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Review Article

The Chemoattractant Receptor Fpr2 and Its Endogenous Ligand CRAMP Contribute to the Maturation and Trafficking of Dendritic Cells in Diseases

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Abstract

The G-protein coupled chemoattractant receptor FPR2 (Fpr2 in mice) interacts with a great number of bacteria-derived and endogenous chemotactic ligands, including cathelicidin-related antimicrobial peptide (CRAMP), which exhibits direct antibacterial activity but also acts as a chemoattractant for myeloid cells and enhances adaptive immunity of the host. Recently, owing to the development of genetically engineered mouse strains, the in vivo role of Fpr2 and CRAMP has been increasingly recognized. In this review, we will summarize the involvement of Fpr2 and CRAMP in the trafficking of dendritic cells (DCs) in pathophysiological conditions and their capacity to promote DC maturation during immune responses. These molecules are thus considered as potential targets for mobilizing host responses in disease conditions.

Keywords: *Fpr2; CRAMP; Dendritic cells; Maturation; Trafficking*

Introduction

Human and mouse Formylpeptide receptors (FPRs)

Formylpeptide receptors (FPRs) belong to the G-protein coupled chemoattractant receptor (GPCR) family, which is recognized as important mediators in inflammatory and immune responses [1,2]. The human FPR subfamily consists of three members, FPR1, FPR2 and FPR3 [1,2]. FPR1 is a high affinity receptor for the bacterial and mitochondrial formylpeptides such as formyl-methionyl-leucyl phenylalanine (fMLF) and mediates phagocyte chemotaxis and activation. FPR1 also mediates the leukocyte chemotactic activity of a host-derived neutrophil granule protein cathepsin G [3]. *In vivo*, FPR1 plays a critical role in host defense against infection by *Listeria monocytogenes* as shown by evidence obtained in mice deficient in the FPR1 homologue, Fpr1 [4]. FPR2 and its mouse counterpart Fpr2 are low affinity receptors for bacterial fMLF, but they interact with a greater variety of endogenous chemotactic agonist peptides released during inflammatory and immune responses [2]. Similar to Fpr1, Fpr2 also plays an essential role in mouse resistance against *Listeria* infection [4,5] as shown by experiments performed with Fpr2 single and Fpr1/2 double deficiency mice in which markedly increased mortality was shown after pathogen infection. FPR3 in human recognizes a chemotactic peptide fragment derived from Heme-binding protein that chemoattracts dendritic cells (DCs) [6]. In mice, Fpr2 is likely a receptor that functions as both human FPR2 and FPR3 [4,7].

Human and mouse cathelicidins

Cathelicidins are small, cationic, antimicrobial peptides found in human and other species, including farm animals (cattle, horses,

pigs, sheep, goats, chickens, rabbits and in some species of fish) [8]. One cathelicidin gene has been identified in human, which encodes the peptide LL-37 of 37 aa residues, with a molecular weight of 18 kDa [9,10], also known as hCAP-18, FALL-39 or CAMP-human cationic antimicrobial peptide [9,10]. LL-37 is expressed by various cells and tissues such as bone marrow (BM) myeloid cells, neutrophils, macrophages and epithelial cells. The expression of LL-37 is detected in the skin, gastrointestinal tract including mouth, tongue, esophagus and colon as well as urinary tract and the lung [11-14].

