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The potential impacts of formyl peptide receptor 1 in inflammatory diseases

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1. ABSTRACT

Neutrophils play a critical role in acute and chronic inflammatory diseases. *N*-formyl peptides, which originate from bacterial peptides or mitochondrial proteins bind with a high binding affinity to formyl peptide receptor 1 (FPR1). *N*-formyl peptide-FPR1 is involved in the pathogenesis of sterile and infectious inflammatory processes and causes phagocytosis of pathogens or injured cells by neutrophils. Excessive activation of neutrophils by binding of *N*-formyl peptides is associated with tissue injury requiring drugs that block FPR1-dependent signaling. Here, we review the roles of FPR1 as a critical regulator of inflammatory processes and its involvement in pathological conditions.

2. INTRODUCTION

In the late 19th century, Metchnikoff demonstrated that injury in starfish embryos results in the recruitment of phagocytic cells to the injury site. He also demonstrated that these cells migrate to damaged sites and are involved in microbial digestion. Metchnikoff denoted these cells as polymorphonuclear leucocytes (PMNs) (1). Neutrophils are a type of PMN and play a major role in acute and chronic inflammation (2). They are typically the first leucocytes to be recruited in inflammatory areas and can eliminate invasive pathogens. Neutrophils are generated in the bone marrow from hematopoietic stem cells, and their maturation includes several stages, such as myeloblast, promyelocyte, myelocyte, metamyelocyte, band cell, and PMN (3). In humans, among circulating leucocytes, 50-70 percent of leucocytes are neutrophils. The average diameter of mature neutrophils in circulation is 7-10 micrometer. Neutrophils have a segmented nucleus and their cytoplasm is enriched with granules and secretory vesicles. In humans, the lifespan or half-life of neutrophils in circulation is approximately 8 h (4). However, during inflammation, neutrophils are activated and their lifespan increases. They are responsible for eliminating invasive pathogens through multiple mechanisms, namely chemotaxis, phagocytosis,

respiratory burst, degranulation, neutrophil extracellular trap (NET) formation, and cytokine release (5-7).

These immune responses, including respiratory burst and degranulation, in activated neutrophils involve a two-stage process: the "trigger" or priming stage and the "activation" stage. Circulating neutrophils do not express their full microbicidal capacity anywhere in the body when exposed to bioactive agents unless they have first been primed. Priming is thought to be a process through which the response of neutrophils is potentiated by the activating stimulus (8). Priming can facilitate the clustering of surface receptors, such as Fc gamma receptor IIa and beta2-integrins, and the formation of the NADPH oxidase complex, which is responsible for the synthesis of reactive oxygen species (ROS) (9-10). Priming agents do not trigger effector functions by themselves, except when they are used at excessive concentrations (11). The primed neutrophils in circulation are trapped in the pulmonary microvascular circulation, but they return to the circulatory system in the steady state if no additional stimulants are present (12). Because neutrophil activation plays a major role in the pathogenesis of inflammatory diseases, regulating an adequate immune response in human neutrophils is essential for treating inflammatory diseases.

Neutrophils express numerous pathogen recognition receptors (PRRs) to sense inflammatory stimulus for priming and activation. G-protein coupled receptors (GPCRs) are primarily groups of PRRs. Among such GPCRs, the first discovered PRR on the neutrophil surface was formyl peptide receptor 1 (FPR1) (13). Increasing evidence shows that endogenous damage-associated molecular patterns (DAMPs) released from damaged tissues in addition to infectious stimulation trigger FPR1 activation on the neutrophils surface (14-16). In particular, research has focused on the importance of FPR1 in the pathogenesis of infectious and sterile inflammatory diseases. Therefore, this review summarizes the available knowledge about the signaling and pathological functions of FPR1 as well as focuses on the roles of formyl peptides in sterile and infectious inflammatory processes.

