcellular metabolism at the inflammatory site [32, 33]. Despite precursor AA as a ω−6 pro-inflammatory lipid, the metabolites LXs mainly act to resolve inflammatory responses. From acute inflammation to resolution phase, the action of LXs on neutrophil infiltration and efferocytosis facilitates resolution and repairs damaged tissues [34, 35]. Ongoing studies on lipid biosynthesis demonstrate the presence of several ω−3 SPMs including resolvins [36], maresins [37] and protectins (neuroprotectins) [38] in inflammation. Resolvins of D, E and T series show effects of controlling the duration and resolution of inflammation [36]. RvE1 was the first identified SPM derived from EPA and isolated from resolving exudates and disease models that reduced neutrophil infiltration [39]. RvD1 and AT-RvD1 are potent regulators of phagocytes, stimulating the phagocytosis of microbes and dying cells [40]. In a recent RvT study, Chiang et al. revealed the role of RvTs in modulating phagocyte functions and neutrophil extracellular traps (NETs) [41]. Additionally, DHA-derived protectin D1 (PD1) is biosynthesized through 15-LOX-initiated mechanisms in exudates and neural tissues and shows strong neuroprotective effects in stroke models [42]. Existing protectin studies focused on resolution and repair processes of traumatic brain injury, such as PD1 and AT-PD1 actions in controlling neutrophil and macrophage functions to attenuate experimental stroke [43, 44]. As DHA-derived and 12/15-LOX-catalyzed macrophage mediators, maresins play an essential role in tissue repair and regeneration [45]. The complete stereochemistry was determined for maresin 1 (MaR1) possessing robust regenerative, repairing and neuroprotective capability. Meanwhile, synthetic MaR1 was shown to promote planarian regeneration after head resection in freshwater flatworm models [46, 47]. Together, existing data highlight that SPMs exert an essential action in resolution and repair (Summary in Table 1).

Neutrophil death-related inflammation

Neutrophil death is finely regulated under physiological conditions [48]. Response to infection or injury is characterized by early and sustained release of the 'Go' signals, consisting of pro-inflammatory cytokines and cell adhesion molecules, thereby promoting migration of leukocytes to tissues. Such events are offset by parallel discharge of the 'Stop' signals (IL-10, prostaglandin E2, and factors controlling Toll-like receptor and NF-κB signaling) [49]. Neutrophils associated with these signals possess different attacking strategies to invading microorganisms: phagocytosis, release of ROS, generation of pro-inflammatory mediators and NETs [50]. Neutrophils are the first responder (followed by macrophages) to acute inflammatory reaction. Infiltration to the inflammatory site and subsequent cytotoxicity are essential to host defense against infection or injury [51]. Taking advantage of depolymerized DNA structure as their skeleton, NETs contain histone, myeloperoxidase (MPO), cathepsin G, and other bactericidal and pro-inflammatory mediators released to the extracellular space [52]. Clinical observations showed that a handful of NETs were detected in the intestinal tract of IBD patients, suggesting that with the activation of neutrophils in IBD, more NETs could be released to kill pathogens [53, 54]. An increased neutrophil life-span contributes to the effective clearance of

Table 1. Pro-resolving lipids and their biological characteristics

Representative lipid mediator	Biosynthetic pathway	Key pro-resolving function	Resolution receptor	Reference
SPMs				
LXs (LXA4, LXB4)	AA (metabolized by 5/12-LOX or 5/15-LOX)	Neutrophil infiltration ↓ Pro-inflammatory cytokine production ↓ Phagocytosis, efferocytosis ↑	**LXA4**–FPR2/ALX; GPR32	[12, 13, 177]
RvDs (RvD1-RvD3, RvD5)	DHA (metabolized by 15-LOX and 5-LOX)	Pro-inflammatory mediator production ↓ Neutrophil infiltration ↓ Inflammasome activation ↓ Phagocytosis, efferocytosis ↑ Tissue regeneration ↑	**RvD1, RvD3**–FPR2/ALX; GPR32 **RvD2**–GPR18 **RvD5**–GPR32	[13, 90, 151, 152] [91, 153] [154]
RvDn-3 (RvD5n-3)	n-3 DPA	Phagocytosis of bacteria ↑ Efferocytosis ↑	**RvD5n-3**–GPR101	[94]
RvEs (RvE1)	EPA (metabolized by COX-2-ASA or P_{450}, and 5-LOX or 15-LOX)	Neutrophil apoptosis ↑ Oxidative stress ↓ Wound healing ↑ Efferocytosis of apoptotic neutrophils ↑	**RvE1**–Chemerin1 (ChemR23)	[89, 92, 178]
RvTs (RvT1-RvT4)	n-3 DPA (metabolized by COX-2-ASA)	Phagocytosis ↑ NETosis ↓ Macrophage NET clearance ↑	Unknown	[41]
MaRs (MaR1, MaR2)	DHA (metabolized by 12/15-LOX)	Neutrophil infiltration ↓ Oxidative stress ↓ Phagocytosis, efferocytosis ↑ Tissue regeneration ↑	**MaR1**–LGR6	[96]
Protectins (PD1)	DHA (metabolized by 15-LOX)	Neutrophil infiltration ↓ Wound healing ↑	**PD1**–GPR37	[42, 93]
Other lipids				
PGEs (PGE2)	AA (metabolized by PLA2 and COX-1/2)	Cytotoxic T cell function ↓ Neutrophil reverse-migration away from the injury site (sooner not at a greater speed) ↑ Epithelial cell necroptosis ↓	**PGE2**–EP4	[95, 179]
LTs (LTB4)	AA (metabolized by 5-LOX and LTA4H)	Macrophage phagocytosis ↑ Recruitment of effector $CD8^+$ T and $CD4^+$ T cells ↑ Th1-type reaction ↑	**LTB4**–BLT1	[97]

AA arachidonic acid, *BLT1* B-type leukotriene 1, *Chemerin1 (ChemR23)* chemokine receptor-like 1, *COX-1/2* cyclooxygenase-1/2, *COX-2-ASA* aspirin-acetylated cyclooxygenase-2, *DHA* docosahexaenoic acid, *DPA* docosapentaenoic acid, *EPA* eicosapentaenoic acid, *EP4* E-type prostanoid receptor 4, *FPR2/ALX* formyl peptide receptor 2, *GPR18* G protein-coupled receptor 18, *GPR32* G protein-coupled receptor 32, *GPR37* G protein-coupled receptor 37, *GPR101* G protein-coupled receptor 101, *LGR6* leucine-rich repeat-containing G-protein coupled receptor 6, *LTs* leukotrienes, *LXs* lipoxins, *PD1* protectin D1, *MaRs* maresins, *NET* neutrophil extracellular trap, *NETosis* neutrophil extracellular trap related cell death, *PGEs* E-type prostaglandins, *PLA2* phospholipases A2, P_{450} cytochrome P_{450}, *RvDs* resolvins D series, *RvEs* resolvins E series, *RvTs* resolvins T series, *SPMs* specialized pro-resolving mediators, *12-LOX* 12-lipoxygenase, *15-LOX* 15-lipoxygenase, *5-LOX* 5-lipoxygenase

invading pathogens [55], but excessively delayed neutrophil death may lead to chronic inflammation [51]. When neutrophils are not cleared in time, some of their proteases would cause tissue damage and amplification of the inflammatory response via release of pro-inflammatory cytokines and chemokines from the extracellular matrix (ECM) [56]. Therefore, the action of neutrophils should be properly regulated such as cell death including apoptosis, autophagy, pyroptosis, necroptosis, NET-related cell death (NETosis), and necrosis [48]. Dead neutrophils are recruited to an efferocytosis process by phagocytes [57]. Abnormally increased neutrophil life-span due to reduced apoptosis could elevate disease severity of chronic inflammation such as asthma [58], chronic obstructive pulmonary disease (COPD) [59], and IBD [60]. It appears that neutrophil death may serve as a therapeutic strategy for inflammatory diseases [61].

Efferocytosis by phagocytes

Carried out by macrophages and other phagocytes like monocytes, dendritic cells (DCs), and intestinal epithelial cells (IECs), efferocytosis is a critical component of the resolution processes, and its failure prolongs the inflammatory response and may lead to chronic inflammation [57, 62]. The M2 macrophages exhibit higher phagocytosis capacity and undertake host defense and wound healing tasks, with contributions to the inhibition of pro-inflammatory cytokines and the production of anti-inflammatory cytokines to down-regulate inflammation [63]. Phagocytes (mainly macrophages) can recruit dying cells (e.g., apoptotic neutrophils) to a phagocytosis process called efferocytosis, which in general consists of four steps: recruitment, binding, internalization/engulfment and degradation [64]. Apoptotic neutrophils release 'Find-me' signals (modified membrane lipids [65], nucleotides [66] and chemokines [67]), which guide macrophage recruitment to the site of apoptotic neutrophils [68]. In contrast to apoptosis, plasma membrane integrity of non-apoptotic cells is compromised, and these ruptured dying cells liberate inflammatory signals allowing phagocytes to recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) [57, 68], and then bind to targeted neutrophils

via 'Eat-me' signals (phosphatidylserine [69] and calreticulin [70]) present in these dying cells. Actin remodeling will follow to facilitate phagosome formation and dying-cell internalization/engulfment [71]. Rac1, as the Rho family of small GTPases, is a key regulator in the reorganization of actin. Its activation is mediated through two different mechanisms [57], namely, LDL receptor-related protein 1 (LRP1) and adapter protein (e.g., GULP96), or the assembly of guanine nucleotide exchange factor (e.g., Dock180) and phagocytic regulatory protein [e.g., engulfment and cell motility protein (ELMO)]. To date, the precise mechanism of activating Rac1 by LRP1 and GULP is still elusive, but its activation by the Dock180-ELMO complex to trigger cytoskeleton rearrangement and internalization for phagocytosis has been documented [72]. Degradation of these internalized cells occurs via lysosomes with subsequent actions of membrane recovery and processing of dying cell-derived metabolites. Additionally, phagocytes that carry out efferocytosis are regulated by 'Good-bye' signals (spermidine, guanosine, fructose-1,6-bis-phosphate, etc.) and some metabolites from internalized dying cells, which effects include increased release of anti-inflammatory molecules, cytoskeleton rearrangement that promotes phagocytosis, promoting energy production and preventing apoptosis of phagocytes [73].

Aberration in efferocytosis pathways has been linked recently with autoimmune diseases [74, 75], wound healing [76], atherosclerosis [77, 78], arthritis [79], neurodegeneration [80], and organ inflammation or injury [81–83], including systemic lupus erythematosus (SLE). Non-cleared dead cells were detected in the blood, skin, and lymph nodes of SLE patients, and the severity of the disease was positively correlated with defective efferocytosis and dead cell accumulation [84]. IECs possess a high turnover of cells in the intestinal tissue, and efferocytosis is constantly required to prevent unnecessary inflammation. It was reported that defects in the binding mechanism of efferocytosis (upon cleaning dying IECs) caused by ablation of CD300f (a phosphatidylserine receptor as an 'Eat-me' signal) were associated with IBD and colon cancer [85]. In the dextran sulfate sodium (DSS)-induced colitis model, mice with genetic deletion of G2A (a lipid product receptor as a 'Find-me' signal) exhibited worsened colitis and had fewer $CD4^+$ lymphocytes recruited to the inflamed colon that impaired efferocytosis [81]. Besides, other mouse models revealed that blockade of phosphatidylserine recognition or ablation of MerTK (an 'Eat-me' signal) triggered efferocytosis defects and then impaired tissue repair in lung and intestinal injury [86]. Obviously, efferocytosis dysfunction can contribute to failed resolution of intestinal inflammation in IBD.

