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# Developmental and homeostatic signaling transmitted by the G-protein coupled receptor FPR2

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## Abstract

Formyl peptide receptor 2 (FPR2) and its mouse counterpart Fpr2 are the members of the G protein-coupled receptor (GPCR) family. FPR2 is the only member of the FPRs that interacts with ligands from different sources. FPR2 is expressed in myeloid cells as well as epithelial cells, endothelial cells, neurons, and hepatocytes. During the past years, some unusual properties of FPR2 have attracted intense attention because FPR2 appears to possess dual functions by activating or inhibiting intracellular signal pathways based on the nature, concentration of the ligands, and the temporal and spatial settings of the microenvironment in vivo, the cell types it interacts with. Therefore, FPR2 controls an abundant array of developmental and homeostatic signaling cascades, in addition to its “classical” capacity to mediate the migration of hematopoietic and non-hematopoietic cells including malignant cells. In this review, we summarize recent development in FPR2 research, particularly in its role in diseases, therefore helping to establish FPR2 as a potential target for therapeutic intervention.

## Contribution to the field

FPR2 controls an abundant array of developmental and homeostatic signaling cascades, in addition to its capacity to mediate the migration of hematopoietic and non-hematopoietic cells including malignant cells. During the past years, some unusual properties of FPR2 have attracted intense attention. In this paper we summarized FPR2-mediated signals and latest development such as dual functions by activating or inhibiting intracellular pathways, crosstalk with other G protein-coupled receptors (GPCRs), the hematopoietic stem/progenitor cell differentiation. In the light of great challenges posed by inflammatory diseases and inflammation related cancer, further

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understanding pathophysiology of FPR2 and ligands should assist in the design of therapeutic agents.

**Keywords**

FPR2; Ligands; Pro-inflammation; anti-inflammation; Crosstalk; Macrophage polarity; Homeostasis

## 1. Overview of FPR family

Formyl peptide receptor 2 (FPR2) and its mouse counterpart Fpr2 often referred to as FPR2/ALX since it binds lipoxin A4 (1). FPR2 belongs to the formylpeptide receptor (FPR) subfamily of G-protein-coupled chemoattractant receptors (GPCRs) (2). Although there are three types of human FPRs (FPR1, FPR2, and FPR3) and eight types of murine FPRs (Fpr1, Fpr2, Fpr3 (Fpr-rs1), and Fpr-rs3 to 7), the research work on mouse Fprs has been focused mostly on Fpr1 and Fpr2, which are widely expressed in mouse myeloid cells, epithelial cells, endothelial and show high similarity to both human FPR1 and FPR2 (3–5). In addition, the sequence of mouse Fpr2 is similar to human FPR2 and FPR3 (6), and mouse Fpr2 interacts with F2L (a naturally occurring acylated peptide derived from the N-terminal sequence of heme-binding protein 1) (7), which is a potent agonist for human FPR3 (8).

Although both FPR1 and FPR2 are expressed in bone marrow, gastrointestinal (GI) tract, skin, appendix, spleen, FPR1 is most highly expressed in lung, testis, epididymis, heart muscle, skeletal muscle, lymph node and tonsil (ENSG00000171051-FPR1), and FPR2 is highly expressed in brain, liver, pancreas, placenta, endocrine glands (ENSG00000171049-FPR2) (9).

Both FPR1 and FPR2 recognize same ligands, however, FPR1 prefers to bind short peptides with flexible structures, such as the Gram-negative bacterial peptide fMLF (10). In contrast, FPR2 interacts with all types of ligands of FPRs (10,11). Functionally, FPR1 and FPR2 share overlapping functions such as migration of myeloid cells because they recognize some of the same ligands. Recently, FPR2 has been highlighted other functions, including calcium efflux, clearance of invading bacteria, pro-resolving properties, and multiple roles in diseases and the ability to mediate several unique biological effects which may be traced to different agonists-binding different domains (12). This uniqueness of FPR2 function is associated with its recognition of ligands of diverse origin (4,9). In this review, we summarize the findings on signaling cascades triggered by FPR2 ligands in different cell types as well as on the cross-link between FPR2 and other receptors.

## 2. FPR2 ligands and signaling pathways

### 1). FPR2 ligands

Unlike FPR1, FPR2 exhibits complex and diverse biological activity because it is activated by various types of endogenous ligands including peptides, proteins, and lipid mediators, thereby displays diverse expression patterns on myeloid cells and other cell types (1). Many host-derived ligands of FPR2 are associated with multiples human diseases (4). According

to the source, FPR2 ligands can be divided natural ligands including pathogen-derived, host-derived, and synthetic ligands including synthetic peptides and small molecule compounds (10,11).

**A**). In pathogen-derived FPR2 ligands (Table 1), the staphylococcal-derived Phenol-soluble modulins (PSMs) is the most prominent (13). There are also other bacteria-derived FPR2 ligands derived from *Listeria monocytogenes* (14), *Enterococcus faecium* (15), and *Helicobacter pylori* (16,17) and *Streptococcus pneumoniae* (18,19) as well as *Escherichia coli*-derived peptide N-formylmethionyl-leucyl-phenylalanine (fMLP) peptide (20,21). Interestingly, human immunodeficiency virus (HIV) envelop protein may release FPR2 ligands including T21/DP107, F peptide and V3 peptide (22–24), but whether these peptides are indeed released by HIV or due to the present of potential ligand domains remains to be determined.

**B**). In host derived ligands (Table 2), both fMMYALF and Mitocryptide-2 come from mitochondria of broken cells (25–27). LL-37 (Mouse CRAMP), an antimicrobial peptide (AMP) is released by myeloid and epithelial cells (28). FAM3D is mainly produced by gut epithelial cells (29). Other host derived FPR2 ligands include Aβ42 (30) which is associated with Alzheimer's disease. Ac2–26 derived from annexin A1 is related with inflammatory responses (31). Serum amyloid A (SAA) presents in the sera of patient with inflammation or auto immune diseases (20). Lipoxin A4 (LXA4), an endogenous lipoxygenase-derived eicosanoid mediator, has potent dual pro-resolving and anti-inflammatory properties (20,32,33). Other host derived FPR2 ligands include 15epi-lipoxin A4/ aspirin-triggered lipoxin (ATL) (34) and Resolvin D1 and aspirin-triggered RvD1 (35).

**C**). In synthetic FPR2 ligands (Table 3), W-peptides (36) include WKYMVm and WKYMVm-NH2. W-peptides induces Ca2+ mobilization responses in leukocytes by FPR1 and FPR2 (37). W-peptides has the capacity of anti-inflammation in most inflammatory diseases by increasing the chemotaxis of phagocytes and regulating the secretion of inflammatory factors and promote angiogenesis (38). Other synthetic peptides include MMK-1 (39), CGEN-866A (40) and MMHWAM (41), P2Y2PalIC2 pepducin (42).

**D**). Small molecule compounds as FPR2 ligands (Table 4) are synthetic non-peptide compounds include FPR2 agonists and antagonists with a wide range of chemical diversity. The strategy for design of non-peptide FPR ligands has not been using the chemical structure of FPR2 endogenous ligands, but by high-throughput screening (HTS), structure–activity relationship SAR analysis, and computer-aid drug design (43). The quinazolinone derivative Quin-C1 is one of small molecule compounds as FPR2 ligands, which reduces inflammatory cytokines and clears neutrophils and lymphocytes in murine models of lung injury (44). Compound 17b (Cmpd17b) is another small molecule compound as a FPR2 ligand, which is demonstrable as superior cardioprotection in both in vitro (cardiomyocytes and cardiofibroblasts) and MI injury in mice in vivo (45). Other small molecule compounds include Compound (S)-17 (46), Chiral pyridazines (47), PD176252 and PD168368 (48).

### 2). FPR2-mediated signaling pathways

FPR2 on myeloid cells stimulated by the ligands exhibits dissociation of heterotrimeric G proteins into α and βγ subunits, thereby to activate downstream signaling pathways involved in antimicrobial responses, the recruitment of immune cells to infection sites, phagocytosis of invading pathogen and tissue debris, the release of antimicrobial products such as reactive oxygen species and antimicrobial peptides (AMPs). LL-37 or its mouse counterpart CRAMP is one kind of AMPs and produced in response to bacterial infection (28). FPR2-mediated signaling pathways have been demonstrated by using *FPR2*$^{-/-}$ mouse models, as well as in ex vivo tests with *FPR2*$^{-/-}$ primary mouse leukocytes and FPR2 gene silenced human leukocytes (Fig. 1).

## 3. Biased allosteric modulation of FPR2 leads to distinct receptor conformational states

In the FPR subfamily of GPCRs, FPR2 is particularly amenable to biased agonism (1). Because FPR2 can recognize a variety of ligands with different chemical and physical feature (9) and is expressed on diverse types of cells, FPR2 can modulate divergent cellular responses such as pro- and anti-inflammatory responses.