3. DIFFERENT TYPES OF FPR

3.1. FPR 1

The FPR family is a group of Class A GPCRs, and their function is to trigger leucocyte responses during inflammation. In humans, the FPR family comprises three members: FPR1, FPR2, and FPR3. Human FPR1 is mainly expressed on neutrophils, monocytes, and macrophages, and triggers immune reactions in response to several formyl peptide ligands derived from bacteria or mitochondria (17-20). FPR1 is the first neutrophil GPCR to be cloned and sequenced, and it comprises a single 350–370-amino acid polypeptide chain (13). FPR1 is a seven-transmembrane receptor with the N-terminus and three loops, which interact with ligands and extend onto the cell surface, as well as the C-terminus and additional loops, which are necessary for intracellular signaling and extend into the cytoplasm (21). Two orphan but relatively conserved low-affinity receptors, initially termed FPR-like 1 and FPR-like 2, were cloned from an mRNA library of neutrophil-like HL-60 cells (22-23). These receptors have been respectively renamed FPR2 and FPR3 (24). All three receptors are clustered on chromosome 19q13.3 and share substantial sequence homology. FPR1 shares 69 percent of amino acid identity with FPR2 and 56 percent with FPR3, whereas FPR2 and FPR3 share 83 percent identity (25). Increasing evidence shows that damage signals released from injured tissues can stimulate immune cells to induce inflammatory responses (26-28). FPR1 present on immune cells should recognize these signals for activating inflammatory responses. Zhang *et al.* revealed that mitochondrial lysates released from damaged tissues, such as tissues in trauma-related injuries, recruited neutrophils to induce systemic inflammatory response syndrome (SIRS) by activating FPR1 (29). In addition to being related to immune functions, FPR1 is associated with other cellular responses. Growing evidence suggests that FPR1 is closely related to tumor cell growth and proliferation (30-31).

3.2. FPR 2

In contrast to the specificity of FPR1, FPR2 binds to *N*-formylmethionine-leucyl-phenylalanine (FMLP) with low affinity. FPR2 can bind proteins and lipids with ligands, including serum amyloid A and lipoxin A4 (LXA_4) (32). In particular, these ligand-specific interactions induce either proinflammatory or anti-inflammatory effects (33-34). For example, annexin A1 and LXA_4 trigger FPR2 activation to inhibit leucocyte recruitment, enhance neutrophil apoptosis, and stimulate macrophage efferocytosis (35-37). Serum amyloid A can bind to FPR2 to induce proinflammatory responses and increase neutrophil recruitment to inflammation sites (38).

3.3. FPR3

Compared with the function of other FPR family members, that of FPR3 remains poorly understood. FPR3 is expressed on eosinophils, monocytes, macrophages, and dendritic cells, but not on human neutrophils. It may have a role in the pathogenesis of allergic diseases. Moreover, FPR3 is relatively insensitive to formyl peptides, and few specific endogenous ligands have been identified. F2L, an endogenous acetyl 21-amino acid peptide, is the most specific ligand for FPR3 (39-40).

4. FPR1 AGONISTS

FPR1 belongs to the PRR family and can aid immune cells to sense and eliminate pathogens, leading to the release of formyl peptides. Consequently,

Table 1. Predominant agonists and related physiological mechanisms of human formyl peptide receptors

FPR1 agonist	Origin	Inflammation	Function	Ref
N-formyl peptide	Bacteria	Inflammation	Trigger neutrophil respiratory burst, degranulation, chemotaxis	18, 41-43
	Mitochondria	Inflammation	Trigger neutrophil respiratory burst, degranulation, chemotaxis	19, 26, 29, 44-46
WKYMVm	Synthetic	Inflammation	Induce chemotaxis and calcium flux in human phagocytes	47, 48
FMLP-OMe	Synthetic	Inflammation	Induce neutrophil chemotaxis and enhance cAMP and calcium level	49-51
T20/DP178	Virus	Inflammation	Induce neutrophil migration and calcium flux in human phagocytes	52
gG-2p20	Virus	Inflammation	Induce the release of ROS in monocytes and neutrophils	53
Cathepsin G	Granular enzyme	Inflammation	Induce phagocyte migration	54
Annexin 1 and derived peptides	Glucocorticoid-induced protein	Anti-inflammation	Inhibit neutrophil migration	55,56
			Inhibit neutrophil NADPH oxidase	57

several bacterial *N*-formyl peptides are potent chemoattractants for neutrophils, indicating that FPR1 participates in innate immune defense mechanisms against bacterial infection (18, 41-42). FMLP is the most commonly used peptide for assessing immune cell functions (43). FPR1 also recognizes *N*-formyl peptides derived from mitochondrial proteins (44). Studies have recently demonstrated that mitochondrial protein-derived *N*-formyl peptides released from damaged tissues induce neutrophil activation and systemic inflammatory response, suggesting that FPR1 plays a major role in the association between trauma and inflammation (19, 26, 29, 45-46). In addition to formyl peptides, Table 1 lists examples of proteins and peptides that are FPR1 agonists (Table 1).

