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Formyl peptide receptors at the interface of inflammation, angiogenesis and tumor growth

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ABSTRACT

N-formyl peptide receptors (FPRs) belong to the family of pattern recognition receptors (PRRs) that regulate innate immune responses. Three FPRs have been identified in humans: FPR1–FPR3. FPR expression was initially described in immune cells and subsequently in non-hematopoietic cells and certain tissues. Besides their involvement in inflammatory disorders, FPRs have been implicated in the regulation of tissue repair and angiogenesis. Angiogenesis is not only a key component of pathogen defence during acute infection and of chronic inflammatory disorders, but also plays a critical role in wound healing and tissue regeneration. Moreover, pathologic uncontrolled angiogenesis is central for tumour growth, progression, and the formation of metastases. In this review, we summarise the evidence for a central role of FPRs at the intersection between inflammation, physiologic angiogenesis and pathologic neovascularisation linked to cancer. These findings provide insights into the potential clinical relevance of new treatment regimens involving FPR modulation.

Contents

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1. Formyl peptide receptors

Bacteria are mostly eliminated by the innate immune system, which recognizes pathogens through receptors known as pattern recognition receptors (PRRs). These receptors sense conserved molecular motifs known as pathogen- or danger-associated molecular patterns (PAMPs, DAMPs), which in turn activate the recruitment and activation of immune cells leading to inflammation (Fig. 1) [1]. *N*-formyl peptides, such as the *Escherichia coli*-derived fMet-Leu-Phe (fMLF), are PAMPs recognized by formyl peptide receptors (FPRs) [2].

The three FPRs identified in humans (FPR1–FPR3) are encoded by three different genes clustered on chromosome 19q13.3–19q13.4 (Fig. 1) [3]. FPRs (FPRs) are seven transmembrane G protein-coupled receptors that can be inhibited by pertussis toxin [4–8], indicating that the G proteins associated with these receptors belong to the G_i family [9]. FPR triggering activates various signalling pathways, including: phospholipase C (PLC)-dependent production of inositol (3,4,5)-trisphosphate (IP3), inducers of Ca^{2+} increase, and diacyl glycerol (DAG), which in turn activates protein kinase C (PKC); and RAS-dependent activation of the mitogen-activated protein kinases (MAP kinases) cascade [3].

The first FPR1 ligand described is the fMLF peptide, which binds with high affinity (in the nM range) to and activates FPR1. Formylated peptides derived from *Listeria monocytogenes* also selectively activate FPR1 [10] (Table 1). Formylation of peptides also occurs in mitochondria. Thus, the release of formylated peptides secondary to cell death might allow attraction of phagocytic leukocytes through FPRs [2]. FPR2, aka "lipoxin A4 (LXA4) receptor (ALX/FPR2)", is considered a low-affinity receptor for formylated peptides given its activation upon exposure to high fMLF concentrations (in the μM range) *in vitro* [11] (Table 2). FPR3 does not bind or respond to fMLF, and shares some non-formylated chemotactic peptide ligands with FPR2 [3] (Table 3).

Ligand diversity is a feature of the FPR family (Tables 1-3) (Fig. 1). In the last 10 years, several natural and synthetic small-molecular-weight, even non-formylated, ligands for FPRs have been identified through compound library screening. Amongst agonists, several microbe-derived formylated or non-formylated peptides have been identified that can bind FPRs. In addition to "exogenous", a large number of "endogenous" peptides of various molecular nature, functioning as DAMPs, have been identified as agonists at FPRs [3] (Tables 1–3) (Fig. 1). Some FPR agonists can activate FPR anti-inflammatory signalling properties: annexin A1 (AnxA1) and its N-terminal peptide Ac2–26, and the two nonpeptidic ligands lipoxin A4 (LXA4) and resolvin D1 (RvD1) [12] (Table 2). Among antagonists, cyclosporin H (CsH), an optical isomer of the immunosuppressant cyclosporin A, is a cyclic undecapeptide produced by fungi that displays selective antagonistic activity at human FPR1 [13,14] (Table 1).