Cell types		Reference
Leukocytes	Neutrophils Macrophages B-cells γδ T cells Mast cells	Tjabringa G., *et al.* "The human cathelicidin LL-37: a multifunctional peptide involved in infection and inflammation in the lung". *Pulmonary pharmacology &therapeutics* 18.5 (2005): 321-327.
	Dendritic cells	Chen K., *et al.* "The Formylpeptide Receptor 2 (Fpr2) and Its Endogenous Ligand Cathelin-related Antimicrobial Peptide (CRAMP) Promote Dendritic Cell Maturation". *The Journal of biological chemistry* 289.25 (2014): 17553-17563.
Epithelial cells	Lung	Kovach M., *et al.* "Cathelicidin-related antimicrobial peptide is required for effective lung mucosal immunity in Gram-negative bacterial pneumonia". *Journal of Immunology* 189.1 (2012): 304-311.
	Stomach	Hase K, *et al.* "Expression of LL-37 by human gastric epithelial cells as a potential host defense mechanism against Helicobacter pylori". *Gastroenterology* 125.6 (2003): 1613-1625.
	Colon	Hase K., *et al.* "Cell differentiation is a key determinant of cathelicidin LL-37/human cationic antimicrobial protein 18 expression by human colon epithelium". *Infection and Immunity* 70.2 (2002): 953-963.
	Urinary tract	Chromek M., *et al.* "The antimicrobial peptide cathelicidin protects the urinary tract against invasive bacterial infection". *Nature Medicine* 12 (2006): 636-641.
	Cervix	Frew L, *et al.* "Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men". *PLOS One* 9.1 (2014): e85805.
	Inflamed skin	Reinholz M., *et al.* "Cathelicidin LL-37: an antimicrobial peptide with a role in inflammatory skin disease". *Annals of Dermatology* 24.2 (2012): 126-135.
Body fluids	Bronchoalveolar lavage fluid	Agerberth B., *et al.* "Antibacterial Components in Bronchoalveolar Lavage Fluid from Healthy Individuals and Sarcoidosis Patients". *American Journal of Respiratory and Critical Care Medicine* 160.1 (1999): 283-290.
	Seminal plasma	Malm J., *et al.* "The human cationic antimicrobial protein (hCAP-18) is expressed in the epithelium of human epididymis, is present in seminal plasma at high concentrations, and is attached to spermatozoa". *Infection and Immunity* 68.7 (2000): 4297-4302.
	Cervicovaginal secretion	Frew L, *et al.* "Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men". *PLOS One* 9.1 (2014): e85805.
	Saliva	Murakami M., *et al.* "Cathelicidin Antimicrobial Peptides Are Expressed in Salivary Glands and Saliva". *Journal of Dental Research* 81.12 (2002): 845-850.
	Plasma	Sorensen O., *et al.* "An ELISA for hCAP-18, the cathelicidin present in human neutrophils and plasma". *Journal of Immunological Methods* 206.1-2 (1997): 53-59.

Table 1: *Presence of LL-37 in various cell types and body fluids.*

The mouse homologue of LL-37 is cathelin-related antimicrobial peptide (CRAMP). The gene, named *Cramp* for CRAMP, was mapped to chromosome 9 at a region of conserved synteny, homologous to the map locations of cathelicidins in human [15]. CRAMP was expressed abundantly by granulocytes and bone marrow cells of the myeloid lineage, which agrees with the sites of expression of cathelicidins in human and during embryogenesis as early as E12, the earliest stage of blood development [15-18]. The expression of CRAMP is detectable in adult mouse testis, spleen, stomach, and intestine but not in the brain, liver, heart, or skeletal muscle [15]. Multitudes of biological functions have been defined for CRAMP, which not only acts as a host-derived natural antibiotic [8], but also chemoattractant for myeloid cells and promotes the immune responses in mice [19,20].

Fpr2 and CRAMP in DC Maturation

DC maturation

Dendritic cells (DCs) are bone marrow–derived, specialized antigen-presenting cells (APCs) and consist of heterogeneous populations. DCs are abundantly distributed in body surface tissues such as the skin, pharynx, upper oesophagus, vagina, ectocervix and anus. It is also expressed in tissues of the so called internal or mucosal surfaces including respiratory and gastrointestinal systems. This distribution increases the opportunity for DC capture of antigens from the environment even when there is no overt infection or inflammation, which may allow for the silencing of the immune system to harmless environmental antigens. In response to danger signals such as bacterial and viral infection, the DC network rapidly promotes T-cell-mediated immunity to selectively eliminate infected cells. The hallmarks of DC functions are their ability to capture antigens, to process and present antigenic peptides in the context of MHC, and to migrate through tissues to reach secondary lymphoid organs, where stimulation of naïve T cells takes place. There is also evidence for the steady-state migration of DC into the lymph nodes under normal conditions which may serve to tolerize T cells against self and non-dangerous antigens.

DCs undergo a complex process of maturation, a 'metamorphosis' from an antigen-capturing cell into APCs. This process includes changes in morphology such as the loss of adhesive structures, cytoskeleton reorganization, the acquisition of high cellular motility [21], loss of endocytic/phagocytic capabilities, secretion of chemokines, up-regulation of costimulatory molecules, such as CD40, CD80, and CD86, translocation of MHC class II to the cell surface and production of cytokines that differentiate and polarize effector cells [22]. DCs are activated by numerous agents derived from microbes, dying cells and cells of the innate and adaptive immune system.