Trp-Lys-Tyr-Val-D-Met (WKYMVm) is a synthetic leucocyte-activating peptide postulated to use seven-transmembrane GPCRs, and can induce considerable chemotaxis and calcium flux in human phagocytes. Both FPR1- and FPR2-expressing cells mobilize calcium in response to picomolar WKYMVm concentrations, indicating that WKYMVm applies both FPR1 and FPR2 to stimulate phagocytes (47). In addition, WKYMVm is a more potent stimulus than FMLP is for NADPH oxidase in murine neutrophils (48).

FMLP-OMe, a synthetic methyl ester FMLP derivative, is a potent chemoattractant for phagocytes. It can bind to FPR1 and induces neutrophil responses. FMLP-OMe and its derivatives evoke chemotaxis and enhance cAMP and calcium levels in human neutrophils (49). Several FMLP-OMe analogs have been synthesized to characterize FPR1 interaction in phagocytes and resultant cellular activation. They trigger chemotaxis as well as produce superoxide and lysosomal enzymes at high concentrations in neutrophils (50-51).

HIV-envelope proteins contain domains that can interact with chemoattractant receptors on human phagocytes and have been identified as exogenous agonists for FPR1. The peptide domains, namely T20/DP178, are potent chemoattractants and activators of human peripheral blood phagocytes. These domains specifically induce the migration and elevation of intracellular calcium concentration by activating FPR1 in phagocytes. This suggests that the peptide domains of HIV-1 gp41 may activate the host innate immune response by interacting with FPR1 in human neutrophils (52). In addition, gG-2p20, a synthetic peptide derived from the secreted portion of herpes simplex virus type 2 glycoprotein G, has proinflammatory properties *in vitro*. This peptide was demonstrated as a chemoattractant for both monocytes and neutrophils in a dose-dependent manner, and it also induced the release of ROS from neutrophils. The responses were mediated through FPR1 (53).

Cathepsin G, an antimicrobial and proinflammatory neutrophil granule protein, is a chemoattractant for human leucocytes. Cathepsin G-induced phagocyte migration was specifically attenuated by the bacterial chemotactic peptide FMLP. Hence, cathepsin G did not induce a strong calcium flux and was a relatively weak activator of mitogen-activated protein kinases (MAPKs) through FPR1. Overall, cathepsin G acts as a host-derived chemotactic agonist for FPR1 (54).

Annexin 1 and derived peptides are glucocorti coid-induced proteins with several immunomodulatory actions and are considered endogenous FPR1 agonists. Initially, the low levels of annexin 1 induce calcium transients without completely activating the MAPK pathway. This inhibits the transendothelial migration of

neutrophils, which suggests that annexin 1 mediates potent anti-inflammatory effects (55-56). Furthermore, annexin 1-derived peptides induced neutrophils to reduce NADPH oxidase activity through FPR1 and inhibited oxidase activity in neutrophils triggered by FPR1-specific agonists (57). Annexin 1 acted on FPR1 in other tissues, except for leucocytes. Annexin 1-derived from necrotic glioblastoma cell supernatant induced the migration, invasion, proliferation, and colony formation of live tumor cells through the activation of FPR1 (58). The ablation of annexin 1 induced defects in intestinal mucosal wound repair, whereas the systemic administration of annexin 1 promoted wound recovery, suggesting that annexin 1 triggered the intestinal epithelial FPR1 signaling pathway to promote mucosal wound repair (59).