FPR2/ALX: TOWARDS A PRO-RESOLVING STRATEGY

GPCRs in the resolution phase

SPMs exert pro-resolving actions through a variety of GPCRs, capable of identifying PAMPs and DAMPs, interacting with a large number of ligands to process extracellular signals [87], and regulating pro-inflammatory mediators (IL-1, IL-6, IL-7, IL-8, TNF-α, etc.). Reduction of leukocyte aggregation in the inflammatory tissue, promotion of apoptosis, and efferocytosis of neutrophils will follow [88]. In the gastrointestinal (GI) tract, GPCRs participate in key functional processes including digestion, immune cell infiltration, pain perception, and tissue repair. Certain studies highlighted the role of GPCRs in intestinal mucosal repair [88]. Expression of GPCRs in the GI epithelial membrane is up-regulated by pro-inflammatory cytokines, while SPMs can bind to GPCRs at orthosteric or allosteric sites and promote the migration and proliferation of IECs aiming at restoring homeostasis and GI wound repair [89]. It is known that resolution-related GPCRs may include FPR2/ALX [12], GPR32 [90], GPR18 [91], chemerin1 (ChemR23) [92], GPR37 [93], GPR101 [94], EP4 [95], LGR6 [96] and BLT1 [97] (Table 1), although definite receptors for some SPMs have yet to be identified [88]. These GPCRs have been studied as pro-resolving targets for IBD. An overview of the association [98–100] between pro-resolving GPCRs and their clinical application in IBD [95, 99–104] is summarized in Fig. 1. Among them, FPR2/ALX, a high-affinity receptor for AA-derived LXA4 and DHA-derived RvD1, mediates the actions of SPMs by inhibiting and resolving a wide range of inflammatory reactions [12]. The following parts of review give an overview of FPR2/ALX as a potential pro-resolving target to treat inflammatory diseases including IBD.

Formyl peptide receptor 2

FPRs belong to class A GPCR family and are expressed in different cell types [105]. Earlier understanding was that FPRs cause a series of cellular signaling events resulting in myeloid cell migration and inflammatory mediator release [12]. More recent studies indicate that FPRs not only control inflammation but also participate in many key pathophysiological processes [106]. The human FPRs include FPR1, FPR2/ALX, and FPR3 with their genes located in chromosome 19q13.3, while the mouse *FPR* gene family has 8 members (*Fpr1* – *Fpr3* and *Fpr-rs3* – *Fpr-rs7*) that localize to chromosome 17A3.2 [105]. In human non-immune organs and tissues, FPR1 and FPR2/ALX show a broader distribution than FPR3 and are expressed in a variety of non-myeloid cells, including astrocytoma cells, epithelial cells, hepatocytes, microvascular endothelial cells, and neuroblastoma cells. In the immune system, they are expressed mainly in innate immune cells like neutrophils, monocytes/macrophages, DCs, etc. [107]. They bind to a large number of structurally diverse ligands in the inflammatory environment [105, 108], such as PAMP-derived formylated bacterial peptides (e.g., f-MLF), PAMP-derived non-formylated microbe peptides [e.g., Hp(2–20)], DAMP-derived formylated mitochondria peptides (e.g., f-MMYALF), host-derived molecules (e.g., LXA4 and RvD1) and some synthetic compounds (e.g., WKYMVm and Quin-C1). The effects of these ligands are mediated by FPR signaling causing Ca^{2+} mobilization, superoxide production, transcriptional regulation, chemotaxis, and phagocytosis [108]. Neutrophils, macrophages, and other leukocytes are important participants of inflammatory responses that are partially regulated through FPRs and other GPCRs on the cell surface [88]. It was found that mitochondrial *N*-formyl peptide induced aggregation of pulmonary neutrophils via FPRs and damaged lung tissues through hemorrhagic shock in rats [109]. In a mouse acute lung injury model, FPR1 antagonism was demonstrated to reduce lipopolysaccharide (LPS)-induced neutrophil aggregation and to improve acute pulmonary edema and alveolar injury [110]. FPRs can recognize formylated peptides and guide chemotactic neutrophils to phagocytose bacterial pathogens or damaged tissues. In the *Fpr1/2*$^{-/-}$ (gene deletions of *Fpr1* and *Fpr2*) mouse model, chemotactic phagocytosis of neutrophils against bacterial pathogens was impaired [111]. Similarly, FPR1 [112] and FPR2/ALX [113] are implicated in the migration of macrophages and phagocytosis (efferocytosis) of apoptotic neutrophils.

Based on the recommendation of the International Union of Basic and Clinical Pharmacology (IUPHAR), the nomenclature of human FPRs follows these descriptions: FPR1 as a cognate receptor for N-formylated peptides of bacterial and mammalian origins, FPR2/ALX to which binds N-formylated peptides with low affinity as well as LXA4 and AT-LXs (ALX as a receptor for LXA4 and AT-LXs), and FPR3 as another receptor that binds and responds to the mitochondrial peptide fMMYALF [105]. Among them, FPR2/ALX is recognized as a resolution receptor [12]. Although it remains unclear how FPR2/ALX binds to different ligands and changes its conformation to activate different signaling pathways [114], current studies have implied a few potential mechanisms of receptor agonism, including signal bias either towards G protein activation (pro-inflammation; Fig. 2a) or towards β-arrestin recruitment (pro-resolution; Fig. 2b) [114, 115]. FPR2/ALX can also be phosphorylated to mediate heterologous desensitization

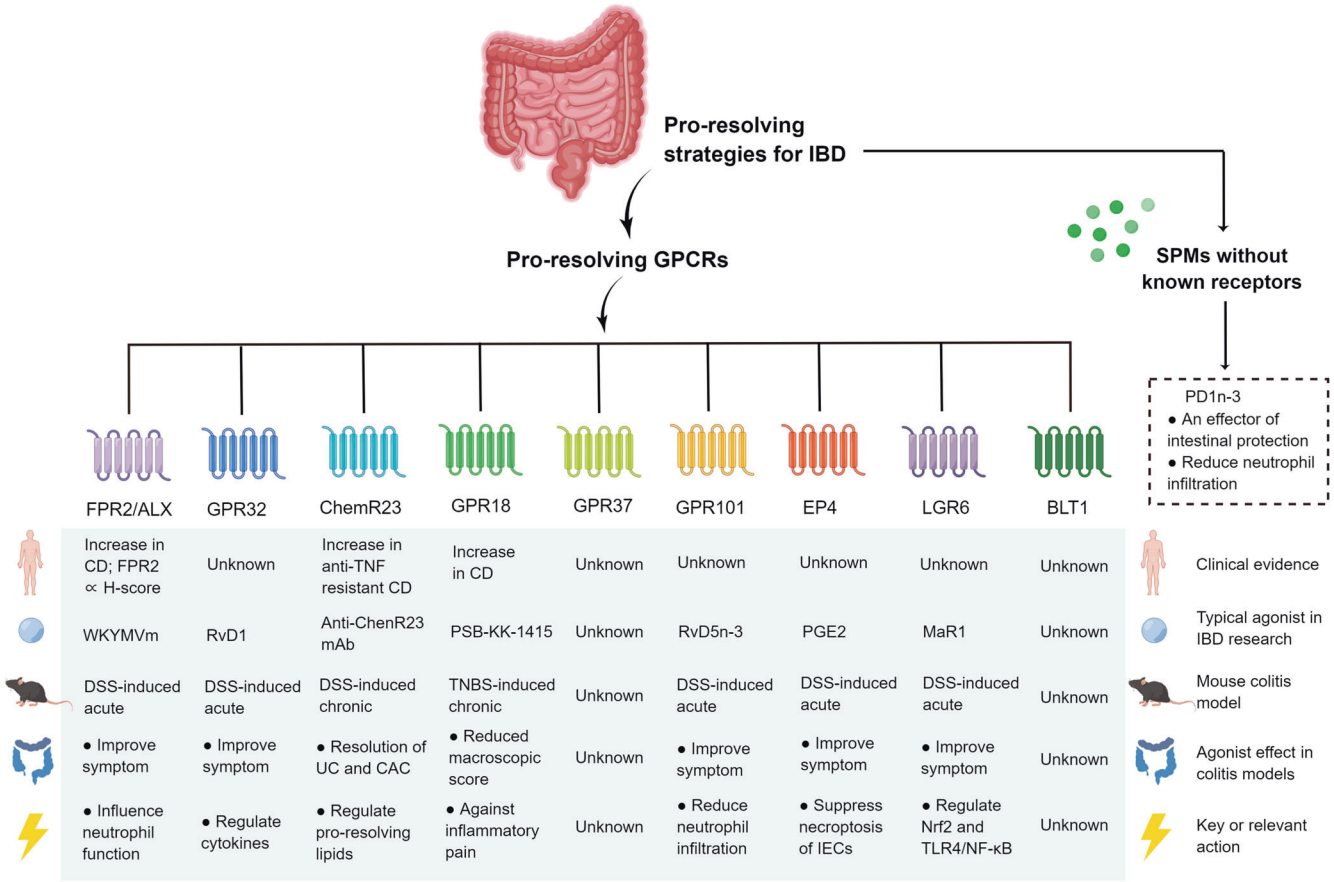

Fig. 1 Typical studies regarding IBD treatment using pro-resolving strategies. BLT1 B-type leukotriene 1, CAC colitis-associated cancer, CD Crohn's disease, Chemerin1 (ChemR23) chemokine receptor-like 1, DSS dextran sulfate sodium, EP4 E-type prostanoid receptor 4, FPR2/ALX formyl peptide receptor 2, GPCR G protein-coupled receptor, IBD inflammatory bowel disease, IECs intestinal epithelial cells, LGR6 leucine-rich repeat-containing G-protein coupled receptor 6, LXA4 lipoxin A4, mAb monoclonal antibody, MaR1 maresin 1, PD1n-3 n-3 protectin D1, PGE2 prostaglandin E2, RvD1 D series resolvin 1, TNBS 2,4,6-trinitrobenzene sulfonic acid, UC ulcerative colitis, SPMs specialized pro-resolving mediators. This figure was generated by an open-type platform FigDraw (http://www.figdraw.com/).

through inhibition of PKA/PKC pathway [116] (Fig. 2c). For example, ACT-389949 was found to cause FPR2/ALX desensitization in a phase I clinical trial despite its elusive mechanism of action [117]. In addition, FPR2/ALX internalization is associated with LXA4/AnxA1 stimulation and desensitization process [118] (Fig. 2d).