### 1). Two endogenous ligands compete for FPR2, regulating both pro- and anti-inflammatory processes

Serum amyloid A (SAA) or LXA4 exhibit the opposing effects of on FPR2 in human fibroblast-like synoviocytes. SAA promotes the production of metalloproteinase-1 and -3 (MMP-1 and MMP-3) and upregulates NF-κB and AP1 DNA binding activity. While LXA4 induces the production of tissue inhibitors of metalloproteinase-2 (TIMP-2) to inhibit NF-κB and AP1 DNA binding activity. Thus, two endogenous FPR2 ligands targeting a common receptor, regulate both pro- and anti-inflammatory processes (49–51). Endogenous $A\beta_{42}$ is a FPR2 ligand and possesses proinflammatory activities including inflammatory cell recruitment, production of inflammatory cytokines, degranulation, and superoxide (52,53). Synthetic WKYMVm (W-pep) is also an agonist of FPR2 and plays an anti-inflammatory role in most inflammatory diseases by increasing the chemotaxis of phagocytes and regulating the secretion of inflammatory factors (38). Other FPR2 ligands such as AnxAI and its N-terminal peptide ($Ac_{2–26}$) and $LXA_4$ are FPR2 ligands with anti-inflammatory property (33,54). Thus, FPR2 modulates both pro- and anti-inflammatory response by interacting with ligands with different properties.

### 2). FPR2 homologous desensitization

Methicillin-resistant *Staphylococcus aureus* secretes PSMa2 and PSMa3 which activate neutrophils to increase the cytosolic concentration of $Ca^{2+}$ and release NADPH oxidase–derived reactive oxygen species through FPR2, respectively (13). However, FPR2 homologous desensitization is induced by PSMa2 or PSMa3 stimulation, resulting in actin polymerization and reactivation of neutrophils (13). *Fpr2*$^{-/-}$ mice showed that lower numbers of infiltrating leukocytes in peritoneal cavity after intraperitoneal infection with *S. aureus* (55), indicating the relationship of FPR2 and PSMa.

### 3). FPR2 conformation status

FPR2 can form homodimers or heterodimers with FPR1 based on the nature of FPR2 ligands (54), which confer texture to agonist signaling in different cell-types. the anti-inflammatory and pro-resolving agonists ANXA1, compound 43, Ac-ANXA1 (2–26) and LXA4, promote FPR1-FPR2 heterodimerization (1,5,54). In contrast, the pro-inflammatory ligand serum amyloid A (SAA) and the FPR1 antagonists cyclosporin H (CsH) and WRW4, a FPR2 antagonist, have no significant effect on FPR1-FPR2 heterodimerization (1). AnxA1 and LXA4 promote FPR2 homodimerization, but FPR2 homodimerization will be decreased in the presence of serum amyloid A (SAA) (1). Studies revealed that function shifting of FPR2 depends on its conformation status. LXA4 binding to FPR2 causes conformational change of the receptor, preventing other ligands, e.g., amyloid β or SAA from binding to FPR2 or forcing pro-inflammatory ligands to detach from the receptor to exert anti-inflammatory effects (11,52,54). In addition, the anti-inflammatory activity of LXA4 is associated with the inhibition of the NF-κB and AP-1 translocation, up-regulation of the receptor nuclear factor erythroid 2-related factor 2 (Nrf2), increased level of mRNA for cytokine signaling suppressors (SOCS) and peroxisome proliferator-activated receptor gamma (PPARγ), therefore, suppressing the transcription and expression of pro-inflammatory genes (56–58). Thus, ligand-dependent FPR2 conformational changes determines FPR2 function and biological activity of cells where FPR2 is expressed (59). Physically, protein and lipid FPR2 ligands bind to different domains of FPR2. For example, SAA interacts with the protein binding domain of FPR2, while LXA4 binds the lipid binding domain of FPR2 (49–51). SAA bind to the NH2-terminal domain or 1st two extracellular loops, in contrast, LXA4 binds at 7TM and 3rd extracellular loop of the receptor (5,59), (Fig. 2).

Recent studies further revealed that aspirin-triggered 15-epi-lipoxin A4 (ATL) and Ac2–26 could induce FPR2 conformational changes in a concentration-dependent manner. By a dual regulatory mechanism, ATL and Ac2–26 exerts anti-inflammatory effects through FPR2 (52,60).

Although the mechanism for FPR2 to control both pro- and anti-inflammatory signals is not fully understood, the unusual properties of FPR2 by switching from a pro-inflammatory to anti-inflammatory response make FPR2 in the unique position in host homeostatic and disease control (5,43,61), meanwhile, understanding how FPR2 operates in a cell-specific manner can guide the development of its ligands as new therapeutics for several diseases (61).

## 4. Crosstalk of FPR2 with other receptors

### 1). FPR2 activation and desensitization

Synthetic peptides derived from putative HIV envelope protein sequences, V3 (24), N36 (62), and T21/DP107 (22) activated FPR2 in myeloid cells to induce cell calcium mobilization and migration. The activation of FPR2 by F, V4 and N36 peptides in monocytes downregulated CCR5 and CXCR4 expression based on a protein kinase C

(PKC)-dependent manner, indicating that FPR2 activation may lead to desensitization of cell response to other chemoattractant using GPCRs (23,24,62).

### 2). Crosstalk of FPR2 with TLRs

Bacterial lipopolysaccharide (LPS) by activating TLR4 up-regulates the function of Fpr2 in mouse microglial cells (63), which are major phagocytic cells in the brain and related with inflammation and neurodegenerative diseases (64,65). Other TLRs such as TLR2 (66) is activated by peptidoglycan (PGN) derived from Gram-positive bacterium *Staphylococcus aureus* or polyinosine–polycytidylic acid (Poly(I:C)); TLR3 and TLR7 (67) activated by Imiquimod (R837). Activation of TLR2, TLR3 and TLR7 markedly increased chemotaxis of microglial cells in response to Fpr2 agonists, and enhanced FPR2-mediated uptake of Aβ42 by microglial cells through ERK1/2 and p38 MAPK signaling pathways (66,67). Blockage of TLRs such as TLR2 in microglial cells by short interfering RNA attenuated the functional FPR2 expression stimulated by TLR2 ligands (66). These observations indicate a close control of FPR2 expression and function by TLRs. In LPS-induced acute lung injury (ALI), macrophages in lung tissues showed increased FPR2 expression (68). *Fpr2*$^{-/-}$ macrophages significantly decreased LPS-induced inflammatory responses (68). *Fpr2*$^{-/-}$ mice showed reduced inflammatory responses to LPS challenge and attenuated damage to lung tissues (68).

### 3). Crosstalk of Fpr2 with proinflammatory cytokines

Aside LPS, TNF-α has also been shown to increase Fpr2 expression. TNF-α is the prime mediator of the inflammatory response seen in sepsis and septic shock (69). In the mouse model of nonlethal polymicrobial sepsis obtained by cecal ligature and puncture (CLP), *Fpr2/3*$^{-/-}$ mice exhibited higher sensitivity to polymicrobial sepsis (70), reduced recruitment of monocytes into the peritoneal cavity where the bacterial clearance was impaired and there was higher level of TNF-α (70). TNF-α was able to increase Fpr2 expression in mouse macrophages and FPR2 expression in human primary blood monocytes (70). TNF-α also induced Fpr2 expression in mouse microglia, one of phagocytic cells in the CNS (71). IL-4 inhibited Fpr2 expression induced by TNF-α (71), in contrast, IL-10 enhanced Fpr2 expression on TNFα-activated microglia (72). Since IL-4, IL-10 and TNF-α are produced in the CNS under pathophysiological conditions, Fpr2 expression controlled by proinflammatory cytokines may play an important role in the maintenance of CNS homeostasis.

### 4). Crosstalk of FPR2 with HGF receptor (c-Met)

The synthetic hexapeptide WKYMVm (W-peptide) (38) activated FPR2 to induce crosstalk with hepatocyte growth factor (HGF) receptor in human prostate epithelial cells (73). HGF receptor, also known as c-Met tyrosine kinase receptor (c-Met), interacts with HGF (74). W-peptide-induced FPR2 activation and the downstream signaling cascade (73) resulted in NADPH oxidase-dependent superoxide generation, which induces the phosphorylation of multifunctional residues of c-Met and triggers responses of downstream signal pathways such as STAT3, PLC-c1/PKCa and PI3K/Akt pathways. In the crosstalk between FPR2 and c-Met, NADPH oxidase-dependent superoxide generation plays a critical role because blockade of NADPH oxidase function prevents c-Met trans-phosphorylation induced by

FPR2. The molecular event associated with crosstalk between FPR2 and c-Met in human prostate epithelial cells is illustrated in Fig. 3.

### 5). Crosstalk of FPR2 with EGFR

Lung cancer cell line CaLu-6 cells and human lung cancer tissues express FPR2 (73,75) which is activated by W-peptide, leading the heterotrimeric G proteins dissociated into Gα and Gβγ subunits that activates PLCγ, PKCα and PKCγ. FPR2 activation leads superoxide generation by NADPH oxidase and p47phox phosphorylation and c-Src kinase to induce EGFR phosphorylation on its tyrosine residues, thereby promoting CaLu-6 cell growth (76). EGFR phosphorylation induced by W-peptide-FPR2 interaction can be prevented by the FPR2 antagonist WRW4, or a GPCR inhibitor pertussis toxin (PTX), or by the c-Src inhibitor PP2. Like FPR2 crosstalk with c-Met, NADPH oxidase-dependent superoxide generation plays a critical role in the crosstalk of FPR2 and EGFR (Fig. 4). These results also demonstrated FPR2 activation links with c-Met and EGFR activation.

## 5. Signal relay of FPR2 with other cell surface receptors

During infection or inflammation, myeloid cells are recruited to the diseased sites by signals sequentially relayed through multiple GPCRs in which FPR2 plays an important role.