5. FPR1 SIGNAL TRANSDUCTION

In response to stimuli, specific receptors on the neutrophil surface are activated to trigger several downstream signaling pathways. FMLP, a strong chemoattractant that induces neutrophil activation (41), can bind to FPR1, a type of GPCRs (60). After binding to FPR1, Gi-type G-protein is activated, following which the conversion of GDP to GTP induces the dissociation of alpha subunits from beta gamma subunits. Next, the beta gamma subunits activate both the phospholipase C (PLC) beta and phosphoinositide 3-kinase (PI3K) gamma signaling cascades. PLC beta hydrolyses membrane-bound phosphoinositol-4,5-bisphosphate into diacylglycerol and inositol trisphosphate to mediate the release of intracellular calcium stores, which are abundant in the endoplasmic reticulum. Chemoattractants also activate protein kinase C and trigger the assembly of NADPH oxidases to produce ROS (24). Furthermore, the regulation of neutrophil cytoskeletal reorganization, respiratory burst, and chemotactic response after FPR1 activation involves the PI3K gamma-mediated conversion of phosphoinositol-4,5-bisphosphate into phosphoinositol-3,4,5-trisphosphate (61). As the beta gamma subunits activate and pull PI3K gamma toward the plasma membrane, the activities of Src-like tyrosine kinases are increased, further triggering MAPK signaling pathways. Erk and p38 MAPKs predominantly influence chemotaxis and FPR1-mediated transcriptional activity (62). cAMP is a vital secondary messenger for several cellular physiological functions. It can down-regulate immune responses, such as respiratory burst and degranulation, particularly in FMLP-activated neutrophils (63-64). Raf serine/threonine kinases are major signal transducers of diverse extracellular stimuli that activate the MAPK signaling pathways. The receptor-mediated activation of the small GTPase Ras recruits Raf to the plasma membrane where Raf kinase activity is regulated (65). The Raf-MEK-Erk signaling pathway is a protein kinase cascade that regulates cell growth, proliferation, and differentiation in response to growth factors, cytokines, and hormones (66-67). Furthermore, activation of FPR1 and beta 2-integrin stimulates protein tyrosine phosphorylation in human neutrophils is associated with the activation of the Src protein tyrosine kinase family member, Fgr. The activation of Fgr and Lyn is correlated with neutrophil adhesion. Complexes of phosphorylated Lyn and Shc with phosphatidylinositol 3-kinase are rapidly formed in stimulated neutrophils, correlating with phosphatidylinositol 1,4,5-trisphosphate formation and cell activation (68-69). In general, several signaling pathways are triggered to induce immune reactions in response to stimulation in human neutrophils.

6. FPR1-RELATED HUMAN DISEASES

6.1. Infectious inflammation

Inflammation is an essential immune mechanism in mammalian species that neutralizes invasive pathogens and eradicates any non-self materials. It is imperative for the immune system to distinguish self from non-self materials when triggering an immune response. In neutrophils, the recognition of non-self materials depends on specialized PRRs located on the cell surface. Numerous PRRs, such as FPRs, CXCR2 receptors, and toll-like receptors, have been identified recently (70-71). Among these PRRs, FPR1 was the first reported receptor that senses inflammatory stimuli and surrounding environments. An *in vitro* study demonstrated that the typical role of FPR1 was to facilitate the migration of neutrophils in the presence of FMLP, an *N*-formyl peptide derived from *Escherichia coli* (18, 41). *N*-formyl peptides from *Listeria monocytogenes* also stimulated superoxide anion generation and calcium mobilization in FPR1-expressing myelocytes (44). The ablation of FPR1 increased the probability of bacterial infection. Mice with ablated FPR1 exhibited a diminished survival rate and an increased bacterial load after infection with *L. monocytogenes,* though they developed normally. Neutrophils from FPR1$^{-/-}$ mice impaired chemotaxis in response to inflammatory stimuli (72-73). Furthermore, FPR-deficiency resulted in a higher mortality rate, which was associated with an increased bacterial burden in a mouse model of *Streptococcus pneumoniae*-induced meningitis. In the FPR1-deficient mice, pneumococcal infection increased immune cell density in brain tissue, and reduced anti-inflammatory cytokine and antimicrobial peptide expression (74). By contrast, the upregulation of FPR1 mRNA in neutrophils was observed after exposure to lipopolysaccharides (LPS), which were derived from gram-negative bacteria (75). The ablation of FPR1 reduced neutrophil recruitment in pulmonary tissue after exposure to LPS in mice. The level of pulmonary edema was attenuated in the absence of FPR1 in LPS-induced lung injury, suggesting that the protective role of FPR1 included neutralizing strategies in acute lung injury (76).

6.2. Sterile inflammation

N-formyl peptides are cleavage products of bacterial peptides as well as mitochondrial proteins (19).