FPR2/ALX dysfunction and diseases

Owing to its critical roles in lipid metabolism, neutrophil functions, and efferocytosis-related resolution processes, FPR2/ALX dysfunction could develop inflammation and cause failure in resolution [35]. Pro-resolving studies highlighted a partial contribution of SPMs via FPR2/ALX to key immune cell events [10, 119–121] during inflammation and injury (Fig. 3). Another piece of evidence suggested that rs11666254 polymorphism that decreases FPR2/ALX expression was associated with compromised immune responses in patients with severe trauma [122]. The gene products of both *Fpr2* and *Fpr3* (previously named *Fpr-rs1*) are mouse orthologs of human FPR2/ALX. They facilitated the use of *Fpr2/3* knockout (*Fpr2/3*$^{-/-}$) mice to characterize human FPR2/ALX dysfunction [123–125]. In 2010, Dufton et al. [124] and Chen et al. [126] reported the creation of a mouse colony in which *Fpr2* was deleted, but Dufton et al. made a correction in 2011 that their targeting strategy would have also resulted in the deletion of *Fpr3* because this gene incorporated an exon found in *Fpr2* [125].

Essential roles of FPR2/ALX in regulating inflammation of different diseases are summarized in Table 2. Machado et al. demonstrated that *Fpr2/3*$^{-/-}$ mice were highly susceptible to infection, displaying uncontrolled inflammation, increased bacterial dissemination, and pulmonary dysfunction, associated with the loss of lung barrier integrity and increased neutrophil activation upon *Streptococcus pneumoniae* stimulation [127]. This suggests that FPR2/ALX signals control inflammation and bacterial dissemination during pneumococcal pneumonia by promoting host defense. Another study found that *Fpr2/3*$^{-/-}$ mice showed phagocytosis impairment in macrophages with the expansion of neutrophils and reduced SPM levels in the infarcted heart and spleen. Lack of murine Fpr2/3 led to obesity and leukocyte dysfunction, and facilitated profound inter-organ non-resolving inflammation in mice, i.e., obesogenic cardiomyopathy and renal inflammation [128]. Since FPR2/ALX was thought to be protective against inflammation and tissue injury [129], the role of Fpr2/3 in orchestrating intestinal resolution and repair was explored. It was found that *Fpr2/3* knockout mice were susceptible to experimental colitis. In the DSS-induced mouse model of colitis, such a role in mucosal homeostasis and resolution was revealed by impaired epithelial restitution in the colon and delayed mucosal restoration after injury of *Fpr2/3*$^{-/-}$ mice compared to that of the wild-type [130]. Birkl et al. showed a similar impairment in *Fpr2/3*$^{-/-}$ colitis mice and suggested the contribution of FPR2/ALX in facilitating monocyte recruitment to mucosal injury sites for intestinal wound repair [120].

Clinical studies revealed the relationship between FPR2/ALX and inflammatory diseases showing different receptor

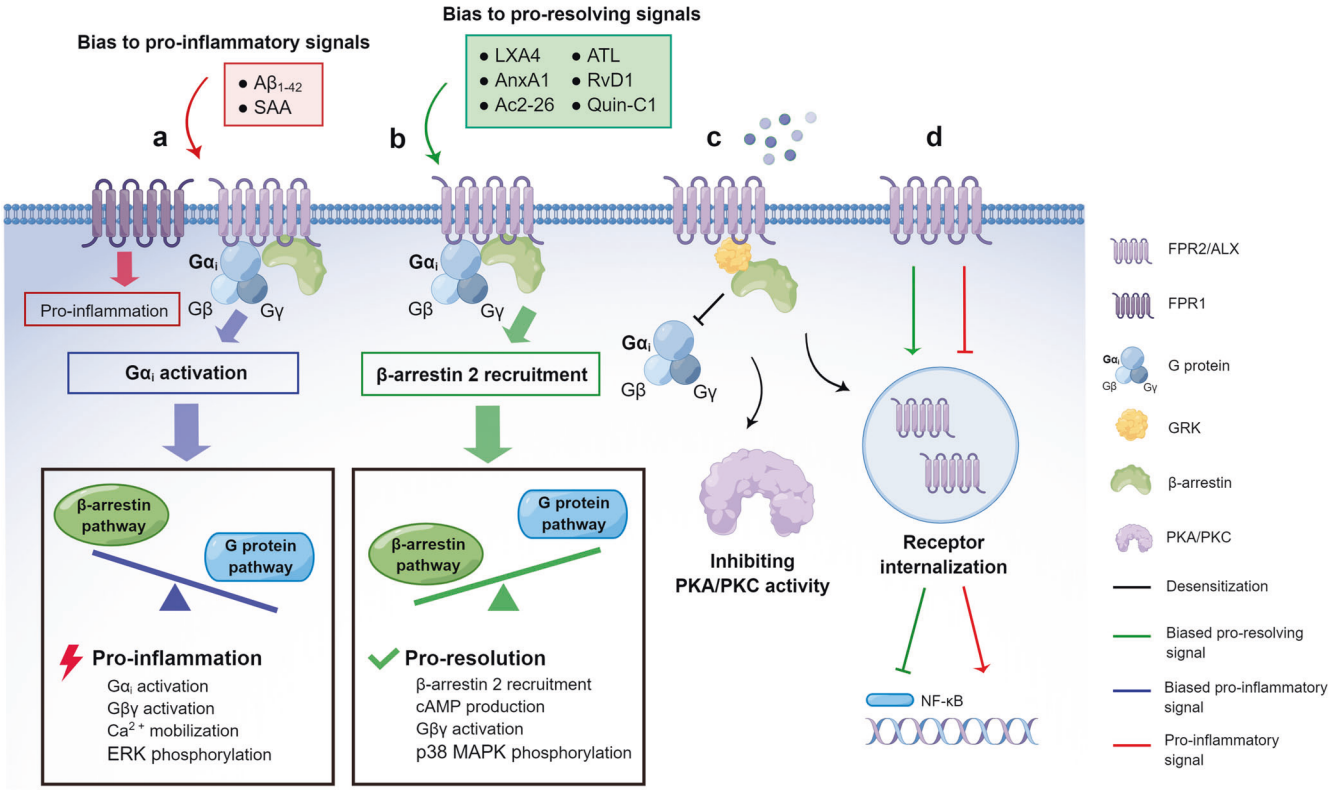

Fig. 2 Potential mechanisms of FPR2/ALX mediated responses induced by various ligands. Like other chemoattractant receptors, FPR2/ALX couples to the G_i class of heterotrimeric G proteins. Bifurcation of FPR2/ALX signaling exists. **a** Some ligands like amyloid $\beta_{1\text{-}42}$ ($A\beta_{1\text{-}42}$) and serum amyloid A (SAA) can activate FPR1 to trigger pro-inflammatory signals directly, or they activate FPR2/ALX by coupling to $G\alpha_i$ resulting in Ca^{2+} mobilization and ERK phosphorylation, thereby showing biased pro-inflammation. **b** Most FPR2/ALX agonists (LXA4, AnxA1, Ac2-26, ATL, RvD1 and Quin-C1) induce biased pro-resolving signals via β-arrestin 2 recruitment, cAMP production and p38 MAPK phosphorylation. **c** Heterologous desensitization of FPR2/ALX is probably mediated by β-arrestins. FPR2/ALX is phosphorylated by G protein-coupled receptor kinases (GRKs) to recruit β-arrestins, which then inhibit protein kinase A/C (PKA/PKC) signaling pathways. **d** FPR2/ALX internalization is essential to LXA4- and AnxA1-stimulated pro-resolution as the internalized receptor inhibits NF-κB activity. Some desensitized FPR2/ALX receptors are also internalized into cells. This figure was generated by an open-type platform FigDraw (http://www.figdraw.com/).

expression profiles depending on the disease stages [10]. FPR2/ALX (*FPR2*) down-regulation was found in advanced stages with failed resolution, while its up-regulation appeared in early stages with active resolution (Table 2). In children with severe asthma (SA), FPR2/ALX expression was reduced in sputum cells compared to healthy controls [131]. In the placenta of patients with chorioamnionitis (CAM), RvD1 decreased while FPR2/ALX increased, accompanied by inhibition of PPARγ and NF-κB nuclear translocation [132]. *FPR2* expression was associated with clinical outcomes in trauma patients, and those had uncomplicated recoveries displayed significantly higher *FPR2* expression and lower gene expression ratio of leukotriene compared to that seen among patients experiencing complicated recoveries [133]. Colonic FPR2/ALX mRNA level was also positively correlated with the histology scores of IBD patients and the intestinal stricture of CD patients [98], exhibiting a 6-fold increase in the inflamed region of patients with CD [134]. In early-stage tendon pathology, expression of FPR2/ALX vs. healthy tendons was elevated, suggesting tendons mount a counter-resolution response to inflammation, while that in intermediate-advanced disease tendons dropped indicating a failure of the resolution process [135].

Pharmacology of FPR2/ALX agonists

Agonism at FPR2/ALX has been reported in animal models of renal fibrosis [136], rheumatoid arthritis (RA) [137, 138], IBD [101], myocardial ischemia-reperfusion [139], diabetic complications [140], sepsis [141], COPD [142], neuroinflammation [143] and cancer [144]. An overview of key findings is provided in Table 3.

SPMs and lipid analogs. Typical SPMs, such as LXA4 and RvD1, are FPR2/ALX agonists with pro-resolving capability. Interaction between LXA4 and FPR2/ALX activates several intracellular signaling pathways and the conformational changes induced by LXA4 prevent the binding of pro-inflammatory amyloid β or serum amyloid A (SAA) [12]. Current data suggest that LXs exert strong endogenous pro-resolving effects. However, chemical and metabolic liability of them hampers the therapeutic development. Particularly, LXA4 is metabolized by prostaglandin dehydrogenase (PGDH) at C15 and omega-oxidation at C20 [145]. Some synthetic LX analogs are less susceptible to PGDH with a longer half-life and better pro-resolving properties [13]. Thus, they are under development with several showing the potential in treating inflammatory disorders such as colitis and IBD. ZK-192 as a LXA4 analog was protective in trinitrobenzene sulphonate (TNBS)-induced colitis mice [146]. Another LXA4 analog BML111 was found to rescue CD-like intestinal inflammation in cyclooxygenase-2 (COX-2) myeloid knockout (MKO) mice [147]. Meanwhile, NAP1051 showed LXA4-like in vitro features and anti-tumor activity in colorectal cancer xenograft models via inhibiting neutrophils, reducing NETosis and stimulating T cell recruitment in the tumor microenvironment (TME) [148]. In a non-colitis inflammation study, synthetic dimethyl-imidazole-containing LXA4 mimetic AT-01-KG was effective in RA animal models by decreasing the number of neutrophils