Activation of DCs

Activation of DCs is initiated largely by signals from pattern recognition receptors (PRRs) expressed by immature DCs, which respond to evolutionarily conserved molecular signatures of microbes, parasites, and viruses, known as pathogen-associated molecular patterns (PAMPs) [22,23]. PAMPs are recognized through at least four PRR families: Toll-like receptors (TLRs), cell surface C-type lectin receptors (CLRs), and intracytoplasmic nucleotide oligomerization domain (NOD)-like receptors (NLRs) as well as retinoic acid inducible gene I (RIG-I)-like receptors (RLRs). These signals convert resting immature DCs into potent antigen-presenting cells (mature DCs) capable of promoting the expansion and differentiation of naive pathogen-specific effector T cells [24-26]. Microbes also activate a wide repertoire of cells, such as epithelial cells, fibroblasts, and cells of the innate immune system, to secrete cytokines capable of indirectly activating DCs, [27,28].

Fpr2 and CRAMP in DC maturation

CRAMP as a chemoattractant and anti-microbial peptide is not able to directly promote the differentiation of immature DCs into mature DCs, but rather, by increasing the response of immature DCs to differentiation and maturation signals. BM-derived immature DCs from wild type (WT) mice express CRAMP and its receptor Fpr2 [29]. The interaction of Fpr2 with CRAMP via an autocrine or paracrine loop primes immature DCs to enhance the sensitivity to LPS stimulation. This was demonstrated by the fact that in DC culture, neutralization of either Fpr2 or CRAMP decreased DC maturation in response to LPS. In contrast to the stimulating effect of exogenous CRAMP, LPS-

treated DCs from Fpr2 deficiency ($Fpr2^{-/-}$) mice failed to express normal levels of maturation markers with reduced production of IL-12 and diminished chemotaxis in response to the DC homing chemokine CCL21 mediated by the receptor CCR7. DCs also failed to induce a robust allogeneic T-cell proliferation *in vitro*, and their recruitment into the T-cell zones of the spleen was reduced after antigen immunization of $Fpr2^{-/-}$ mice. The involvement of CRAMP in DC maturation was further confirmed by the observation showing that addition of exogenous CRAMP to immature $Fpr2^{-/-}$ DC culture failed to increase the cell sensitivity to LPS stimulation. After treatment with LPS, mature DCs differentiated from $CRAMP^{-/-}$ mice showed a considerably lower level of expression of the mature DC markers CD86, CD80, and MHC II as compared with the cells from WT mice. The addition of exogenous CRAMP restored the responses of iDCs from $CRAMP^{-/-}$ mice to LPS. Mechanistic studies showed that there was a rapid phosphorylation (5 min) of p38 MAPK in iDCs from WT mice stimulated by a low level of (0.1 μg/ml) LPS. In contrast, much higher levels of LPS (0.5 μg/ml) were required to stimulate a delayed phosphorylation of p38 (30 min) in iDCs from $Fpr2^{-/-}$ mice, albeit the cells from both mice showed comparable levels of ERK1/2 MAPK phosphorylation. There was also a delayed degradation of IkB-α in $Fpr2^{-/-}$ mouse DCs after LPS stimulation as compared with WT mouse DCs, an indication of reduced NF-κB activation. Therefore, both CRAMP and Fpr2 are important contributors to DC differentiation and maturation (Fig. 1).