Certain *N*-formyl peptides were identified and induced superoxide generation, calcium mobilization and MAPK activation by triggering FPRs (44). Increasing evidence shows that *N*-formyl peptides are DAMPs induced in response to cell damage and tissue injury to trigger sterile inflammatory responses (14, 77-79). An *in vitro* study demonstrated that mitochondrial formyl peptides released from necrotic cells activated monocytes through the binding of FPRs (45). Zhang *et al*. recently revealed that tissue injury induced the release of mitochondrial DAMPs into circulation. The mitochondrial DAMPs promoted calcium flux and MAPK phosphorylation in neutrophils, thus leading to neutrophil migration and degranulation *in vitro* and *in vivo*. In addition, they induced SIRS and lung injury *in vivo*, which was similar to the effects induced by bacteria pathogen-associated molecular patterns (29). The disrupted mitochondria of hepatocytes acted on FPR1 to trigger a chemotactic response and induce oxidative burst (46). The mitochondrial DAMPs of bones after fractures can activate neutrophils to release matrix metallopeptidase 9 and interleukin (IL)-8 through calcium and Erk MAPK, and induce inflammatory responses in pulmonary tissue (80). Moreover, Menezes *et al*. used a mouse liver thermal injury model and demonstrated that necrotic cells recruited neutrophils to the damaged area. The recruitment was reduced in the absence of FPR1, indicating that mitochondrial DAMPs from necrotic cells enabled neutrophils to promote localization directly in the existing areas of liver injury (26). The authors showed that in addition to liver thermal injury, mitochondrial products, including formyl peptides and mitochondrial DNA, collaborated in neutrophil-mediated injury and systemic inflammation during acute liver failure induced by acetaminophen overdose. Hepatocyte death was amplified by liver neutrophil infiltration, and the release of mitochondrial products into circulation possibly elicited a systemic inflammatory response and caused lung injury (81).

6.3. Glioblastoma

Human malignant astrocytic tumors are classified into high-grade astrocytomas (also called glioblastoma multiforme) and low-grade astrocytomas. Glioblastoma multiforme is characterized by difficult-to-treat and lethal brain tumors, which are usually resistant to treatment modalities such as chemotherapy and radiotherapy. The massive infiltration of high-grade tumor cells into brain tissue renders complete surgical resection impracticable. Although evidence shows that the prevalence of molecular feature is increasing, the origin cell types are still being explored (82). The roles of GPCRs associated with inflammation and glioma progression have been increasingly studied in recent years. In 2000, FPR1 was the first *N*-formyl peptide receptor identified in a glioma cell line, and the activation of FPR1 could induce intracellular calcium mobilization and cell migration in the glioma cell line (83). In addition, gene expression profiles indicated that FPR1 expression is higher in gliomas than it is in astrocytomas (84). Remarkably, FPR1 expression is high in high-grade human glioma tissue and enhances tumor cell migration as well as vascular endothelial growth factor (VEGF) production (85). The level of FPR1 expression in a glioma cell line is proportional to the tumor cell's ability in cell motility and invasion. Tumor cells with high levels of FPR1 expression were more invasive in mice connective tissue compared with those without FPR1 expression (86). Annexin 1, an FPR1 activator, was identified in the supernatant of necrotic glioma cells, and annexin 1-induced stimulation triggered glioma cell growth and invasion (58). Angiogenesis is crucial for tumor cell growth. FPR1 agonists can stimulate glioma cells to produce VEGF and IL-8 (85, 87). VEGF was produced in the presence of FPR1 agonists in glioma stem cells (88). These studies have confirmed that FPR1 expression is strongly associated with highly malignant glioma cells. FPR1 induces glioma cell growth and differentiation through several intracellular signaling pathways. The methylation of *p53*, a major tumor suppressor gene, reduces its expression and promotes tumor differentiation. Treatment using a methyltransferase inhibitor to reduce DNA methylation increases the *p53* level and reduces FPR1 expression. Therefore, *p53* methylation up-regulates FPR1 expression and promotes tumor cell differentiation (30). In addition, epidermal growth factor is a crucial growth-stimulating factor and its receptor is expressed in glioma cell lines. Evidence shows that epidermal growth factor receptors promote tumor cell motility and proliferation through the cooperation of FPR1 (89).

6.4. Gastric tumors

FPRs are associated with the progression of gastric cancer. They are expressed on gastric epithelium and are required for wound repair and the restitution of barrier integrity. FPR1 silencing in gastric cancer cell lines enhanced xenograft growth through cell proliferation induction and vascular density augmentation (90). However, higher FPR1 expression in gastric cancer tissues was associated with stronger tumor progression, implying poor overall survival in patients with gastric cancer (31). Nevertheless, the role of FPR1 in the progression of gastric cancer is controversial.