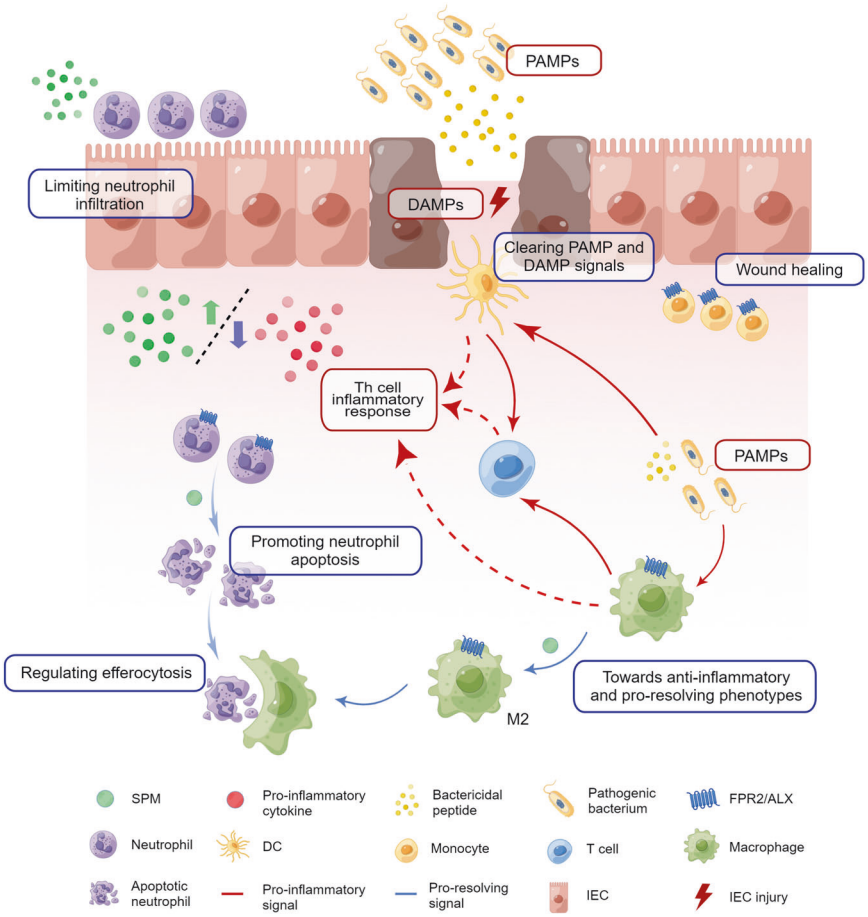

Fig. 3 FPR2/ALX in the resolution of inflammation. Taking the gastrointestinal tract as a model, when injury or infection occurs, neutrophils migrate to the inflamed site attracted by chemokines. DAMPs and PAMPs invade via IECs to the damaged tissues and the production of pro-inflammatory cytokines is up-regulated to clear pathogens after activating T helper (Th) cells, resulting in inflammatory response. In the resolution phase, an increase in SPMs is accompanied by a decrease in pro-inflammatory cytokines. After recognizing LL-37 (an anti-microbial peptide) and SPMs via FPR2/ALX, DCs are activated with elevated phagocytosis and CD40 expression to clear PAMP and DAPM signals. Upon completing their mission of resisting pathogen invasion, neutrophils enter into the apoptosis process associated with SPMs and FPR2/ALX. SPMs reprogram macrophages towards M2 pro-resolving phenotypes, and apoptotic neutrophils are phagocytosed by M2 macrophages thereafter. FPR2/ALX expression is related to that of CCR6 in monocytes thereby facilitating the latter to the inflamed site and the epithelial remodeling in the wound. CCR chemokine receptor; DAMP damage-associated molecular pattern; DC dendritic cell; FPR2/ALX formyl peptide receptor 2; IEC intestinal epithelial cell; PAMP pathogen-associated molecular pattern; SPM specialized pro-resolving mediator. This figure was generated by an open-type platform FigDraw (http://www.figdraw.com/).

in the knee exudate [137]. It also reduced tissue damage and hyper nociception in MSU-induced gout model [149]. Such effects were not observed in *Fpr2/3*$^{-/-}$ gout mice [149]. Additionally, a recent phase 1 clinical trial (NCT02342691) demonstrated that benzo-LXA4 analog BLXA4 was safe and efficacious in periodontitis patients showing an increased level of pro-resolving mediators systemically [150].

Unlike LXs, DHA-derived RvDs not only bind to FPR2/ALX but also GPR32 and GPR18 [13, 90, 91, 151–154]. RvD1 and RvD2 were shown to prevent DSS- or TNBS-induced colitis and improve colon epithelial damage and macrophage infiltration in mice [155]. Several RvD1 analogs were developed, such as 17-(R/S)-methyl-RvD1 methyl ester, 17R-hydroxy-19-para-fluorophenoxy-RvD1 methyl ester and benzo-diacetylenic-17R-RvD1-methyl ester (BDA-RvD1). Although they have yet to be evaluated in animal models of colitis or IBD, their therapeutic potential was demonstrated in lung injury via neutrophil suppression and phagocytosis stimulation [156–158].

Proteins and peptides. Some endogenous proteins, their peptide analogs and synthetic peptides are considered as FPR2/ALX agonists as well. Annexin A1 (AnxA1) is a calcium-dependent phospholipid-binding protein widely seen in eukaryotic cells and regulates inflammatory response through FPR2/ALX [140]. In DSS-induced colitis mice, exogenous AnxA1 activated the FPR2/STAT3 pathway and enhanced the therapeutic effect of anti-TNF nanobody V7 [159]. AC2-26, as an AnxA1 mimetic, was found to modulate the function of human mast cells (MCs) and capable of interfering with intestinal MC degranulation via FPR2/ALX [160]. Apolipoprotein A-I (APOA1) is the main structural protein of high-density lipoprotein (HDL) associated with inflammation [161]. Its mimetic peptides 4F and Tg6F either mitigated COX-2-MKO/CCHF and piroxicam-accelerated *IL-10*$^{-/-}$ models of IBD or effectively reduced intestinal inflammation in COX-2-MKO/CCHF model [147]. FAM3D is a newly found endogenous protein for FPRs, essential to colon homeostasis and host defense against inflammation, as *FAM3D*$^{-/-}$ mice showed increased spontaneous colitis, impaired colonic mucosal integrity, and excessive sensitivity to chemically induced colitis-associated cancers [162]. Unlike natural AnxA1 and APOA1, WKYMVm (Trp-Lys-Met-Val-D-Met) is a modified hexapeptide with high potency for both FPR1 and FPR2/ALX [163]. WKYMVm displayed therapeutic value in mouse models of

Table 2. Disease-associated FPR2/ALX dysfunction in mouse models and humans

Disease	Lesion	Intervention or observation	Outcome (vs. WT/control)[a]	Reference
Mouse				
IR injury	Gene deletion	*Fpr2/3* KO	IR insult • Cell adherence ↑ • Emigration in mesenteric microcirculation ↑	[124, 125]
Paw edema	Gene deletion	*Fpr2/3* KO; carrageenan-induced paw edema	In carrageenan-induced paw edema • Acute response ↑	[124, 125]
Arthritis	Gene deletion	*Fpr2/3* KO; K/B × N serum-induced arthritis	After K/B × N serum induced • Sensitivity to arthritis ↑	[124, 125]
Lung barrier	Gene deletion	*Fpr2/3* KO; *S. pneumoniae* infection	Pulmonary dysfunction • Susceptible to infection ↑ • Bacterial dissemination ↑ When treated with Fpr2/3 agonist • Ac2–26 peptide ineffective to afford protection	[127]
CAM	Gene deletion	*Fpr2/3* KO; LPS injection	Worsen CAM symptoms • Susceptible to LPS with shorter preterm time ↑ • Necrotic areas in the placenta ↑ • IL-6, IL-1β and TNF-α ↑	[132]
Cardiorenal defects	Gene deletion	*Fpr2/3* KO	Obesogenic cardiomyopathy • 5/12/15-LOX and SPMs ↓ • COX-1 and COX-2 ↑ Renal inflammation • NGAL, TNF-α, CCL2, IL-1β and creatinine in aging mice ↑ Cell level • Macrophage phagocytosis impairment • Expansion of neutrophils	[128]
Colitis	Gene deletion	*Fpr2/3* KO; DSS-induced acute colitis	Defects in gut homeostasis • Absence of responses to N-formyl peptide stimulation • Colonic crypt size ↓ In DSS-induced colitis • Impaired epithelial proliferation • Delayed recovery and colonic mucosal wound repair • Monocyte recruitment to heal mucosal wound ↓ • Chemotaxis towards CCL20 ↓	[120, 130]
Clinical				
Sepsis	SNP	Pyrosequencing	Functional SNP of rs11666254 • FPR2/ALX mRNA and protein expression ↓ • Sepsis susceptibility after traumatic injury ↑	[122]
Pediatric SA	Protein	IHC; FACS	Compared with healthy controls • FPR2/ALX expression in induced sputum cells ↓	[131]
CAM	Protein	IHC; WB	Compared with healthy controls • FPR2/ALX expression in the placenta ↑	[132]
Trauma	Gene	Full genomic profiling	Uncomplicated recoveries compared with complicated recoveries • *FPR2* expression in the peripheral blood ↑	[133]
IBD	mRNA	qPCR	Compared with healthy controls • Colonic FPR2/ALX mRNA increased approximately 6-fold in the inflamed region of CD In UC/CD patients • Colonic FPR2/ALX mRNA expression positively associated with histological damage	[134] [98]
Tendon diseases	Protein	IHC	Early-stage diseases compared with healthy controls • FPR2/ALX expression in the tendons ↑ Intermediate-advanced tendons compared with early-stage tendons • FPR2/ALX expression in the tendinopathic supraspinatus ↓	[125]

[a]Outcome of mouse *Fpr2/3* KO is compared with that of wild-type (WT) controls, and clinical outcome of FPR2/ALX dysfunction in different diseases is compared with selected control subjects

CAM chorioamnionitis, *CCL* chemokine ligand, *CD* Crohn's disease, *COX* cyclooxygenase, *DSS* dextran sulfate sodium, *FACS* fluorescence activated cell sorting, *FPR2/ALX* formyl peptide receptor 2, *IBD* inflammatory bowel disease, *IHC* immunohistochemistry, *IL* interleukin, *LPS* lipopolysaccharide, *IR* ischemia reperfusion, *NGAL* neutrophil gelatinase-associated lipocalin, *KO* knockout, *LOX* lipoxygenase, *qPCR* quantitative polymerase chain reaction, *SA* severe asthma, *SNP* single nucleotide polymorphism, *SPMs* specialized pro-resolving mediators, *TNF* tumor necrosis factor, *UC* ulcerative colitis, *WB* Western blotting

Table 3. Characteristics of FPR2/ALX agonists reported in the literature

Agonist	Category	pEC_{50}[a]	Pharmacological action	Reference
LXA4 and AT-LXA4	SPMs	~12.0	Improve mortality of DSS-induced colitis in mice • Through NF-κB • Pro-inflammatory cytokines ↓ • Phagocytic clearance of bacteria ↑	[134, 180]
AT-RvD1, RvD2	SPMs	11.1–11.9	Prevent DSS- or TNBS-induced colitis in mice • Improve colitis symptoms • Epithelial damage ↓ • Macrophage infiltration ↓	[155, 177]
ZK-192	LX mimetic	NA	Protective effects in TNBS-induced colitis in mice	[146]
BML111	LX mimetic	NA	Rescue CD-like intestinal inflammation in COX-2-MKO/CCHF mice	[147]
NAP1051	LX mimetic	NA	Anti-tumor activity in CAC • Inhibit neutrophils • NETosis ↓ • T-cell recruitment in TME ↑	[148]
AnxA1	Endogenous protein	5.8–6.1	Exogenous AnxA1 • Therapeutic effect of anti-TNF ↑ • Th17 cells in mesenteric lymphocyte nodes and colon ↓	[159]
FAM3D	Endogenous protein	NA	FAM3D KO • Spontaneous colitis ↑ • Impaired colonic mucosal integrity • Sensitivity to CAC ↑	[162]
AC2-26	AnxA1 mimetic peptide	5.8–6.1	Interfere with intestinal MC degranulation • Release of MC mediators ↓ • Intestinal allergic inflammation ↓	[160]
4 F and Tg6F	APOA1 mimetic peptide	NA	Rescue intestinal inflammation • CD-like intestinal inflammation in COX-2-MKO/CCHF mice ↓ • Prevent IBD in piroxicam-accelerated *IL-10* KO mice	[147]
WKYMVm	Synthetic peptide	9.0–10.1	Therapeutic effect on DSS-induced UC in mice	[101]

[a]Data of pEC_{50} are from IUPHAR/BPS Guide (https://www.guidetopharmacology.org/) with target as the human FPR2/ALX. *NA* data not available. *AnxA1* annexin A1, *APOA1*, apolipoprotein A-I, *CAC* colitis-associated cancers, *CCHF* cholate-containing high-fat diet, *CD* Crohn's disease, *COX cyclooxygenase*, *DSS* dextran sulfate sodium, *FPR2/ALX* formyl peptide receptor 2, *IBD* inflammatory bowel disease, *IL* interleukin, *KO* knockout, *LX* lipoxin, MC mast cell, *MKO* myeloid knockout, *pEC_{50}* negative logarithm of the concentration for 50% of maximal effect, *RvD* resolvin D series, *SPMs* specialized pro-resolving mediators, *TNBS* 2,4,6-trinitrobenzene sulfonic acid, *TNF* tumor necrosis factor, *UC* ulcerative colitis

ischemia [164, 165], diabetic wounds [166], pneumosepsis [167], and colitis [101]. Other synthetic peptides LESIFRSLLLFRVM (MMK1) [168] and TIPMFVPESTSKLQKFTSWFTSWFM-Amide (CGEN-855A) [169] are also FPR2/ALX agonists exhibiting pro-resolving effects on neutrophil infiltration in an air pouch model.