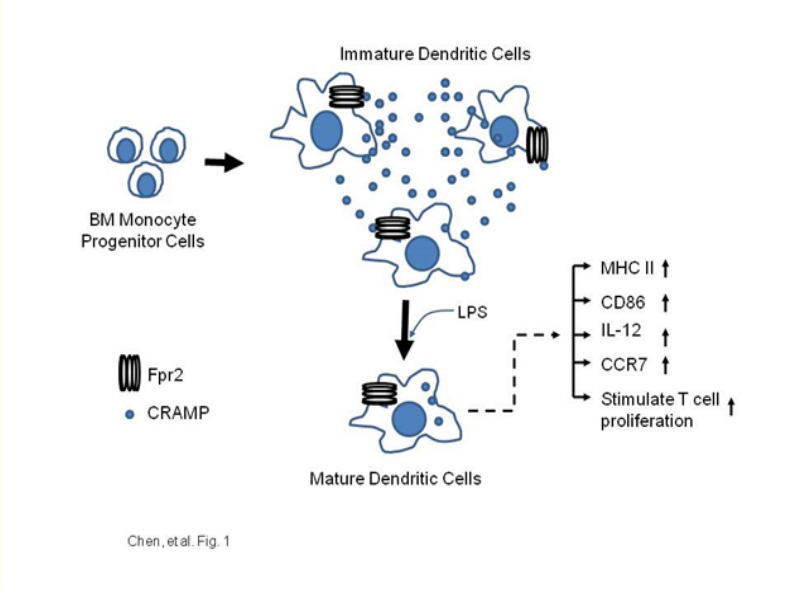

Figure 1: *Fpr2/CRAMP interaction increases the sensitivity of immature DCs to maturation signals.*

DC maturation is regulated by autocrine or paracrine signaling pathways. For instance, human monocyte-derived DCs (MoDCs) and the $CD1c^+$ and $CD123^+$ peripheral blood DC populations express both activin-A and the type I and II activin receptors. MoDCs and $CD1c^+$ myeloid DCs rapidly secrete high levels of activin-A after exposure to bacteria, TLR ligands or CD40 ligand (CD40L). Blocking autocrine activin-A signaling in DCs enhances the production of cytokines (IL-6, IL-10, IL-12p70, and TNF-α) and chemokines (CXCL8, CXCL10, CCL5, and CCL2) by DCs upon CD40L stimulation, accompanied by enhanced expansion of viral antigen-specific effector $CD8^+$ T cells [30]. The anti-inflammatory cytokine IL-10 also regulates DC maturation. After stimulation with bacteria, LPS, lipoteichoic acid, or soluble CD40 ligand, DCs secrete high levels of IL-10. Addition of an anti-IL-10-neutralizing Ab to immature DC culture with soluble CD40 ligands or LPS resulted in enhanced expression of CD83, CD80, CD86, and MHC molecules by DCs and markedly augmented release of TNF-a and IL-12 in association with increased capacity to activate allogeneic T cells and polarize naive T cells to more prominent Th1 phenotype [31]. These

data indicate that both autocrine activin-A and IL-10 prevent spontaneous maturation of DCs, limiting LPS- or CD40-mediated maturation. In contrast, naive DCs exposed to cytokines and chemokines released by Newcastle Disease Virus (NDV)-infected DCs are relatively resistant to virus infection and primed to more rapidly respond to viral infection with accelerated and augmented levels of costimulatory molecules. Therefore, primed antiviral expression of DCs was induced by paracrine signaling from infected DCs [32]. By analogy, autocrine and paracrine signaling via Fpr2 and CRAMP is also an important component of regulatory network in DC maturation, thereby to sustain DC sensitivity to LPS stimulation.

Fpr2 and CRAMP Axis in DC Trafficking in the Lung During Airway Inflammation

Cathelicidin expression and antimicrobial activity in airway diseases

The airway is continuously bombarded by a vast array of inhaled microbial pathogens. To combat these infectious insults, the respiratory tract is equipped with diverse mechanisms of innate mucosal immunity, including the expression of antimicrobial peptides. Prominent among these antimicrobial peptides are the cathelicidin family members [33]. In human, LL-37 was expressed in the trachea and lung [11]. Over-expression of LL-37 analog in mouse airways reduced bacterial load while systemic over-expression decreases the mortality following bacterial challenge [34]. In mice, lung macrophages and alveolar epithelial cells are the main sources of CRAMP following exposure to the microbial pathogen *K. pneumonia* [33].

Asthma is a chronic inflammatory disorder characterized by airway inflammation and hyperresponsiveness. The disease is mediated by increased levels of T-helper 2 (Th2) cytokines, IL-4, IL-5, and IL-13 and elevated serum IgE [35]. The expression of CRAMP in the lung is up-regulated during asthmatic syndrome [36,37]. Glucocorticoids are regarded as the most effective treatment for asthma and as a first line medicine recommended by international guidelines [36]. However, glucocorticoids such as budesonide suppresses pulmonary antibacterial host defense in asthmatic mouse model and inhibits the function of lung epithelial cells because the effect of budesonide is dependent on the down-regulation of CRAMP [36]. Therefore, the production of CRAMP by airway epithelial cells and inflammatory cells plays an important role in the antibacterial immune responses.