### 1). FPR2 and Cxcr2 sequentially mediate neutrophil recruitment at site of bacterial infection.

*Staphylococcus aureus*-derived phenol-soluble modulin (PSM) peptides are efficient ligands for FPR2 (13). Intraperitoneal infection in *Fpr2*$^{-/-}$ mice with *S. aureus* resulted in lower numbers of infiltrating neutrophils while are normally recruited by the chemokine CXCL2, indicating that *Fpr2*$^{-/-}$ neutrophils failed to recognize PSM, but response to CXCL2 (55). *Listeria monocytogenes* produces FPR2 ligand fMIVIL (14). The infection of *L. monocytogenes* results in febrile gastroenteritis, fetal abortion, perinatal infection, and systemic infections (77). Fpr1-, Fpr2-, Frp1/2-deficient mice infected with *L. monocytogenes* showed higher mortality and increased Listeria load and reduced neutrophil accumulation in the liver (17). The mechanism study revealed that the neutrophils were rapidly recruited and accumulated in the liver of Wide type (WT) mice infected with *L. monocytogenes*. In contrast, the neutrophil recruitment and accumulation was markedly reduced in the liver of Fpr1-, Fpr2-, Frp1/2-deficient mice infected with *L. monocytogenes* and accompanied by a more rapid mortality (17). Thus, Fpr1 and Fpr2 play an important role in host defense against early *L. monocytogenes* infection through starting up early wave of neutrophil recruitment and accumulation in infected liver for elimination of invading pathogen.

Another study reported that chemokine receptor Cxcr2 may mediate the next wave of neutrophil recruitment (78). *Fpr2*$^{-/-}$ mice with infected with *Streptococcus agalactiae*, which cause pneumonia, meningitis, and bacteremia, death of newborns (79), showed decreased neutrophil recruitment, and bactericidal ability, and increased mortality (78). Fpr2 activation up-regulated key downstream signal molecules and increased chemokines Cxcl1/2 production and interacted with Cxcr2 to mediate neutrophil recruitment (78). *Cxcl1/2*$^{-/-}$

mice showed impaired host's ability to defend against *S. agalactiae* infection, indicating that Fpr2-Cxcr2 may mediate neutrophil recruitment against *S. agalactiae* infection by signal sequentially relay.

### 2). Signal relay of CCR2-FPR2-CCR7 in dendritic cell trafficking

In mouse model of ovalbumin (OVA)-induced lung inflammation, the chemokine CCL2 plays an important role for the migration of immature dendritic cells (DCs) from BM to the circulation and subsequent trafficking into the regions around blood vessels in the lung because *Ccr2*$^{-/-}$ mice showed reduced accumulation of DCs around perivascular area thereby reduced Th2 responses (80–83). Fpr2 interacted with its ligand CRAMP mediated DC trafficking from perivascular area to peribrochiolar regions inside the inflamed lungs as the allergy progresses (84) because *Fpr2*$^{-/-}$ mice showed reduced recruitment of CD11c$^{+}$ DCs into peribronchiolar regions and *CRAMP*$^{-/-}$ mice showed that DCs was trapped around the blood vessels and failed to migrate to peribrochiolar regions (84). *Ccr2*$^{-/-}$, *Fpr2*$^{-/-}$, and *CRAMP*$^{-/-}$ mice showed reduced OVA-induced allergic airway inflammation associated with diminished recruitment of CD11c$^{+}$ DCs into peribronchiolar regions of the inflamed lung with reduced Type 2 immune responses (84). These results establish a paradigm of sequential DC trafficking from bone marrow-circulation-lung perivascular area-peribronchiolar regions to local lymph nodes through signal relay initiated by CCR2 followed by Fpr2 and CCR7 to complete the journey of DCs to LN for Th2 priming.

## 6. FPR2 and macrophage polarity

Macrophages are important members of the innate immune response and present in every human tissue and exhibit functional diversity (85).

Macrophages are identified based on their markers into M0, M1 and M2 (86). M0 macrophages is a group of origin macrophages which can polarize into specific macrophage subtypes (87). M1 macrophages are the group of differentiated macrophages which possess the capacity of production of pro-inflammatory cytokines, protection against pathogen and microbicidal effects (88). M2 macrophages are a group of anti-inflammatory macrophages that participate in tissue remodeling, angiogenesis, and allergic responses and activation of T-helper type-2 but inhibition of Th1 responses (86,88–92).

In tumor microenvironment (TME), cancer cells directly control the differentiation and polarization of tumor-associated macrophages (TAMs) (86,93). The M1/M2 phenotypic ratio changes presents the status of cancer progresses. M1 macrophages possess anti-tumor properties, while M2 macrophages contribute tumor development (86). M1 macrophages were accounted for the majority in the early state of tumor development, but as cancer cells expand, the M2 macrophage population drastically increases. Malignant tumor cells can secrete M2-like cytokines such as IL-10, CCL2/3/4/5/7/8, CXCL12, VEGF, and platelet derived growth factor (PDGF) to recruit more monocytes and M0 macrophages to the TME and differentiate into the M2 phenotype (86,94).

### 1). FPR2 and M1 macrophages in Lewis lung carcinoma (LLC)

Lewis lung cancer (LLC) is a spontaneously developed epidermoid carcinoma in the lung of mice and expresses Fpr2 (38,95). *Fpr2*$^{-/-}$ mice exhibited significantly increased mortality due to more rapidly growing tumors after subcutaneously implanted LLC cells. In contrast, in Fpr2-transgenic mice significantly increased survival because tumors grew more slowly after subcutaneously implanted LLC cells (96). The mechanistic study revealed that *Fpr2*$^{-/-}$mouse macrophages expressed higher level of chemokine receptor CCR4 to increase chemotaxis in response to CCR4 ligand CCL2 secreted by LLC cells (96). TAMs isolated from *Fpr2*$^{-/-}$ mice showed decreased expression of M1 but increased M2 markers. the ratio of M2/M1 macrophages is increased in LLC tumors grown in *Fpr2*$^{-/-}$ mice (96). Therefore, Fpr2 controls macrophages in an M1 phenotype against tumor development.

### 2). FPR2 and M2 macrophages in ovarian cancer

Ovarian cancer cells overexpress FPR2 and produce Th2 cytokines to induce macrophages in tumor microenvironment (TME) to differentiate into an M2 phenotype (97). Meanwhile, ovarian cancer cells overexpressing FPR2 with significantly increased RhoA expression. RhoA is a member of the Rho family small GTPases and is involved with cell proliferation, survival and FPR signals (97,98). RhoA inhibitor (C3 transferase) impairs ovarian cancer cell migration and stimulates ovarian cancer cells to produce Th1 cytokines, which induce macrophages in TME to differentiate into an M1 phenotype (97). FPR2 knockdown in ovarian cancer cells inhibited the invasion and migration of ovarian cancer cells (99). These studies indicate that FPR2 is related with M2 macrophage polarization in TME and the invasion and metastasis of ovarian cancer cells.

### 3). FPR2 and M2 macrophages in prostate cancer

LL-37 is an endogenous ligand for FPR2 (28) and is overexpressed in primary prostate cancer and its metastatic tumor focuses (100). By comparison of tumor growth between mouse prostate cancer cells with and without the expression of CRAMP, a mouse counterpart of LL-37, (TRAMP-C1 and TRAMP-C1CRAMP-sh, respectively) in immunocompetent mice, *CRAMP*$^{-/-}$ TRAMP-C1CRAMP-sh tumor cells significantly delayed growth as compared with *CRAMP*$^{+/+}$ TRAMP-C1 tumor cells, indicating that CRAMP promote prostate cancer cell growth (100–102). CRAMP mediated immune cell recruitment to the CRAMP-enriched tumor microenvironment (TME) in vivo. This recruitment of immature myeloid progenitors (IMPs) can be blocked by an FPR2 antagonist WRWWWW (WRW4) (101,102). In CRAMP-enriched TME, CRAMP upregulated FPR2 expression in prostate cancer cells and overproduction of M-CSF and MCP-1 through NF-kB and STAT3 activation (102). CRAMP stimulates immature macrophages to differentiate into M2 macrophages (102).This process is depicted in Fig. 5.

### 4). FPR2 and M2 macrophages in myocardial Infarction

Dysregulated and unresolved inflammation is an important cause for the heart failure and mortality following myocardial infarction (MI) (103). In rat and mouse model, a FPR2 ligand BMS-986235 was able to improve post-MI healing and preserves heart function (104,105). BMS-986235 treatment significantly increased number of M2 macrophages

expressing CD206 in infarcted hearts. Meanwhile, BMS-986235 treatment reduced the number of total neutrophils (105), enhanced neutrophil apoptosis and upregulation FPR2 expression in macrophages (105). M2 macrophages with high CD206 expression mediate clearance of proinflammatory glycoproteins such as myeloperoxidase and apoptotic neutrophils (105,106).

Therefore, interaction of BMS-986235 with FPR2 is able to improve post-MI healing and preserves heart function.