1.1. FPRs in the inflammatory response

FPRs are expressed in abundance on cells of the host defence system, where they exert immune surveillance against *N*-formyl peptides from bacteria. FPR expression has primarily been described in myeloid cells, although the distribution of the three receptors varies within myeloid cell subsets (Fig. 1) [15]. The FPR family has evolved as chemoattractant receptors that assist the organism in counteracting bacterial infections, in particular by facilitating the trafficking of phagocytes to the site of bacterial invasion [3]. At sites of inflammation, FPR signalling has been reported to modulate also the survival [16] and the phagocytic activity of infiltrating cells [17,18].

During an acute inflammatory response, leukocytes migrate towards an increasing concentration gradient (range from nM to μM concentrations) of chemotactic factors, including formylated-peptides. In a later inflammatory phase, a number of anti-inflammatory FPR2/ALX ligands are generated (RvD1, AnxA1 and LXA4). These could exert inhibitory effects on the leukocyte migratory response [17,19]. Thus, it is conceivable that generation of formylated-peptides by microorganisms and local necrotic cells would control leukocyte trafficking during the acute stage of the inflammatory response thereby overcoming the functions of the endogenous anti-inflammatory FPR2/ALX agonists. The production of such endogenous anti-inflammatory mediators may become increased at a later stage of the innate immune response to induce resolution of the inflammation [12]. Accordingly, FPR2/ALX agonists promote the removal of apoptotic neutrophils by macrophages [17,20]. Furthermore, the activation

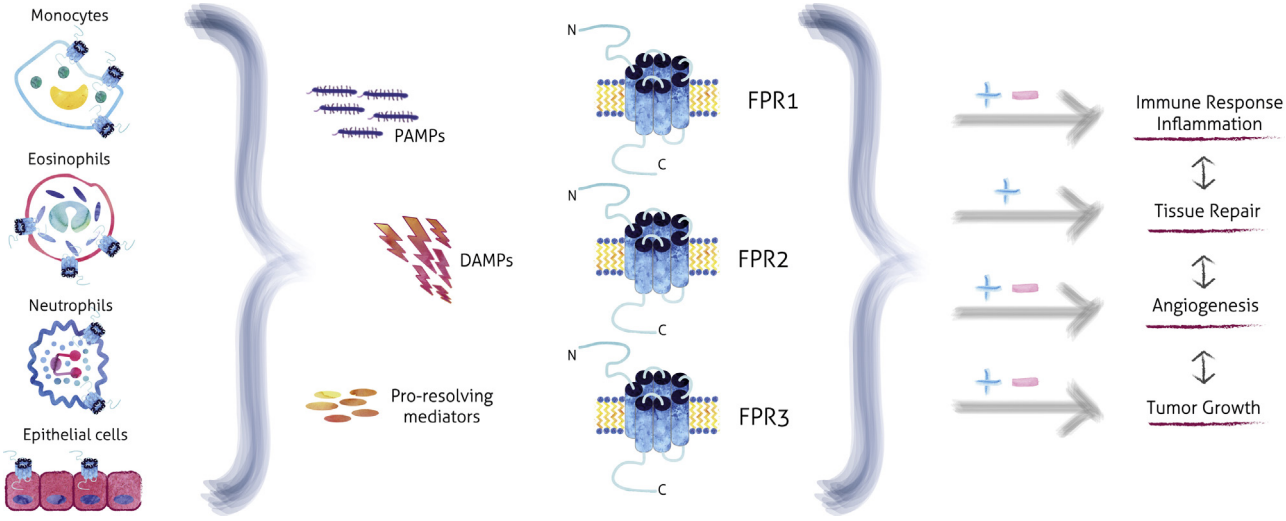

Fig. 1. Three FPRs have been identified in humans: FPR1–FPR3. FPR expression has primarily been described in myeloid cells and subsequently in multiple tissues and cell types, including epithelial cells. These receptors sense conserved molecular motifs known as pathogen- or danger-associated molecular patterns (PAMPs, DAMPs). Some FPR agonists can activate FPR anti-inflammatory and pro-resolving signalling properties. The activation of FPRs play a crucial role in the modulation of inflammatory response depending on the ligands involved (pro- or anti-inflammatory). FPR stimulation, in epithelial cells is involved in tissue regeneration and wound healing. FPRs promote angiogenesis in various inflammatory settings. However, FPRs also exhibit anti-angiogenic properties. The involvement of FPRs in cancer has been investigated in only a few models thus far, and the results obtained suggest that the roles differ in relation to the specific tissue affected.