Small molecule modulators. A number of small molecule FPR2/ALX agonists with promising therapeutic potential have been developed. Their structural types include phenyl urea (compound 17), ureido-propanamide (MR-39), pyridazinone (compound 43), pyridinone/pyrimidindione (compound 47), quinazolinone (Quin-C1), aminotriazole (ACT-389949), pyrrolidinone (BMS-986235), etc. Some of them were evaluated in mouse inflammatory models. Compounds 17 blocked neutrophil infiltration and promoted punch dermal wound healing [170]. MR-39 exerted a pro-resolving action in LPS-stimulated microglia [171]. In myocardial infarction models, compound 43 showed a positive effect on viable myocardium and induced phagocytic resolution [172]. In rat models of RA, compound 47 displayed the potential of decreasing pain hypersensitivity [173]. In addition, Quin-C1 induced FPR2/ALX-mediated intracellular Ca^{2+} mobilization and showed therapeutic efficacy in bleomycin-induced lung injury [174]. Phase I clinical trials are underway with respect to two FPR2/ALX agonists. ACT-389949 was found to be as potent as WKYMVm [175] and relevant trial results of which (NCT02099071 and NCT02099201) showed its safety and tolerability in healthy subjects despite rapid receptor desensitization [117]. Phase I clinical trial of BMS-986235 (NCT03335553) was concluded but the results have not been disclosed. However, BMS-986235 was protective against experimental heart failure [176].

Clinical translation of FPR2/ALX agonism

Given the solid evidence that FPR2/ALX dysfunction is associated with IBD, FPR2/ALX agonists may be used as therapeutic candidates for IBD. Biased FPR2/ALX agonism towards pro-resolution is likely to induce mild-to-moderate suppression of inflammation without immunosuppression, thus suitable to patients intolerant to immunosuppressants or resistant to antibody treatment. Major challenges for clinical translation of the pro-resolving strategy that harnesses FPR2/ALX activation include: (i) receptor desensitization as seen with a few agonists (e.g., ACT-389949); (ii) application of biased signaling property by guiding receptor-mediated response towards pro-resolving outcomes; (iii) available biomarkers to accurately monitor mucosal healing [6]; and (iv) unintended consequences of such a therapeutic approach.

CONCLUSION

Failed resolution of inflammation can underpin the pathogenesis of chronic inflammatory diseases including IBD. Existing data revealed the resolution mechanisms in the early stage (neutrophil functions, cytokines, and SPMs) and intermediate to advanced

stages (efferocytosis and adaptive immunity). Resolution or repair agents for patients with IBD are not available at present but potential therapeutic targets like FPR2/ALX may fill the gap. FPR2/ALX centric pro-resolving strategy will address a key issue on the recurrence of inflammation and mucosal injury in IBD. Ongoing studies cover a variety of FPR2/ALX agonists including lipids, peptides and small molecules. Of which, the latter may offer advantages such as oral bioavailability, easy to use, better compliance, and low cost.

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ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

REFERENCES

1. Chang JT. Pathophysiology of inflammatory bowel diseases. N Engl J Med. 2020;383:2652–64.
2. Kaplan GG, Windsor JW. The four epidemiological stages in the global evolution of inflammatory bowel disease. Nat Rev Gastroenterol Hepatol. 2021;18:56–66.
3. Kaplan GG. The global burden of IBD: From 2015 to 2025. Nat Rev Gastroenterol Hepatol. 2015;12:720–7.
4. Mayberry J. The history of 5-ASA compounds and their use in ulcerative colitis-trailblazing discoveries in gastroenterology. J Gastrointestin Liver Dis. 2013;22:375–7.
5. Chan HC, Ng SC. Emerging biologics in inflammatory bowel disease. J Gastroenterol. 2017;52:141–50.
6. Ho GT, Cartwright JA, Thompson EJ, Bain CC, Rossi AG. Resolution of inflammation and gut repair in IBD: Translational steps towards complete mucosal healing. Inflamm Bowel Dis. 2020;26:1131–43.
7. Amiot A, Peyrin-Biroulet L. Current, new and future biological agents on the horizon for the treatment of inflammatory bowel diseases. Ther Adv Gastroenterol. 2015;8:66–82.
8. Colombel JF, Panaccione R, Bossuyt P, Lukas M, Baert F, Vaňásek T, et al. Effect of tight control management on Crohn's disease (CALM): A multicentre, randomised, controlled phase 3 trial. Lancet. 2017;390:2779–89.
9. Li J, Liu Z, Hu P, Wen Z, Cao Q, Zou X, et al. Indicators of suboptimal response to anti-tumor necrosis factor therapy in patients from china with inflammatory bowel disease: Results from the explore study. BMC Gastroenterol. 2022;22:44.
10. Rogler G. Resolution of inflammation in inflammatory bowel disease. Lancet Gastroenterol Hepatol. 2017;2:521–30.
11. Boal Carvalho P, Cotter J. Mucosal healing in ulcerative colitis: A comprehensive review. Drugs. 2017;77:159–73.
12. Perretti M, Godson C. Formyl peptide receptor type 2 agonists to kick-start resolution pharmacology. Br J Pharmacol. 2020;177:4595–600.
13. Maciuszek M, Cacace A, Brennan E, Godson C, Chapman TM. Recent advances in the design and development of formyl peptide receptor 2 (FPR2/ALX) agonists as pro-resolving agents with diverse therapeutic potential. Eur J Med Chem. 2021;213:113167.
14. Fullerton JN, Gilroy DW. Resolution of inflammation: A new therapeutic frontier. Nat Rev Drug Discov. 2016;15:551–67.
15. Buckley CD, Gilroy DW, Serhan CN, Stockinger B, Tak PP. The resolution of inflammation. Nat Rev Immunol. 2013;13:59–66.
16. Takeuchi O, Akira S. Pattern recognition receptors and inflammation. Cell. 2010;140:805–20.
17. Serhan CN. Discovery of specialized pro-resolving mediators marks the dawn of resolution physiology and pharmacology. Mol Asp Med. 2017;58:1–11.
18. Murakami M, Hirano T. The molecular mechanisms of chronic inflammation development. Front Immunol. 2012;3:323.
19. Panigrahy D, Gilligan MM, Serhan CN, Kashfi K. Resolution of inflammation: An organizing principle in biology and medicine. Pharmacol Ther. 2021;227:107879.
20. Serhan CN. The resolution of inflammation: The devil in the flask and in the details. FASEB J. 2011;25:1441–8.
21. Serhan CN. Pro-resolving lipid mediators are leads for resolution physiology. Nature. 2014;510:92–101.
22. Schett G, Neurath MF. Resolution of chronic inflammatory disease: Universal and tissue-specific concepts. Nat Commun. 2018;9:3261.
23. Perretti M, Leroy X, Bland EJ, Montero-Melendez T. Resolution pharmacology: Opportunities for therapeutic innovation in inflammation. Trends Pharmacol Sci. 2015;36:737–55.
24. Serhan CN. Treating inflammation and infection in the 21st century: New hints from decoding resolution mediators and mechanisms. FASEB J. 2017;31:1273–88.
25. Chiang N, Serhan CN. Structural elucidation and physiologic functions of specialized pro-resolving mediators and their receptors. Mol Asp Med. 2017;58:114–29.
26. Chan SSM. Docosahexanoeic acid and eicosapentaenoic acid in the aetiology of crohn's disease: Data from a European prospective cohort study (EPIC). Gut. 2011;60:A135–6.
27. Ananthakrishnan AN, Khalili H, Konijeti GG, Higuchi LM, de Silva P, Fuchs CS, et al. Long-term intake of dietary fat and risk of ulcerative colitis and Crohn's disease. Gut. 2014;63:776–84.
28. Khalili H, Håkansson N, Chan SS, Chen Y, Lochhead P, Ludvigsson JF, et al. Adherence to a mediterranean diet is associated with a lower risk of later-onset Crohn's disease: Results from two large prospective cohort studies. Gut. 2020;69:1637–44.
29. Bischoff SC, Escher J, Hébuterne X, Kłęk S, Krznaric Z, Schneider S, et al. Espen practical guideline: Clinical nutrition in inflammatory bowel disease. Clin Nutr. 2020;39:632–53.
30. Sugimoto MA, Vago JP, Perretti M, Teixeira MM. Mediators of the resolution of the inflammatory response. Trends Immunol. 2019;40:212–27.
31. Quiros M, Nusrat A. Saving problematic mucosae: Spms in intestinal mucosal inflammation and repair. Trends Mol Med. 2019;25:124–35.
32. Chiang N, Serhan CN, Dahlén SE, Drazen JM, Hay DW, Rovati GE, et al. The lipoxin receptor ALX: Potent ligand-specific and stereoselective actions in vivo. Pharmacol Rev. 2006;58:463–87.
33. Serhan CN, Hamberg M, Samuelsson B. Lipoxins: Novel series of biologically active compounds formed from arachidonic acid in human leukocytes. Proc Natl Acad Sci USA. 1984;81:5335–9.
34. Maderna P, Godson C. Lipoxins: Resolutionary road. Br J Pharmacol. 2009;158:947–59.
35. Doyle R, Godson C, Chapter 5 - endogenous antiinflammatory and proresolving lipid mediators in renal disease. In: Goligorsky MS, Editor Regenerative nephrology (second edition). United States: Academic Press; 2022. 55-67.
36. Serhan CN, Levy BD. Resolvins in inflammation: Emergence of the pro-resolving superfamily of mediators. J Clin Invest. 2018;128:2657–69.
37. Serhan CN, Yang R, Martinod K, Kasuga K, Pillai PS, Porter TF, et al. Maresins: Novel macrophage mediators with potent antiinflammatory and proresolving actions. J Exp Med. 2009;206:15–23.
38. Serhan CN, Petasis NA. Resolvins and protectins in inflammation resolution. Chem Rev. 2011;111:5922–43.
39. Serhan CN, Clish CB, Brannon J, Colgan SP, Chiang N, Gronert K. Novel functional sets of lipid-derived mediators with antiinflammatory actions generated from omega-3 fatty acids via cyclooxygenase 2-nonsteroidal antiinflammatory drugs and transcellular processing. J Exp Med. 2000;192:1197–204.
40. Gilligan MM, Gartung A, Sulciner ML, Norris PC, Sukhatme VP, Bielenberg DR, et al. Aspirin-triggered proresolving mediators stimulate resolution in cancer. Proc Natl Acad Sci USA. 2019;116:6292–7.
41. Chiang N, Sakuma M, Rodriguez AR, Spur BW, Irimia D, Serhan CN. Resolvin t-series reduce neutrophil extracellular traps. Blood. 2022;139:1222–33.
42. Hansen TV, Vik A, Serhan CN. The protectin family of specialized pro-resolving mediators: Potent immunoresolvents enabling innovative approaches to target obesity and diabetes. Front Pharmacol. 2019;9:1582.
43. Bazan NG, Eady TN, Khoutorova L, Atkins KD, Hong S, Lu Y, et al. Novel aspirin-triggered neuroprotectin D1 attenuates cerebral ischemic injury after experimental stroke. Exp Neurol. 2012;236:122–30.
44. Chiang N, Serhan CN. Specialized pro-resolving mediator network: An update on production and actions. Essays Biochem. 2020;64:443–62.
45. Serhan CN, Chiang N, Dalli J. New pro-resolving n-3 mediators bridge resolution of infectious inflammation to tissue regeneration. Mol Asp Med. 2018;64:1–17.
46. Serhan CN, Dalli J, Colas RA, Winkler JW, Chiang N. Protectins and maresins: New pro-resolving families of mediators in acute inflammation and resolution bioactive metabolome. Biochim Biophys Acta. 2015;1851:397–413.
47. Serhan CN, Dalli J, Karamnov S, Choi A, Park CK, Xu ZZ, et al. Macrophage proresolving mediator maresin 1 stimulates tissue regeneration and controls pain. FASEB J. 2012;26:1755–65.