### 5). FPR2 and M2 macrophages in muscle regeneration

Annexin-A1 (ANXA1) is a phospholipid-binding protein and widely expressed in leukocytes, lymphocytes, epithelial cells, and endothelial cells (107). Annexin-A1 interacts with FPR2 to mediate biological effects on many cells such as inflammatory resolution, promoting neutrophil apoptosis, non-phlogistic monocyte recruitment, and macrophage efferocytosis (108,109). Human PBMC– derived macrophages treated with human recombinant Annexin-A1 (hrANXA1) exhibited significant reduction in expression of the M1 marker protein major histocompatibility complex II (MHCII), accompanied by a significant increase in expression of the M2 marker protein CD206. Meanwhile, mRNA expression for the proinflammatory genes *Tnfa* and *Nos2* were significantly reduced with increased message of Il-10 (109). In a model of skeletal muscle injury and repair, the myofiber cross-sectional area and myonuclei per fiber were significantly reduced 28 days after injury in $AnxA1^{-/-}$ and $Fpr2/3^{-/-}$ mice. The ratio of anti- to proinflammatory macrophages was significantly lower in the injured skeletal muscle of $AnxA1^{-/-}$ and $Fpr2/3^{-/-}$ mice, suggesting a prolonged inflammatory response (109). Thus, AnxA1-Fpr2/3 pathway plays an important role in the polarization of macrophages from a proinflammatory to a pro-resolving/reparative phenotype during the process of muscle regeneration.

## 7. The role of FPR2 and endogenous ligands in colon homeostasis

### 1). The role of FPR2 (Fpr2 in mice) and LL-37 (CRAMP in mice) in colon homeostasis

LL-37 (CRAMP in mice) are expressed in various cells and tissues (110–115). LL-37 activates FPR2 to induce $Ca^{2+}$ mobilization and migration in human monocytes and FPR2-transfected HEK293 cells. LL-37 also induces chemotaxis of human neutrophils and T-lymphocytes through FPR2. These results indicate that LL-37 uses FPR2 as its receptor to mediate cell chemotactic and other activities (116,117).

LL-37 and its mouse counterpart of CRAMP also play an essential role in colon homeostasis and inflammatory responses. In normal human colon, LL-37 is expressed by epithelial cells located on the mucosal surface and upper crypts (118). $CRAMP^{-/-}$ mice contained significantly shorted length of colonic crypts with reduced epithelial cell proliferation of (119). In mouse model of DSS-induced colitis, $CRAMP^{-/-}$ mice displayed higher sensitivity, increased mortality, and more severe acute enteritis including markedly damaged colon epithelial cells with more severe inflammatory response. The recovery of the colon mucosa following DSS exposure was much slower (119). In addition, the composition of colon microbiota was altered in $CRAMP^{-/-}$ mice (119). On the other hand, $Fpr2^{-/-}$ mice also

showed shorter colonic crypts and are highly sensitive to chemically induced colitis with more mortality (120). Similarly, Fpr2 deficiency alters the composition of colon microbiota (120). In mouse model of azoxymethane (AOM)-and dextran sulfate (DSS)-induced colon cancer, *CRAMP*$^{-/-}$ mice or *Fpr2*$^{-/-}$ mice developed more numerous colon tumors with larger sizes (119,120). Thus, LL-37/FPR2-mediated signals protect colon mucosa against tumorigenesis.

Clinically, reduction or complete loss of LL-37 were reported in most human colon cancer cells (121) and low levels of LL-37 was associated with higher grade colorectal cancer (122). Some studies have tried to design short peptides derived from LL-37 sequence for colon cancer treatment. For example, FK-16, a short peptide derived from the residues 17 to 32 of LL-37 sequence, induces the death of colon cancer cells through caspase-independent apoptosis and autophagy (123). Another example is FF/CAP18 designed according as 27-residue analog of LL-37. FF/CAP18 significantly changed the metabolic process of colon cancer cells, blocking the proliferation of cancer cells (124).

Further studies showed that epithelial conditional *CRAMP*$^{-/-}$ mice reduced thickness of Muc2, the number of PAS$^{+}$ goblet cells and the shortening of the crypt length and reduced Ki67+ cells in the colon mucosa. In contrast, myeloid conditional *CRAMP*$^{-/-}$ mice did not show any reduction in Muc2, PAS+ cells, crypt length and Ki67+ cells in the colon mucosa. However, in DSS-induced colitis, myeloid conditional *CRAMP*$^{-/-}$ mice were highly sensitive, more mortality, more severe epithelial cell damage, more invasion of bacteria into colon mucosa as compared to epithelial conditional *CRAMP*$^{-/-}$ mice (125). Thus, epithelial cell-derived CRAMP is associated with development of colon crypt, repair of injured mucosa, and production of colon mucus. On the other hand, myeloid cell-derived CRAMP is associated with the defense of colon epithelial cells against bacterial invasion during acute inflammation (125) because LL-37/CRAMP/ stimulates macrophage differentiation and mature (126), promotes macrophages for bacterial phagocytosis and killing (127–129), and macrophage survival (130,131). The different contribution of epithelial- and myeloid-derived CRAMP to colon mucosal homeostasis was shown in Fig. 6.

### 2). The role of FPR1/FPR2 and FAM3D (Fam3D in mice) in colon homeostasis

Family with sequence similarity 3, member D (FAM3D, Fam3D in mice) (132) is a gut-secreted Protein, which level is associated with nutritional status (133). FAM3D is also a host-derived endogenous chemotactic agonist for FPR1 and FPR2 (134,135). Recent studies showed high-level Fam3D in mouse gastrointestinal tract that plays a key role in protection of colon from dysbiosis, inflammation and inflammation-associated carcinogenesis (29). Fam3D deficiency impaired the integrity of colonic mucosa, promoted epithelial hyper-proliferation, reduced thickness of mucus layer of distal colon, especially, the inner mucus layer, and altered composition of microbiota in the colon and increased sensitivity to chemically induced colitis and associated cancer (29). Clinically, human colorectal cancer (CRC) tissues express lower levels of FAM3D mRNA and protein as compared with normal human colon tissues and all stages of CRC express lower levels of FAM3D transcripts (29). Thus, FPR1/FPR2-mediated signaling pathways support colon homeostasis to fend off inflammation, carcinogenesis and dysbiosis.

### 3). FPR2 promotes malignant phenotype of human colon cancer cells

Although FPR2 plays a critical role in maintaining colon homeostasis, FPR2 expressed in cancer cells promote colorectal cancer progression. Human colon cancer cell lines express FPR2, but the levels of FPR2 expression are different in different colon cancer cell lines (136). FPR2 ligands induced the human cell lines expressing FPR2 for migration and proliferation through activation of ERK1/2. Human colon cancer cells with silenced FPR2 reduced migration and proliferation in vitro, and tumorigenicity in vivo (136). Silencing FPR2 in human colon cancer cell lines SW1116 distinctly suppressed tumor cell proliferation, migration, invasion, and the capacities of anti-apoptosis, and pro-angiogenesis (137). In vivo, the tumorigenicity of SW1116 cells were suppressed after suppression of FPR2 mRNA. FPR2 deficiency resulted in SW1116 cell functional changes, reducing epithelial-mesenchymal transition (EMT) (137). Clinical surgically resected samples collected from patients showed that the expression level of FPR2 was positively correlated with the invasiveness of malignant colon cancer (136).

## 8. The role of FPR2 in the differentiation of hematopoietic stem/progenitor cells

Mice treated with AnxA1, a FPR2 ligand, showed reduced granulocyte–macrophage progenitor (GMP) population, increased mature granulocytes Gr-$1^{+}$Mac-$1^{+}$ cell number in the bone marrow (BM) as well as the number of peripheral granulocytic neutrophils. Meanwhile, the $Lin^{-}$Sca-$1^{+}$c-$Kit^{+}$ (LSK) hematopoietic stem cells (HSC) expressed higher levels of cyclin B1. FPR2 ligand AnxA1 induced-HSC/progenitor cell differentiation was abolished by Boc-2, an FPR2 antagonist (138). These results indicate that FPR2 and its ligands induce HSC differentiation.

*Fpr2*$^{-/-}$ mice showed reduced the number of $Lin^{-}$c-$Kit^{+}$Sca-$1^{+}$ (LKS) HSC cells in BM (3). Mice injected with BrdU showed the BrdU-labeled c-$Kit^{+}$ cells were significantly reduced in BM of *Fpr2*$^{-/-}$ mice. In vitro experiment, CFU-GM formation, c-$Kit^{+}$ cell proliferation was significantly reduced in *Fpr2*$^{-/-}$ HSC (3). In addition, Fpr2 ligands enhanced SCF-mediated proliferation of c-$Kit^{+}$ cells isolated from WT mouse BM, which was attenuated by the Fpr2 antagonist WRW4 (3). In vivo experiment, after mice were challenged with heat-inactivated bacteria, the $CD11b^{+}Ly6G^{+}$ cell population in BM and the recruitment of Gr-$1^{+}$ neutrophils into the lung and $CD11b^{+}Ly6C^{+}TNF\alpha^{+}$ monocytes into the spleen was significantly reduced in *Fpr2*$^{-/-}$mice (3). Interestingly, the chemokine receptor CXCR2 expression was reduced in the neutrophils from *Fpr2*$^{-/-}$mice challenged with inactivated bacteria (3). Fpr2 deficiency also reduced CCR6 expression in monocyte and reduced recruitment of monocytes expressing CCR6 to the colonic mucosal wounds (139). These results demonstrated Fpr2 is important for granulocyte–macrophage progenitor (GMP) cell proliferation, differentiation, and maturation (Fig. 7).