6.5. Emphysema

Chronic obstructive pulmonary disease (COPD) is often induced by long-term smoking and appears in elderly populations. It is characterized by chronic airway inflammation associated with immune cell accumulation. Neutrophils are increased in COPD lungs, and inflammatory products of neutrophils are closely related to disease progression and prognosis (91). FPR1 upregulation has been reported in patients with emphysema. Furthermore, upregulation was more obvious in patients with emphysema who smoke (92). Further research revealed that exposure to cigarette smoke induced neutrophil and macrophage migration

Table 2. FPR1-related human diseases

Disease pathology	Mechanism	References
Infective inflammation	Receptor ablation decreases bactericidal effects	73,74
Sterile inflammation	Increased tissue injuries	29,46,80
Glioblastoma	Increased tumor cell motility and invasion	86
	Enhancing angiogenesis	85,87
Gastric tumor	Associated with tumor progression	31
Emphysema	Upregulated receptor and increased lung injury	92,93
Colitis	Increased inflammatory injury	100,101
Periodontitis	Polymorphism	109-112

in wild-type mice. Mice with ablated FPR1 exhibited a low number of neutrophils and decreased macrophages accumulation in pulmonary tissue (93).

6.6. Colitis

Inflammatory colitis, such as ulcerative colitis and Crohn's disease, begins with the destruction of mucosal barrier integrity. The stimulation of FPR1 agonists has been reported to be closely related to the pathogenesis of inflammatory colitis (94-95). FPRs have been identified in intestine epithelial cells. The stimulation of FPRs by commensal bacteria or their products plays a major role in epithelial cell turnover and wound healing (96-97). Epithelial cell migration might be associated with wound healing. FPR1 activation induced the migration of colorectal tumor epithelial cells through calcium-dependent signaling pathways (98). Furthermore, FPR1 was present in normal human colonic epithelial cells. The stimulation of FPR1 enhanced the restitution of intestinal epithelial cells through PI3k, Rac1, and Cdc42 activation (99). Gut microbiota stimulated FPR1 on intestinal epithelial cells to generate ROS through the activation of NADPH oxidases to promote enteric wound repair (100). Moreover, the absence of FPR1 expression caused less inflammatory injury in a colitis model; however, the recovery was delayed (101).

6.7. Periodontitis

Aggressive periodontitis is characterized by rapid attachment loss and alveolar bone destruction (102). Neutrophils from patients with aggressive periodontitis exhibit reduced neutrophil immune responses (103-104). For example, compared with that from a normal population, the phagocytic activity of neutrophils from patients with progressive periodontitis was reduced (105-106). In addition, neutrophils from patients with aggressive periodontitis demonstrated less chemotactic activity (107-108). Remarkably, impaired FPR1 expression, including various types of single nucleotide polymorphisms, impaired neutrophil chemotaxis and was associated with the development of aggressive periodontitis (Table 2) (109-112).

7. CONCLUSION

Growing evidence shows that excess neutrophil inflammatory responses can be harmful to human health (4, 113-114). Therefore, understanding the mechanisms that trigger and regulate immune responses is imperative. Increasing evidence shows that FPR1 plays critical roles in triggering sterile and infectious inflammation. FPR1 is activated by *N*-formyl peptides, which are derived from bacterial peptides or mitochondrial proteins (19, 42). The endogenous DAMPs from bone and liver mitochondria can activate neutrophils through FPR1 and induce SIRS (29, 46, 80). Therefore, concerns have been raised about the potential of functional FPR1 as a therapeutic target in the development of new drugs to treat inflammatory diseases (24, 115).

In conclusion, this review explores the major role of FPR1 in immunomodulatory effects as well as in tumor progression. Considering the relevance of FPR1-related signaling pathways in inflammatory processes, this review reveals possible venues for developing therapeutic potential drugs to attenuate neutrophil-mediated inflammatory diseases.

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Abbreviation: formyl peptide receptor 1, FPR1; polymorphonuclear leucocytes, PMNs; neutrophil extracellular traps, NETs; reactive oxygen species, ROS; pathogen recognition receptors, PRRs; G-protein coupled receptors, GPCRs; damage-associated molecular patterns, DAMPs; systemic inflammatory response syndrome, SIRS; *N*-formylmethionine-leucyl-phenylalanine, FMLP; lipoxin A4, LXA_4; Trp-Lys-Tyr-Val-D-Met, WKYMVm; mitogen-activated protein kinases, MAPKs; phospholipase C, PLC; phosphoinositide 3-kinase, PI3K; lipopolysaccharides, LPS; metallopeptidase, MMP; interleukin, IL; vascular endothelial growth

factor, VEGF; Chronic obstructive pulmonary disease, COPD

Key Words: Formyl Peptide Receptor; Human Diseases, Review

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