48. Pérez-Figueroa E, Álvarez-Carrasco P, Ortega E, Maldonado-Bernal C. Neutrophils: Many ways to die. Front Immunol. 2021;12:631821.
49. Nathan C. Points of control in inflammation. Nature. 2002;420:846–52.
50. Kolaczkowska E, Kubes P. Neutrophil recruitment and function in health and inflammation. Nat Rev Immunol. 2013;13:159–75.
51. Herrero-Cervera A, Soehnlein O, Kenne E. Neutrophils in chronic inflammatory diseases. Cell Mol Immunol. 2022;19:177–91.
52. Castanheira FVS, Kubes P. Neutrophils and nets in modulating acute and chronic inflammation. Blood. 2019;133:2178–85.
53. He Z, Si Y, Jiang T, Ma R, Zhang Y, Cao M, et al. Phosphotidylserine exposure and neutrophil extracellular traps enhance procoagulant activity in patients with inflammatory bowel disease. Thromb Haemost. 2016;115:738–51.
54. Bennike TB, Carlsen TG, Ellingsen T, Bonderup OK, Glerup H, Bøgsted M, et al. Neutrophil extracellular traps in ulcerative colitis: A proteome analysis of intestinal biopsies. Inflamm Bowel Dis. 2015;21:2052–67.
55. Summers C, Rankin SM, Condliffe AM, Singh N, Peters AM, Chilvers ER. Neutrophil kinetics in health and disease. Trends Immunol. 2010;31:318–24.
56. Wéra O, Lancellotti P, Oury C. The dual role of neutrophils in inflammatory bowel diseases. J Clin Med. 2016;5:118.
57. Boada-Romero E, Martinez J, Heckmann BL, Green DR. The clearance of dead cells by efferocytosis. Nat Rev Mol Cell Biol. 2020;21:398–414.
58. Grunwell JR, Stephenson ST, Tirouvanziam R, Brown LAS, Brown MR, Fitzpatrick AM. Children with neutrophil-predominant severe asthma have proinflammatory neutrophils with enhanced survival and impaired clearance. J Allergy Clin Immunol Pr. 2019;7:516–25.e6.
59. Pletz MW, Ioanas M, de Roux A, Burkhardt O, Lode H. Reduced spontaneous apoptosis in peripheral blood neutrophils during exacerbation of copd. Eur Respir J. 2004;23:532–7.
60. Zhang C, Shu W, Zhou G, Lin J, Chu F, Wu H, et al. Anti-tnf-α therapy suppresses proinflammatory activities of mucosal neutrophils in inflammatory bowel disease. Mediators Inflamm. 2018;2018:3021863.
61. Li Y, Chen J, Bolinger AA, Chen H, Liu Z, Cong Y, et al. Target-based small molecule drug discovery towards novel therapeutics for inflammatory bowel diseases. Inflamm Bowel Dis. 2021;27:S38–62.
62. Soehnlein O, Lindbom L. Phagocyte partnership during the onset and resolution of inflammation. Nat Rev Immunol. 2010;10:427–39.
63. Rőszer T. Understanding the mysterious M2 macrophage through activation markers and effector mechanisms. Mediators Inflamm. 2015;2015:816460.
64. Mao Y. Apoptotic cell-derived metabolites in efferocytosis-mediated resolution of inflammation. Cytokine Growth Factor Rev. 2021;62:42–53.
65. Lauber K, Bohn E, Kröber SM, Xiao YJ, Blumenthal SG, Lindemann RK, et al. Apoptotic cells induce migration of phagocytes via caspase-3-mediated release of a lipid attraction signal. Cell. 2003;113:717–30.
66. Elliott MR, Chekeni FB, Trampont PC, Lazarowski ER, Kadl A, Walk SF, et al. Nucleotides released by apoptotic cells act as a find-me signal to promote phagocytic clearance. Nature. 2009;461:282–6.
67. Truman LA, Ford CA, Pasikowska M, Pound JD, Wilkinson SJ, Dumitriu IE, et al. Cx3cl1/fractalkine is released from apoptotic lymphocytes to stimulate macrophage chemotaxis. Blood. 2008;112:5026–36.
68. Elliott MR, Koster KM, Murphy PS. Efferocytosis signaling in the regulation of macrophage inflammatory responses. J Immunol. 2017;198:1387–94.
69. Segawa K, Nagata S. An apoptotic 'eat me' signal: Phosphatidylserine exposure. Trends Cell Biol. 2015;25:639–50.
70. Gardai SJ, McPhillips KA, Frasch SC, Janssen WJ, Starefeldt A, Murphy-Ullrich JE, et al. Cell-surface calreticulin initiates clearance of viable or apoptotic cells through trans-activation of lrp on the phagocyte. Cell. 2005;123:321–34.
71. Richards DM, Endres RG. The mechanism of phagocytosis: Two stages of engulfment. Biophys J. 2014;107:1542–53.
72. Sévajol M, Reiser JB, Chouquet A, Pérard J, Ayala I, Gans P, et al. The c-terminal polyproline-containing region of ELMO contributes to an increase in the lifetime of the ELMO-dock complex. Biochimie. 2012;94:823–8.
73. Medina CB, Mehrotra P, Arandjelovic S, Perry JSA, Guo Y, Morioka S, et al. Metabolites released from apoptotic cells act as tissue messengers. Nature. 2020;580:130–5.
74. Schittenhelm L, Hilkens CM, Morrison VL. B(2) integrins as regulators of dendritic cell, monocyte, and macrophage function. Front Immunol. 2017;8:1866.
75. Tian L, Choi SC, Murakami Y, Allen J, Morse HC 3rd, Qi CF, et al. P85α recruitment by the CD300f phosphatidylserine receptor mediates apoptotic cell clearance required for autoimmunity suppression. Nat Commun. 2014;5:3146.
76. Bossi F, Tripodo C, Rizzi L, Bulla R, Agostinis C, Guarnotta C, et al. C1q as a unique player in angiogenesis with therapeutic implication in wound healing. Proc Natl Acad Sci USA. 2014;111:4209–14.
77. Boucher P, Herz J. Signaling through lrp1: Protection from atherosclerosis and beyond. Biochem Pharmacol. 2011;81:1–5.
78. Freemerman AJ, Zhao L, Pingili AK, Teng B, Cozzo AJ, Fuller AM, et al. Myeloid slc2a1-deficient murine model revealed macrophage activation and metabolic phenotype are fueled by glut1. J Immunol. 2019;202:1265–86.
79. Waterborg CEJ, Beermann S, Broeren MGA, Bennink MB, Koenders MI, van Lent P, et al. Protective role of the MER tyrosine kinase via efferocytosis in rheumatoid arthritis models. Front Immunol. 2018;9:742.
80. Heckmann BL, Teubner BJW, Tummers B, Boada-Romero E, Harris L, Yang M, et al. Lc3-associated endocytosis facilitates β-amyloid clearance and mitigates neurodegeneration in murine Alzheimer's disease. Cell. 2019;178:536–51.e14.
81. Frasch SC, McNamee EN, Kominsky D, Jedlicka P, Jakubzick C, Zemski Berry K, et al. G2a signaling dampens colitic inflammation via production of ifn-γ. J Immunol. 2016;197:1425–34.
82. Suresh K, Servinsky L, Reyes J, Undem C, Zaldumbide J, Rentsendorj O, et al. CD36 mediates h2o2-induced calcium influx in lung microvascular endothelial cells. Am J Physiol Lung Cell Mol Physiol. 2017;312:L143–53.
83. Li Z, Weinman SA. Regulation of hepatic inflammation via macrophage cell death. Semin Liver Dis. 2018;38:340–50.
84. Liu Z, Davidson A. Taming lupus-a new understanding of pathogenesis is leading to clinical advances. Nat Med. 2012;18:871–82.
85. Lee HN, Tian L, Bouladoux N, Davis J, Quinones M, Belkaid Y, et al. Dendritic cells expressing immunoreceptor CD300f are critical for controlling chronic gut inflammation. J Clin Invest. 2017;127:1905–17.
86. Bosurgi L, Cao YG, Cabeza-Cabrerizo M, Tucci A, Hughes LD, Kong Y, et al. Macrophage function in tissue repair and remodeling requires IL-4 or IL-13 with apoptotic cells. Science. 2017;356:1072–6.
87. Wang W, Qiao Y, Li Z. New insights into modes of gpcr activation. Trends Pharmacol Sci. 2018;39:367–86.
88. Quiros M. Therapeutic opportunities for repair gpcrs during intestinal mucosal wound healing. Trends Mol Med. 2020;26:971–4.
89. Quiros M, Feier D, Birkl D, Agarwal R, Zhou DW, García AJ, et al. Resolvin E1 is a pro-repair molecule that promotes intestinal epithelial wound healing. Proc Natl Acad Sci USA. 2020;117:9477–82.
90. Arnardottir H, Thul S, Pawelzik SC, Karadimou G, Artiach G, Gallina AL, et al. The resolvin D1 receptor GPR32 transduces inflammation resolution and atheroprotection. J Clin Invest. 2021;131:e142883.
91. Chiang N, Dalli J, Colas RA, Serhan CN. Identification of resolvin D2 receptor mediating resolution of infections and organ protection. J Exp Med. 2015;212:1203–17.
92. Kennedy AJ, Davenport AP. International union of basic and clinical pharmacology ciii: Chemerin receptors CMKLR1 (chemerin1) and GPR1 (chemerin2) nomenclature, pharmacology, and function. Pharmacol Rev. 2018;70:174–96.
93. Bang S, Xie YK, Zhang ZJ, Wang Z, Xu ZZ, Ji RR. GPR37 regulates macrophage phagocytosis and resolution of inflammatory pain. J Clin Invest. 2018;128:3568–82.
94. Flak MB, Koenis DS, Sobrino A, Smith J, Pistorius K, Palmas F, et al. Gpr101 mediates the pro-resolving actions of rvd5n-3 dpa in arthritis and infections. J Clin Invest. 2020;130:359–73.
95. Patankar JV, Müller TM, Kantham S, Acera MG, Mascia F, Scheibe K, et al. E-type prostanoid receptor 4 drives resolution of intestinal inflammation by blocking epithelial necroptosis. Nat Cell Biol. 2021;23:796–807.
96. Elder CT, Filiberto AC, Su G, Ladd Z, Leroy V, Pruitt EY, et al. Maresin 1 activates LGR6 signaling to inhibit smooth muscle cell activation and attenuate murine abdominal aortic aneurysm formation. FASEB J. 2021;35:e21780.
97. Saeki K, Yokomizo T. Identification, signaling, and functions of LTB4 receptors. Semin Immunol. 2017;33:30–6.
98. Xu C, Ghali S, Wang J, Shih DQ, Ortiz C, Mussatto CC, et al. CSA13 inhibits colitis-associated intestinal fibrosis via a formyl peptide receptor like-1 mediated hmg-coa reductase pathway. Sci Rep. 2017;7:16351.
99. Trilleaud C, Gauttier V, Biteau K, Girault I, Belarif L, Mary C, et al. Agonist anti-chemr23 mab reduces tissue neutrophil accumulation and triggers chronic inflammation resolution. Sci Adv. 2021;7:eabd1453.
100. Fabisiak A, Fabisiak N, Mokrowiecka A, Malecka-Panas E, Jacenik D, Kordek R, et al. Novel selective agonist of GPR18, PSB-KK-1415 exerts potent anti-inflammatory and anti-nociceptive activities in animal models of intestinal inflammation and inflammatory pain. Neurogastroenterol Motil. 2021;33:e14003.
101. Kim SD, Kwon S, Lee SK, Kook M, Lee HY, Song KD, et al. The immune-stimulating peptide wkymvm has therapeutic effects against ulcerative colitis. Exp Mol Med. 2013;45:e40.
102. Lee HN, Choi YS, Kim SH, Zhong X, Kim W, Park JS, et al. Resolvin D1 suppresses inflammation-associated tumorigenesis in the colon by inhibiting IL-6-induced mitotic spindle abnormality. FASEB J. 2021;35:e21432.
103. Gobbetti T, Dalli J, Colas RA, Federici Canova D, Aursnes M, Bonnet D, et al. Protectin d1n-3 DPA and resolvin D5n-3 DPA are effectors of intestinal protection. Proc Natl Acad Sci USA. 2017;114:3963–8.