## 9. Conclusions

Recently, great progress has been made in understanding the biological roles of FPR2 and endogenous ligands in the homeostasis, the mechanism of FPR2 conformational change and

FPR2 signal bias, and development of synthetic peptides and small molecule compounds as FPR2 ligands to resolve inflammation. However, FPR2 function is complex and linked with the activation of other receptors. Particularly, the mechanism of interaction of FPR2 and its ligands is not fully clear, and although there is a growing appreciation for anti-inflammatory FPR2 agonists, which reduce and orchestrate inflammatory responses (61), only limited number of FPR-related peptides such as LL-37 and LL-37-derived short peptides have used to clinical trials.

In the light of great challenges posed by infectious diseases, inflammation as well as cancer, further understanding the integrated and complex network of FPR2 interacts with pro-inflammatory and anti-inflammatory FPR2 agonists timely and spatially will provides an opportunity for developing new therapeutic agents (61).

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## Data availability

All data generated or analyzed during this study are included in this manuscript. Further inquiries can be directed to the corresponding authors.

## Abbreviations:

| | |
|---|---|
| **ALX** | aspirin triggered LXA4 receptor |
| **AnxA1** | annexin A1 |
| **AMP** | antimicrobial peptide |
| **BM** | bone marrow |
| **c-Met** | c-Met tyrosine kinase receptor |
| **FPR** | formyl peptide receptor |
| **FPR2** | formyl peptide receptor type 2 |
| **fMLF** | N-formyl-Met-Leu-Phe |
| **GI** | gastrointestinal |
| **GPCR** | G protein-coupled receptor |
| **HIV** | human immunodeficiency virus |

| | |
|---|---|
| **PKC** | protein kinase C |
| **PPARγ** | peroxisome proliferator-activated receptor gamma |
| **PSM** | phenol-soluble modulin |
| **RvD** | resolvin |
| **PSM** | phenol-soluble modulin |
| **SAA** | serum amyloid A |
| **SOCS** | Suppressors of cytokine signaling |
| **TLR4** | TLR4, Toll-like receptor 4 |
| **TNF-α** | tumor Necrosis Factor Alpha |
| **TME** | tumor microenvironment |

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**Highlight:**

1. FPR2 is activated by various types of natural and synthetic ligands,
2. FPR2 conformation changes based on the nature, concentration of the ligands,
3. FPR2 is involved in an abundant array of developmental and homeostatic signaling cascades,
4. FPR2 mediates several unique biological effects and is involved in the pathogenesis of several diseases.

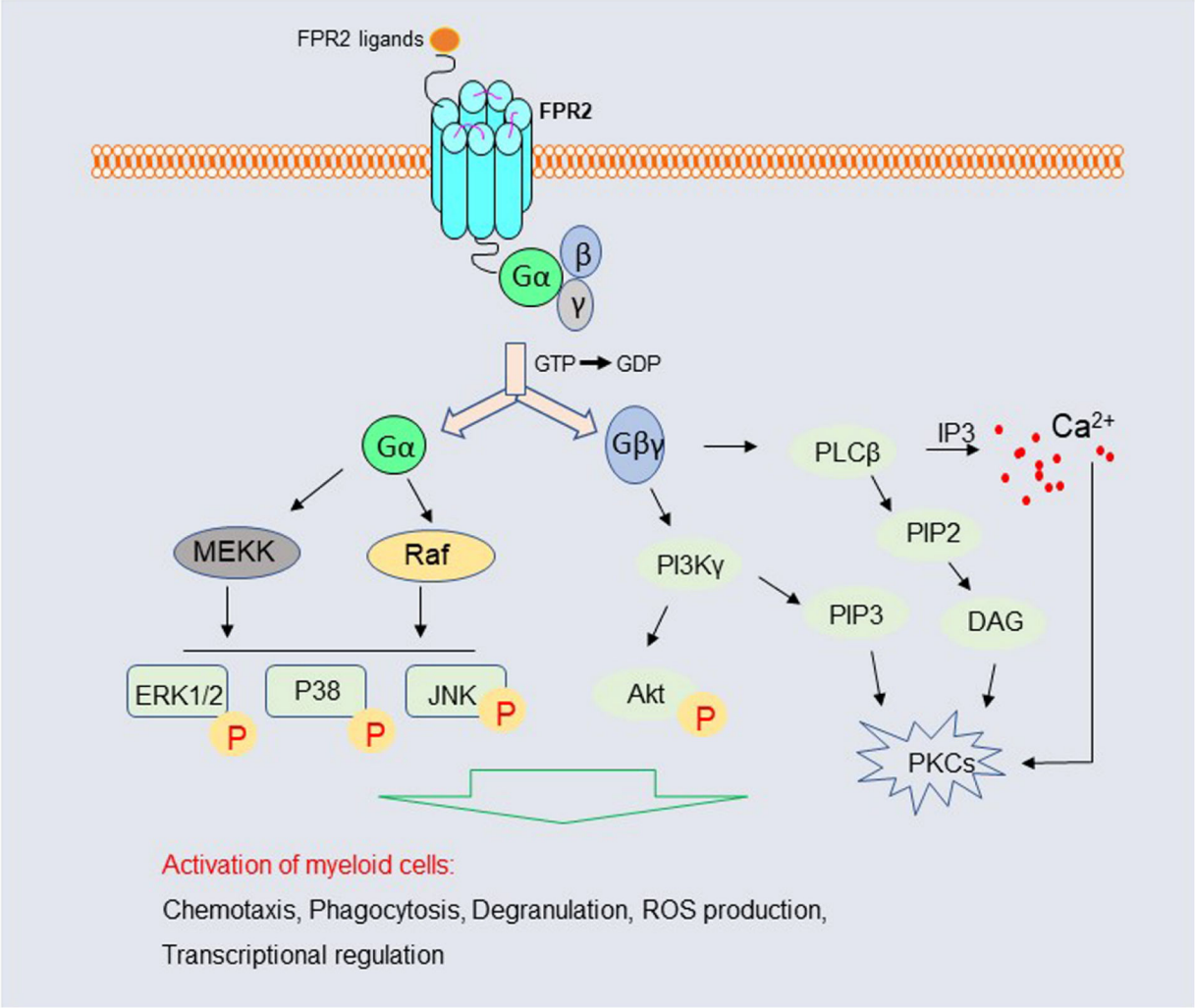


**Figure 1. Signal transduction pathways of formyl-peptide receptor 2 (FPR2) (12,150)**

FPR2 ligands interacted with FPR2 leads to dissociation of G proteins of FPR2 into Gα and Gβγ subunits. The Ga subunit activates downstream MAPK signal pathways. The Gβγ subunit triggers PKCs through activation of PI3Kγ, PLCβ and induces release of $Ca^{2+}$ from intracellular stores and activation of Akt. DAG, diacylglycerol; ERK1/2, extracellular-regulated protein kinase½; IP3, inositol 1,4,5-trisphosphate; JNK, JUN-N-terminal protein kinase; MAPK, the mitogen-activated protein kinase; MEKK, MAP kinase kinase kinase; PI3Kγ, Phosphoinositide-3-kinase-γ; PIP, phosphatidylinositol 4,5-bisphosphat; PKCs, protein kinases C.