104. Qiu S, Li P, Zhao H, Li X. Maresin 1 alleviates dextran sulfate sodium-induced ulcerative colitis by regulating NRF2 and TLR4/NF-kB signaling pathway. Int Immunopharmacol. 2020;78:106018.
105. Ye RD, Boulay F, Wang JM, Dahlgren C, Gerard C, Parmentier M, et al. International union of basic and clinical pharmacology. LXXIII. Nomenclature for the formyl peptide receptor (FPR) family. Pharmacol Rev. 2009;61:119–61.
106. Jeong YS, Bae YS. Formyl peptide receptors in the mucosal immune system. Exp Mol Med. 2020;52:1694–704.
107. Migeotte I, Communi D, Parmentier M. Formyl peptide receptors: A promiscuous subfamily of G protein-coupled receptors controlling immune responses. Cytokine Growth Factor Rev. 2006;17:501–19.
108. Cuomo P, Papaianni M, Capparelli R, Medaglia C. The role of formyl peptide receptors in permanent and low-grade inflammation: Helicobacter pylori infection as a model. Int J Mol Sci. 2021;22:3706.
109. Wenceslau CF, Szasz T, McCarthy CG, Baban B, NeSmith E, Webb RC. Mitochondrial n-formyl peptides cause airway contraction and lung neutrophil infiltration via formyl peptide receptor activation. Pulm Pharmacol Ther. 2016;37:49–56.
110. Tsai YF, Yang SC, Chang WY, Chen JJ, Chen CY, Chang SH, et al. Garcinia multiflora inhibits FPR1-mediated neutrophil activation and protects against acute lung injury. Cell Physiol Biochem. 2018;51:2776–93.
111. Wen X, Xu X, Sun W, Chen K, Pan M, Wang JM, et al. G-protein-coupled formyl peptide receptors play a dual role in neutrophil chemotaxis and bacterial phagocytosis. Mol Biol Cell. 2019;30:346–56.
112. Wang W, Li T, Wang X, Yuan W, Cheng Y, Zhang H, et al. FAM19A4 is a novel cytokine ligand of formyl peptide receptor 1 (FPR1) and is able to promote the migration and phagocytosis of macrophages. Cell Mol Immunol. 2015; 12:615–24.
113. Sun L, Zhou H, Zhu Z, Yan Q, Wang L, Liang Q, et al. Ex vivo and in vitro effect of serum amyloid a in the induction of macrophage M2 markers and efferocytosis of apoptotic neutrophils. J Immunol. 2015;194:4891–900.
114. Liao Q, Ye RD. Structural and conformational studies of biased agonism through formyl peptide receptors. Am J Physiol Cell Physiol. 2022;322:C939–47.
115. Zhang S, Gong H, Ge Y, Ye RD. Biased allosteric modulation of formyl peptide receptor 2 leads to distinct receptor conformational states for pro- and anti-inflammatory signaling. Pharmacol Res. 2020;161:105117.
116. Zhang X, Kim KM. Multifactorial regulation of G protein-coupled receptor endocytosis. Biomol Ther. 2017;25:26–43.
117. Stalder AK, Lott D, Strasser DS, Cruz HG, Krause A, Groenen PM, et al. Biomarker-guided clinical development of the first-in-class anti-inflammatory FPR2/ALX agonist act-389949. Br J Clin Pharmacol. 2017;83:476–86.
118. Maderna P, Cottell DC, Toivonen T, Dufton N, Dalli J, Perretti M, et al. FPR2/ALX receptor expression and internalization are critical for lipoxin A4 and annexin-derived peptide-stimulated phagocytosis. FASEB J. 2010;24:4240–9.
119. Sugimoto MA, Vago JP, Perretti M, Teixeira MM. Mediators of the resolution of the inflammatory response. Trends Immunol. 2019;40:212–27.
120. Birkl D, O'Leary MN, Quiros M, Azcutia V, Schaller M, Reed M, et al. Formyl peptide receptor 2 regulates monocyte recruitment to promote intestinal mucosal wound repair. FASEB J. 2019;33:13632–43.
121. Kim SH, Yang IY, Kim J, Lee KY, Jang YS. Antimicrobial peptide IL-37 promotes antigen-specific immune responses in mice by enhancing Th17-skewed mucosal and systemic immunities. Eur J Immunol. 2015;45:1402–13.
122. Zhang H, Lu Y, Sun G, Teng F, Luo N, Jiang J, et al. The common promoter polymorphism rs11666254 downregulates FPR2/ALX expression and increases risk of sepsis in patients with severe trauma. Crit Care. 2017;21:171.
123. Takano T, Fiore S, Maddox JF, Brady HR, Petasis NA, Serhan CN. Aspirin-triggered 15-epi-lipoxin A4 (LXA4) and LXA4 stable analogues are potent inhibitors of acute inflammation: Evidence for anti-inflammatory receptors. J Exp Med. 1997;185:1693–704.
124. Dufton N, Hannon R, Brancaleone V, Dalli J, Patel HB, Gray M, et al. Anti-inflammatory role of the murine formyl-peptide receptor 2: Ligand-specific effects on leukocyte responses and experimental inflammation. J Immunol. 2010;184:2611–9.
125. Dufton N, Hannon R, Brancaleone V, Dalli J, Patel HB, Gray M, et al. Corrections: Anti-inflammatory role of the murine formyl-peptide receptor 2: Ligand-specific effects on leukocyte responses and experimental inflammation. J Immunol. 2011;186:2684.
126. Chen K, Le Y, Liu Y, Gong W, Ying G, Huang J, et al. A critical role for the g protein-coupled receptor mFPR2 in airway inflammation and immune responses. J Immunol. 2010;184:3331–5.
127. Machado MG, Tavares LP, Souza GVS, Queiroz-Junior CM, Ascenção FR, Lopes ME, et al. The annexin A1/FPR2 pathway controls the inflammatory response and bacterial dissemination in experimental pneumococcal pneumonia. FASEB J. 2020;34:2749–64.
128. Tourki B, Kain V, Pullen AB, Norris PC, Patel N, Arora P, et al. Lack of resolution sensor drives age-related cardiometabolic and cardiorenal defects and impedes inflammation-resolution in heart failure. Mol Metab. 2020;31:138–49.
129. Gavins FN. Are formyl peptide receptors novel targets for therapeutic intervention in ischaemia-reperfusion injury? Trends Pharmacol Sci. 2010;31:266–76.
130. Chen K, Liu M, Liu Y, Yoshimura T, Shen W, Le Y, et al. Formylpeptide receptor-2 contributes to colonic epithelial homeostasis, inflammation, and tumorigenesis. J Clin Invest. 2013;123:1694–704.
131. Gagliardo R, Gras D, La Grutta S, Chanez P, Di Sano C, Albano GD, et al. Airway lipoxin A4/formyl peptide receptor 2-lipoxin receptor levels in pediatric patients with severe asthma. J Allergy Clin Immunol. 2016;137:1796–806.
132. Li A, Zhang L, Li J, Fang Z, Li S, Peng Y, et al. Effect of RvD1/FPR2 on inflammatory response in chorioamnionitis. J Cell Mol Med. 2020;24:13397–407.
133. Orr SK, Butler KL, Hayden D, Tompkins RG, Serhan CN, Irimia D. Gene expression of proresolving lipid mediator pathways is associated with clinical outcomes in trauma patients. Crit Care Med. 2015;43:2642–50.
134. Prescott D, McKay DM. Aspirin-triggered lipoxin enhances macrophage phagocytosis of bacteria while inhibiting inflammatory cytokine production. Am J Physiol Gastrointest Liver Physiol. 2011;301:G487–97.
135. Dakin SG, Martinez FO, Yapp C, Wells G, Oppermann U, Dean BJ, et al. Inflammation activation and resolution in human tendon disease. Sci Transl Med. 2015;7:311ra173.
136. Brennan EP, Cacace A, Godson C. Specialized pro-resolving mediators in renal fibrosis. Mol Asp Med. 2017;58:102–13.
137. Crocetti L, Vergelli C, Guerrini G, Giovannoni MP, Kirpotina LN, Khlebnikov AI, et al. Pyridinone derivatives as interesting formyl peptide receptor (FPR) agonists for the treatment of rheumatoid arthritis. Molecules. 2021;26:6583.
138. Perretti M, Cooper D, Dalli J, Norling LV. Immune resolution mechanisms in inflammatory arthritis. Nat Rev Rheumatol. 2017;13:87–99.
139. Qin CX, May LT, Li R, Cao N, Rosli S, Deo M, et al. Small-molecule-biased formyl peptide receptor agonist compound 17b protects against myocardial ischaemia-reperfusion injury in mice. Nat Commun. 2017;8:14232.
140. Purvis GSD, Solito E, Thiemermann C. Annexin-A1: Therapeutic potential in microvascular disease. Front Immunol. 2019;10:938.
141. Gavins FN, Hughes EL, Buss NA, Holloway PM, Getting SJ, Buckingham JC. Leukocyte recruitment in the brain in sepsis: Involvement of the annexin 1-FPR2/ALX anti-inflammatory system. FASEB J. 2012;26:4977–89.
142. Possebon L, Costa SS, Souza HR, Azevedo LR, Sant'Ana M, Iyomasa-Pilon MM, et al. Mimetic peptide ac2-26 of annexin A1 as a potential therapeutic agent to treat copd. Int Immunopharmacol. 2018;63:270–81.
143. Stama ML, Ślusarczyk J, Lacivita E, Kirpotina LN, Schepetkin IA, Chamera K, et al. Novel ureidopropanamide based n-formyl peptide receptor 2 (FPR2) agonists with potential application for central nervous system disorders characterized by neuroinflammation. Eur J Med Chem. 2017;141:703–20.
144. Weiß E, Kretschmer D. Formyl-peptide receptors in infection, inflammation, and cancer. Trends Immunol. 2018;39:815–29.
145. Tylek K, Trojan E, Regulska M, Lacivita E, Leopoldo M, Basta-Kaim A. Formyl peptide receptor 2, as an important target for ligands triggering the inflammatory response regulation: A link to brain pathology. Pharmacol Rep. 2021;73:1004–19.
146. Fiorucci S, Wallace JL, Mencarelli A, Distrutti E, Rizzo G, Farneti S, et al. A beta-oxidation-resistant lipoxin A4 analog treats hapten-induced colitis by attenuating inflammation and immune dysfunction. Proc Natl Acad Sci USA. 2004;101:15736–41.
147. Meriwether D, Sulaiman D, Volpe C, Dorfman A, Grijalva V, Dorreh N, et al. Apolipoprotein a-i mimetics mitigate intestinal inflammation in COX2-dependent inflammatory bowel disease model. J Clin Invest. 2019;129:3670–85.
148. Dong T, Dave P, Yoo E, Ebright B, Ahluwalia K, Zhou E, et al. NAP1051, a lipoxin A4 biomimetic analog, demonstrates antitumor activity against the tumor microenvironment. Mol Cancer Ther. 2021;20:2384–97.
149. Galvão I, Melo EM, de Oliveira VLS, Vago JP, Queiroz-Junior C, de Gaetano M, et al. Therapeutic potential of the FPR2/ALX agonist AT-01-KG in the resolution of articular inflammation. Pharmacol Res. 2021;165:105445.
150. Hasturk H, Schulte F, Martins M, Sherzai H, Floros C, Cugini M, et al. Safety and preliminary efficacy of a novel host-modulatory therapy for reducing gingival inflammation. Front Immunol. 2021;12:704163.
151. Lee SH, Tonello R, Im ST, Jeon H, Park J, Ford Z, et al. Resolvin D3 controls mouse and human TRPV1-positive neurons and preclinical progression of psoriasis. Theranostics. 2020;10:12111–26.
152. Dalli J, Winkler JW, Colas RA, Arnardottir H, Cheng C-YC, Chiang N, et al. Resolvin D3 and aspirin-triggered resolvin D3 are potent immunoresolvents. Chem Biol. 2013;20:188–201.
153. Siddiqui YD, Omori K, Ito T, Yamashiro K, Nakamura S, Okamoto K, et al. Resolvin D2 induces resolution of periapical inflammation and promotes healing of periapical lesions in rat periapical periodontitis. Front Immunol. 2019;10:307.