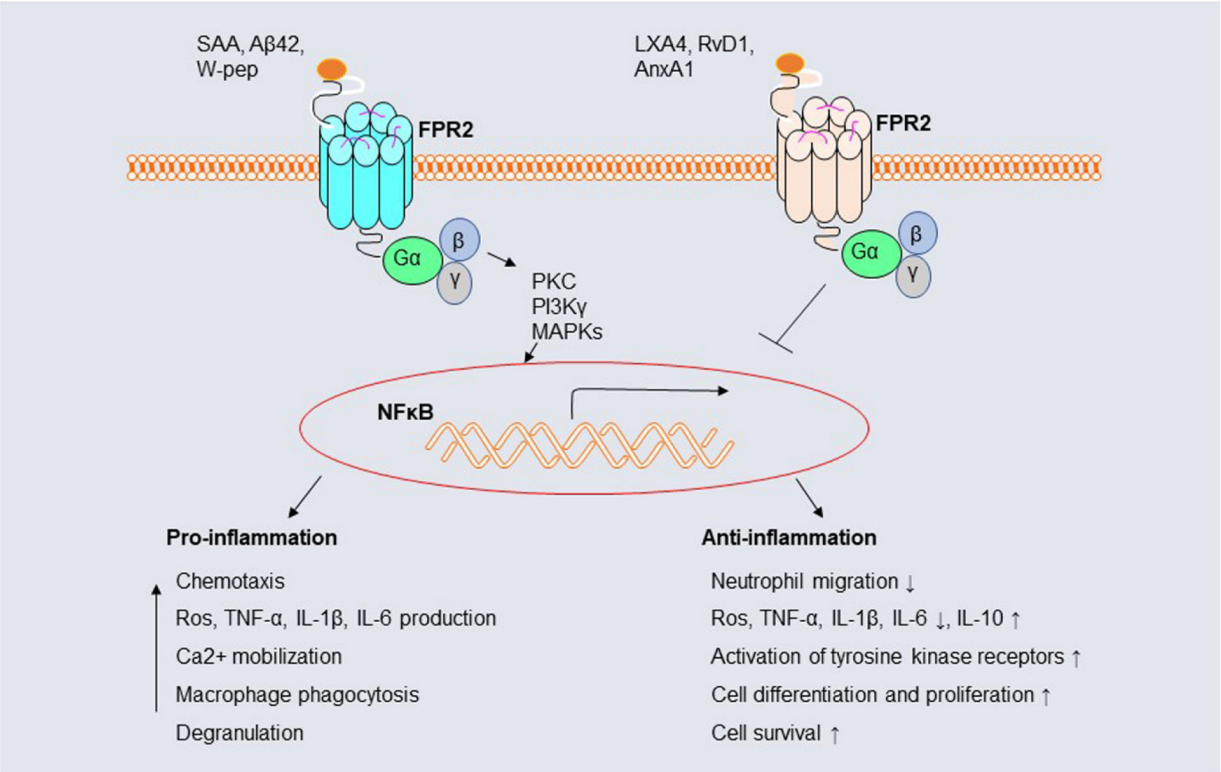


**Figure 2. FPR2 modulate both pro- and anti-inflammatory responses (5,151)**

**Left panel:** A variety of FPR2 ligands exert pro-inflammation such as SAA, Aβ42 and W-peptide, which interact with FPR2 induce pro-inflammatory responses including cell migration, production of superoxide anion and inflammatory cytokine release, calcium mobilization, phagocytosis, and degranulation. **Right panel:** Pro-resolving FPR2 ligands such as LXA4, RvD1 and AnxA1 trigger FPR2 activation to mediate anti-inflammatory actions including reduced cell migration, Ros and inflammatory cytokine production, and increased IL-10 production, activation of tyrosine kinase receptors, cell differentiation, proliferation and survival.

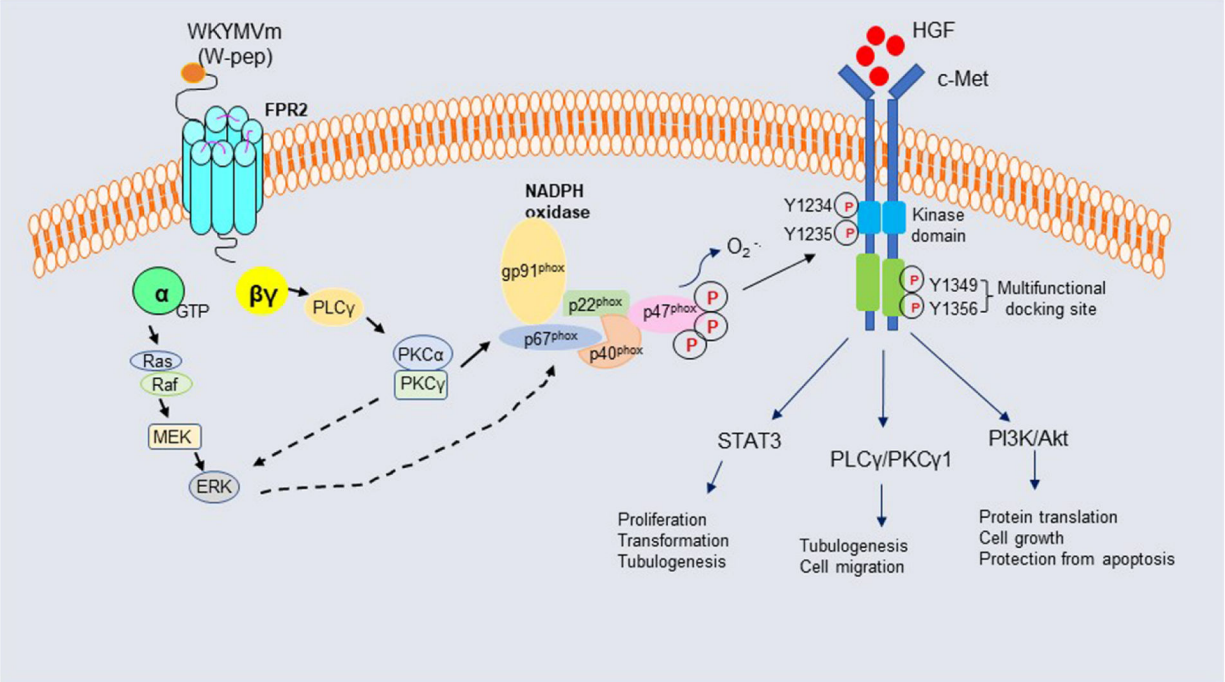


**Figure 3. The ligand-induced crosstalk between FPR2 and c-Met in human prostate epithelial cell line PNT1A (38,73,74)**

FPR2 on human prostate epithelial cell line PNT1A is activated by synthetic W-peptide. The heterotrimeric G proteins coupled to FPR2 was dissociated into Gα and Gβγ subunits. Ga subunit activates the mitogen-activated protein kinase (MAPK) pathways. The Gβγ subunit activates PLCγ, PKCα and PKCγ leading to superoxide generation by NADPH oxidase which activate c-Met.

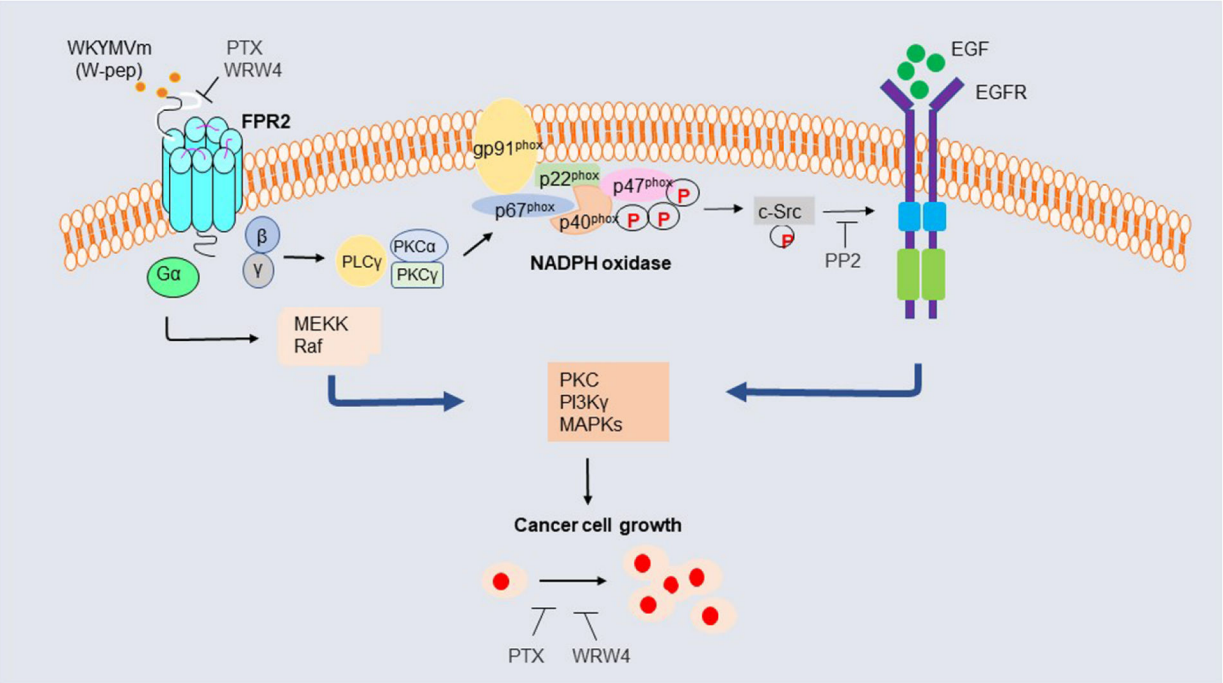


**Figure 4. The crosstalk of FPR2 with EGFR in lung cancer cells (75,76)**

W-peptide interacted with FPR2 in lung cancer cells induce G proteins dissociated into Gα and Gβγ subunits. The activation of FPR2 triggers downstream signal pathways and NADPH oxidase-dependent superoxide generation which induces c-Src phosphorylation, thereby activates EGFR. W-peptide-induced EGFR transactivation can be blocked by the FPR2 antagonist WRWWWW (WRW4), pertussis toxin (PTX), and the c-Src inhibitor PP2. W-peptide promotes CaLu-6 cell growth, which is prevented by PTX and by WRW4. Thus, the crosstalk of FPR2 with EGFR mediates cancer cell growth.