154. Serhan CN, Chiang N, Dalli J, Levy BD. Lipid mediators in the resolution of inflammation. Cold Spring Harb Perspect Biol. 2014;7:a016311.
155. Bento AF, Claudino RF, Dutra RC, Marcon R, Calixto JB. Omega-3 fatty acid-derived mediators 17(r)-hydroxy docosahexaenoic acid, aspirin-triggered resolvin D1 and resolvin D2 prevent experimental colitis in mice. J Immunol. 2011;187:1957–69.
156. Hua J, Jin Y, Chen Y, Inomata T, Lee H, Chauhan SK, et al. The resolvin D1 analogue controls maturation of dendritic cells and suppresses alloimmunity in corneal transplantation. Invest Ophthalmol Vis Sci. 2014;55:5944–51.
157. Tang H, Liu Y, Yan C, Petasis NA, Serhan CN, Gao H. Protective actions of aspirin-triggered (17r) resolvin D1 and its analogue, 17r-hydroxy-19-para-fluorophenoxy-resolvin D1 methyl ester, in c5a-dependent igg immune complex-induced inflammation and lung injury. J Immunol. 2014;193:3769–78.
158. Orr SK, Colas RA, Dalli J, Chiang N, Serhan CN. Proresolving actions of a new resolvin D1 analog mimetic qualifies as an immunoresolvent. Am J Physiol Lung Cell Mol Physiol. 2015;308:L904–11.
159. Liu X, Zhou L, Xin W, Hua Z. Exogenous annexin 1 inhibits Th17 cell differentiation induced by anti-tnf treatment via activating FPR2 in dss-induced colitis. Int Immunopharmacol. 2022;107:108685.
160. Oliveira MP, Prates J, Gimenes AD, Correa SG, Oliani SM. Annexin A1 mimetic peptide ac(2-26) modulates the function of murine colonic and human mast cells. Front Immunol. 2021;12:689484.
161. Nazir S, Jankowski V, Bender G, Zewinger S, Rye KA, van der Vorst EPC. Interaction between high-density lipoproteins and inflammation: Function matters more than concentration! Adv Drug Deliv Rev. 2020;159:94–119.
162. Liang W, Peng X, Li Q, Wang P, Lv P, Song Q, et al. FAM3D is essential for colon homeostasis and host defense against inflammation associated carcinogenesis. Nat Commun. 2020;11:5912.
163. Corminboeuf O, Leroy X. FPR2/ALXR agonists and the resolution of inflammation. J Med Chem. 2015;58:537–59.
164. Heo SC, Kwon YW, Jang IH, Jeong GO, Yoon JW, Kim CD, et al. Wkymvm-induced activation of formyl peptide receptor 2 stimulates ischemic neovasculogenesis by promoting homing of endothelial colony-forming cells. Stem Cells. 2014;32:779–90.
165. Choi YH, Heo SC, Kwon YW, Kim HD, Kim SH, Jang IH, et al. Injectable plga microspheres encapsulating wkymvm peptide for neovascularization. Acta Biomater. 2015;25:76–85.
166. Kwon YW, Heo SC, Jang IH, Jeong GO, Yoon JW, Mun JH, et al. Stimulation of cutaneous wound healing by an FPR2-specific peptide agonist wkymvm. Wound Repair Regen. 2015;23:575–82.
167. Horewicz VV, Crestani S, de Sordi R, Rezende E, Assreuy J. FPR2/ALX activation reverses lps-induced vascular hyporeactivity in aorta and increases survival in a pneumosepsis model. Eur J Pharmacol. 2015;746:267–73.
168. Klein C, Paul JI, Sauvé K, Schmidt MM, Arcangeli L, Ransom J, et al. Identification of surrogate agonists for the human FPRL-1 receptor by autocrine selection in yeast. Nat Biotechnol. 1998;16:1334–7.
169. Hecht I, Rong J, Sampaio AL, Hermesh C, Rutledge C, Shemesh R, et al. A novel peptide agonist of formyl-peptide receptor-like 1 (ALX) displays anti-inflammatory and cardioprotective effects. J Pharmacol Exp Ther. 2009;328:426–34.
170. Viswanath V, Beard RL, Donello JE, Hsia E, inventors. Use of agonists of formyl peptide receptor 2 for treating dermatological diseases. WOS/2014/138046. 2014.
171. Trojan E, Tylek K, Schröder N, Kahl I, Brandenburg LO, Mastromarino M, et al. The n-formyl peptide receptor 2 (FPR2) agonist mr-39 improves ex vivo and in vivo amyloid beta (1-42)-induced neuroinflammation in mouse models of Alzheimer's disease. Mol Neurobiol. 2021;58:6203–21.
172. García RA, Ito BR, Lupisella JA, Carson NA, Hsu MY, Fernando G, et al. Preservation of post-infarction cardiac structure and function via long-term oral formyl peptide receptor agonist treatment. JACC Basic Transl Sci. 2019;4:905–20.
173. Crocetti L, Vergelli C, Guerrini G, Cantini N, Kirpotina LN, Schepetkin IA, et al. Novel formyl peptide receptor (FPR) agonists with pyridinone and pyrimidindione scaffolds that are potentially useful for the treatment of rheumatoid arthritis. Bioorg Chem. 2020;100:103880.
174. He M, Cheng N, Gao WW, Zhang M, Zhang YY, Ye RD, et al. Characterization of Quin-C1 for its anti-inflammatory property in a mouse model of bleomycin-induced lung injury. Acta Pharmacol Sin. 2011;32:601–10.
175. Lind S, Sundqvist M, Holmdahl R, Dahlgren C, Forsman H, Olofsson P. Functional and signaling characterization of the neutrophil FPR2 selective agonist act-389949. Biochem Pharmacol. 2019;166:163–73.
176. García RA, Lupisella JA, Ito BR, Hsu MY, Fernando G, Carson NL, et al. Selective FPR2 agonism promotes a proresolution macrophage phenotype and improves cardiac structure-function post myocardial infarction. JACC Basic Transl Sci. 2021;6:676–89.
177. Krishnamoorthy S, Recchiuti A, Chiang N, Yacoubian S, Lee C-H, Yang R, et al. Resolvin D1 binds human phagocytes with evidence for proresolving receptors. Proc Natl Acad Sci USA. 2010;107:1660–5.
178. Deyama S, Shimoda K, Suzuki H, Ishikawa Y, Ishimura K, Fukuda H, et al. Resolvin E1/E2 ameliorate lipopolysaccharide-induced depression-like behaviors via chemr23. Psychopharmacology. 2018;235:329–36.
179. Loynes CA, Lee JA, Robertson AL, Steel MJ, Ellett F, Feng Y, et al. Pge(2) production at sites of tissue injury promotes an anti-inflammatory neutrophil phenotype and determines the outcome of inflammation resolution in vivo. Sci Adv. 2018;4:eaar8320.
180. Gewirtz AT, Collier-Hyams LS, Young AN, Kucharzik T, Guilford WJ, Parkinson JF, et al. Lipoxin a4 analogs attenuate induction of intestinal epithelial proinflammatory gene expression and reduce the severity of dextran sodium sulfate-induced colitis. J Immunol. 2002;168:5260–7.