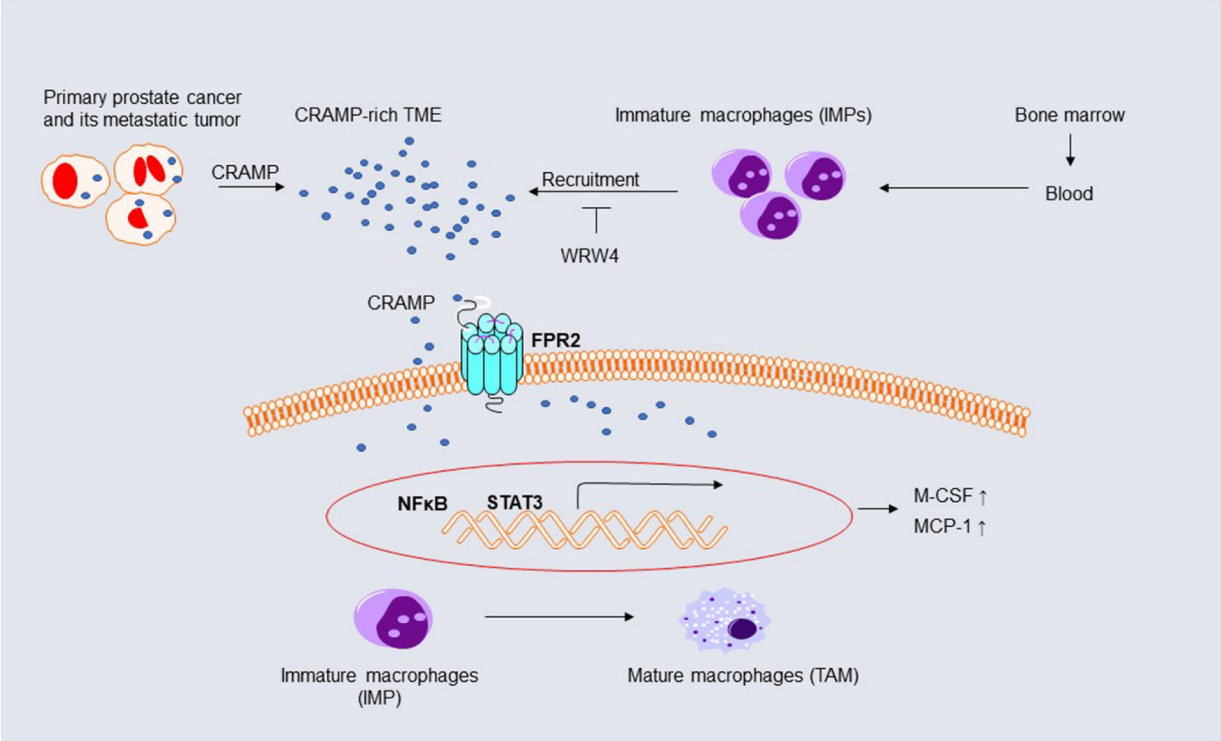


**Figure 5. Prostate cancer-derived LL-37/CRAMP mediates the recruitment of immature macrophages and differentiation forward to M2 TAM (100–102).**

LL-37/CRAMP was overexpressed in primary prostate cancer and its metastatic tumor as well as in the transgenic adenocarcinoma mouse prostate (TRAMP) model. *CRAMP*$^{+/+}$ TRAMP-C1 tumor cells created a CRAMP-enriched tumor microenvironment (TME), CRAMP mediated immune cell recruitment to the CRAMP-enriched tumor microenvironment (TME) in which CRAMP upregulated FPR2 expression in prostate cancer cells and overproduction of M-CSF and MCP-1 through NF-kB and STAT3 activation and stimulates immature macrophages to differentiate into M2 macrophages.

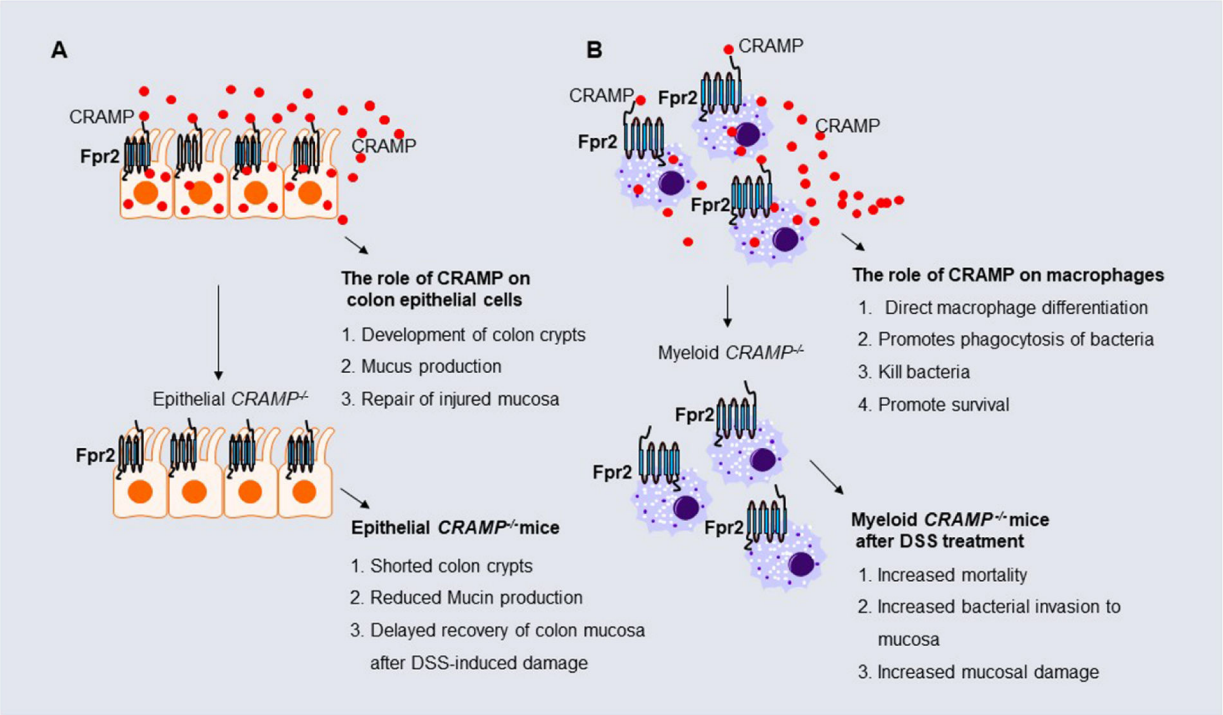


**Figure 6. Distinct contributions of CRAMP derived from epithelial cells and macrophages to colon mucosal homeostasis (125–131)**

**A**. The role of CRAMP derived from epithelial cells. CRAMP stimulates colon epithelial cell proliferation and development, mucus production and repair for damaged colon mucosa. Epithelial *CRAMP*$^{-/-}$ mice showed shorted colon crypts, reduced mucin production, delay recovery of colon mucosa after DSS-induced damage. **B**. The role of CRAMP derived from macrophages. CRAMP directs macrophage differentiation, promotes phagocytosis and killing of bacteria by macrophages, and promotes survival of macrophages. Myeloid *CRAMP*$^{-/-}$ mice showed increased mortality, bacteria invasion into colon mucosa and mucosa damage.

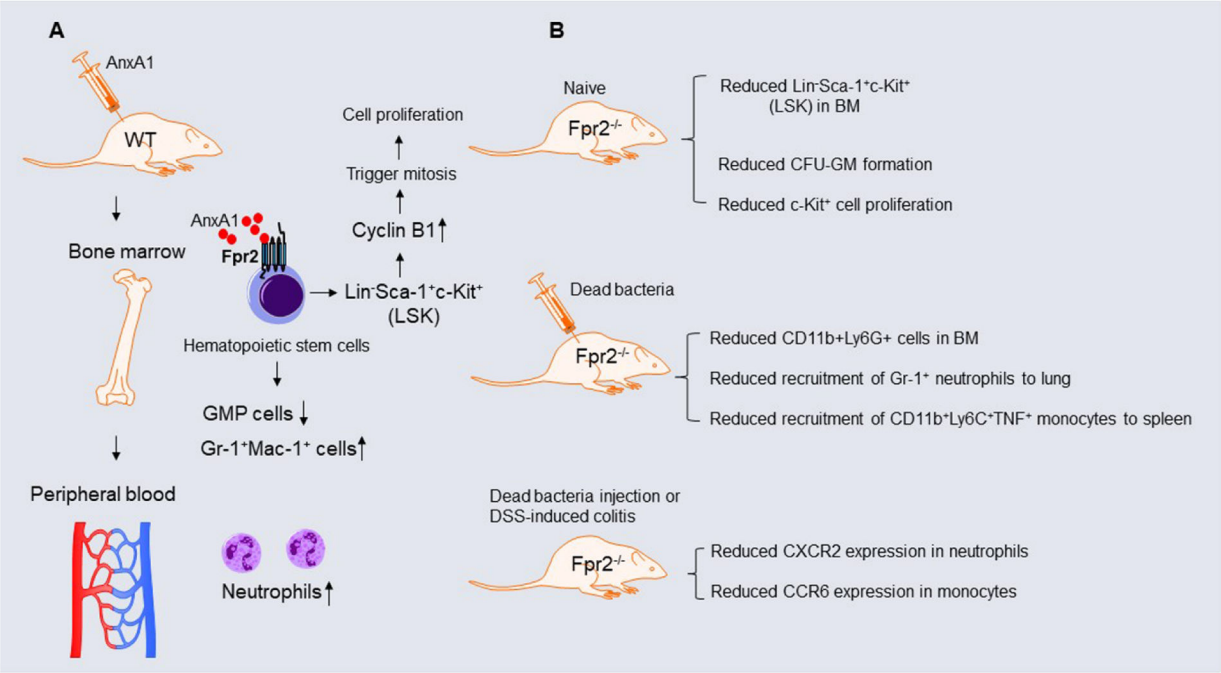


**Figure 7. The role of FPR2 in the differentiation of hematopoietic stem/progenitor cells (3,138,139)**

**A**. FPR2 ligand AnxA1 induces HSC differentiation. Mice treated with AnxA1 showed reduced granulocyte–macrophage progenitor (GMP) population, increased mature granulocytes Gr-1$^{+}$Mac-1$^{+}$ cell number in the bone marrow (BM) as well as the number of peripheral granulocytic neutrophils. Meanwhile, the Lin$^{-}$Sca-1$^{+}$c-Kit$^{+}$ (LSK) stem cells expressed higher levels of cyclin B1 to trigger cell mitosis and proliferation. **B**. Naïve *Fpr2*$^{-/-}$ mice showed reduced the number of Lin$^{-}$c-Kit$^{+}$Sca-1$^{+}$ (LKS) HSC cells in BM, reduced CFU-GM formation, c-Kit$^{+}$ cell proliferation. *Fpr2*$^{-/-}$ mice challenged with heat-inactivated bacteria showed reduced CD11b$^{+}$Ly6G$^{+}$ cell population in BM, reduced recruitment of Gr-1$^{+}$ neutrophils into the lung and CD11b$^{+}$Ly6C$^{+}$TNFα$^{+}$ monocytes into the spleen. In addition, *Fpr2*$^{-/-}$ mice challenged with heat-inactivated bacteria or DSS showed reduced CXCR4 in neutrophils and CCR6 expression in monocytes.

**Table 1.**

Pathogen-derived Fpr2 Ligands

| Ligands | Source/Sequence | Ref. |
|---|---|---|
| fMLF | *E. coli*, N-formyl-Met-Leu-Phe | (4) |
| fMIVIL | *L. monocytogenes*, N-formyl-Met-Ile-Val-Ile-Leu | (14) |
| fMIFL | *S. aureus*, N-formyl-Met-Ile-Phe-Leu | (14) |
| PSMa2 | *S. aureus*, fMGIIAGIIKVIKSLIEQFTGK | (13) |
| PSMa3 | *S. aureus*, fMEFVAKLFKFFKDLLGKFLGNN | (13) |
| Hp2-20 | *H. pylori*, AKKVFKRLEKLFSKIQNDK | (16) |
| T21 (DP107) | HIV gp41, Ac-NNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2. | (22) |
| F peptide | HIV gp120, EGSDTITLPCRIKQFINMWQE | (23) |
| V3 peptide | HIV gp120, TRPNYNKRKRIHIGPGRAFYTTKNIIGTIR-QAH-NH | (24) |

**Table 2.**

Host-derived Fpr2 Ligands

| Ligands | Sequence/Characteristics | Ref. |
|---|---|---|
| fMMYALF | formyl-Met-Met-Tyr-Ala-Leu-Phe. N-formylated hexapeptides corresponding to the N terminus of mitochondrial NADH dehydrogenase subunits 6. It induced calcium mobilization and chemotaxis in the cells expressing FPR2. | (25,26) |
| Mitocryptide-2 | formyl-MTNIRKSHPLMKIIN. Mitocryptide-2 (MCT-2) is one of neutrophil-activating peptides and is produced as an N-formylated pentadecapeptide from mitochondrial cytochrome b. MCT-2 increase of intracellular free Ca2+ concentration in HEK-293 cells expressing FPR2 and induced β-hexosaminidase secretion in neutrophilic/granulocytic differentiated HL-60 cells via FPR2 activation. | (27,140) |
| Aβ42 | DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA. An agonist for FPR2. Aβ42 plays a key role in the pathogenesis of Alzheimer's disease (AD) and is a core biomarker for the diagnosis of AD. | (30) |
| Annexin 1 | Annexin A1 is a $Ca^{2+}$-dependent phospholipid binding protein and is composed of 44 amino acids. Annexin A1 exhibits anti-inflammatory and proinflammatory effects in a variety of inflammatory experimental models. Annexin A1 is highly expressed in multikinds of tumor, but its role is still controversial. | (141) |
| $Ac_{2–26}$ | Ac-AMVSEFLKQAWFIENEEQEYVQTVK. Derived from an active N-terminal peptide of Annexin 1. $Ac_{2–26}$ elicit protective anti-inflammatory actions and anti-neutrophil migration mechanisms. | (31,142) |
| LL-37 (Mouse CRAMP) | LLGDFFRKSKEKIGKEFKRIVQRIKDFLRNLVPRTES. One of antimicrobial peptides. (AMPs). LL-37 can have two distinct functions in different tissues and different microenvironments. On the one side, LL-37 promotes inflammation and immune response and exerts its anti-infective and antitumor effects; on the other side, it has the ability to inhibit inflammation and promote carcinogenesis. | (28,143) |
| FAM3D | Gut-secreted protein, a single, non-glycosylated, polypeptide chain. FPR1/FPR2 agonists. Fam3D is an agonist for FPR1/FPR2 and plays an important role in maintaining the gut microbiota balance and protecting colon mucosa against inflammation and colon tumorigenesis. | (29) |
| Lipoxin-A4 | Fatty acid. It has potent anti-inflammatory properties mediated by FPR2 including inhibiting pro-inflammatory cytokine production, suppressing the activities of metalloproteinases and enhancing the clearance ability of macrophage. | (144) |
| 15epi-lipoxin A4/ aspirin-triggered lipoxin (ATL) | Lipoxins, which are endoge-nous lipid mediators generated during inflammation. It has anti-inflammatory properties including reduced inflammatory cell recruitment, cytokine release, and vascular permeability. | (34) |
| Resolvin D1 and aspirin-triggered RvD1 | 7S,8R,17S-trihydroxy-4Z,9E,11E,13Z,15E,19Z-docosahexaenoic acid. It was derived from ω-3 polyunsaturated fatty acids. RvD1 modulated the resolution phase of the inflammatory response. | (35,145) |

**Table 3.**

Synthetic Fpr2 Ligands

| Ligands | Sequence/Characteristics | Ref. |
|---|---|---|
| MMK-1 | LESIFRSLLFRVM. A FPR2-specific ligand. | (39,146) |
| CGEN-855A | TIPMFVPESTSKLQKFTSWFM-amide. It displayed anti-inflammatory activity and inhibited PMN recruitment to the injured organ. | (40) |
| P2Y2PalIC2 pepducin | P2Y2R pepducin. It interacted with FPR2 in human neutrophils and induced the assembly of the neutrophil superoxide-generating NADPH. | (42) |
| MMHWAM | Met-Met-His-Trp-Ala-Met-CONH2. It induced chemotactic migration of neutrophils as well as stimulated superoxide anion production. | (41) |
| F2Pal16 | Pal-KIHKKGMIKSSRPLRV. It induceed superoxide production in human neutrophils and the activity was sensitive to FPR2 antagonists. | (147) |
| WKYMVm | Trp-Lys-Tyr-Met-Val-D-Met. It played an anti-inflammatory role in most inflammatory diseases. It inhibited or promoteed the progression of different types of tumors and promote angiogenesis, wound healing, and bone repair. | (38,148) |
| WKYMVm(-NH2) | Trp-Lys-TyrMet-Val-D-Met-NH2. It showed similar effects as WKYMVm. | (37,38) |

**Table 4.**

Small molecule compounds as Fpr2 Ligands

| Ligands | Sequence/Characteristics | Ref. |
|---|---|---|
| Compound (S)-17 | (S)-3-(4-Cyanophenyl)-N-[[1-(3-chloro-4-fluorophenyl)cyclopropyl]methyl]-2-[3-(4-fluorophenyl)ureido]propanamide ((S)-17). It reduces IL-1β and TNF-α levels and has anti-inflammatory properties and is a good tool to study the effects of FPR2 activation in CNS with | (46) |
| Quin-C1 | 4-butoxy-N-[2-(4-methoxy-phenyl)-4-oxo-1,4-dihydro-2H-quinazolin-3-yl]-benzamide. It has anti-inflammatory property in a mouse model of bleomycin-induced lung injury and reduced the neutrophil and lymphocyte counts in BALF, diminished expression of TNF-α, IL-1β, KC, and TGF-β1, and decreased collagen deposition in lung tissue. | (44) |
| N-substituted benzimidazole 11 | It stimulates IL-6 secretion and inhibits neutrophil migration. | (149) |
| Compound 17b | N-(4-Bromophenyl)-2-[5-(3-methoxybenzyl)-3-methyl-6-oxo-6H-pyridazin-1-yl]-propionamide. It reduces necrosis in isolated cardiomyocytes when subjected to hypoxia–reoxygenation (H–R), and attenuated gene expression of pro-fibrotic CTGF and pro-inflammatory IL-1b in isolated cardiofibroblasts when stimulated by TGF-b. | (45) |
| Chiral pyridazines | 6-Methyl-2,4-Disubstituted Pyridazin-3(2H)-ones. FPR1/FPR2 agonists. It was able to activate intracellular calcium mobilization and chemotaxis in human neutrophils. | (47) |
| PD168368 | [(S)-amethyl-a-[[[(4-nitrophenyl)amino]carbonyl]amino]-N-[[1-(2-pyridinyl) cyclohexyl]methyl]-1H-indole-3-propanamide]. FPR1/FPR2 agonists. It activates $Ca2^{+}$ flux in human neutrophils murine neutrophils. | (48) |
| PD176252 | [(S)-N-[[1-(5-methoxy-2-pyridinyl)cyclohexyl]methyl]-a-methyl-a-[[-(4-nitrophenyl)amino]carbonyl]amino-1H-indole-3-propanamide]. FPR1/FPR2 agonists. It activates $Ca2^{+}$ flux in human neutrophils murine neutrophils. | (48) |