The leukocyte chemotactic activity of CRAMP

However, in addition to its antimicrobial properties, LL-37 and mouse CRAMP induce migration of neutrophils, monocytes/macrophages, eosinophils, and mast cells [20]. LL-37 activates FPR2 on human monocytes to trigger β1- and β2-integrin conformational change that allows for cell adhesion [38] and induces $Ca2^{+}$ mobilization in the cells [39,40]. Injection of mouse CRAMP into skin air pouches results in the accumulation of neutrophils and monocytes, indicating the capacity of CRAMP to act as a chemoattractant in vivo via Fpr2, the mouse homologue of human FPR2 [19].

Fpr2 and CRAMP in DC trafficking in the lung

Multiple chemokine GPCRs are involved in DC accumulation at the sites of inflammation and immune responses. For instance, the chemokine receptor CCR2 not only is a discriminative marker between inflammatory/classical monocytes ($CCR2^{+}Ly6C^{high}$) and resident/patrolling/non classical monocytes ($CCR2^{+}Ly6C^{low}$), but it also participates in the recruitment of inflammatory monocytes to the sites of infection, trauma, or tumor [41]. In allergic airway inflammation, following short-term allergen inhalation, there is a rapid recruitment of $CCR2^{+}$ $Ly6C^{+}$ myeloid DC precursors from the circulation to the airway mucosa [42,43]. In mouse or rat models of asthma, there is an 80-fold increase in the number of myeloid DCs in the airway mucosal layer and in bronchoalveolar lavage fluid [44-46]. The interaction between DCs and T cells may occur both locally in the airways and in secondary lymphoid tissues. After antigen challenge of primed mice, there is an increased migration of airway DCs into mediastinal lymph nodes (MLNs) where antigen presentation and T cell activation occur. Thus, inflammatory DCs are critical for the progression of allergic airway disease [45-47].

Defects in DC function attenuate the development of ovalbumin (OVA)-induced airway inflammation in animal models. For example, a chemokine CCL2 is critical for the mobilization of DC precursors from BM to the circulation and subsequent trafficking into the perivascular regions in the lung. It is therefore not surprising that mice deficient in the CCL2 receptor CCR2 ($CCR2^{-/-}$) showed defective trafficking of antigen-loaded lung DCs resulting in reduced Th2 responses and protection from OVA-induced airway inflammation [48-51]. Fpr2 is also involved in DC trafficking in mouse model of asthma as $Fpr2^{-/-}$ mice show reduced severity in OVA-induced allergic airway inflammation associated with diminished recruitment of $CD11c^{+}$ DCs into peribronchiolar regions of the inflamed lung and reduced Type 2 immune responses [52]. Further investigation revealed that the endogenous Fpr2 ligand CRAMP controls DC trafficking from the perivascular to the peribrochiolar regions inside the inflamed lungs as the allergy progresses [53]. These observations establish a paradigm of sequential DC trafficking mediated by a chemoattractant receptor signal relay initiated by CCR2 followed by Fpr2 and CCR7 to complete the journey of DCs to LN for Th2 priming.

Perspectives

Studies of antimicrobial peptides identify LL-37 as a broad-spectrum antimicrobial peptide which kills both gram-positive and gram-negative bacteria and fungi with LPS-neutralizing activity [54,55]. $CRAMP^{-/-}$ mice show a decreased capacity to control skin infection and CRAMP protects mice from the insult resulted from inflammatory bowel disease [56,57]. The antimicrobial and immuno-stimulating properties of LL-37 and CRAMP provide important perspectives of such bio-peptides for clinical application. For instance, PG-1 (pig peptide protegrin) had up to 100% systemic protection against infections caused by intraperitoneal injection of *P. aeruginosa*, *S. aureus* and methicillin-resistant *S. aureus* in rats [58]. Ovine cathelicidins SMAP29 and SMAP34 are potential candidates for use in human against bacterial infection and immune-suppression [59].

However, LL-37 may act as a double edged sword in host defense. In cancer, cathelicidin expressed by immune cells in the tumor microenvironment, promotes colon cancer growth through activation of the PTEN/PI3K/Akt and Wnt/β-catenin signaling pathways [60]. Another study showed that CRAMP-deficient mice exposed to cigarette smoke (CS) are more resistant to Lewis lung carcinoma cell implantation because CS exposure-induced recruitment of myeloid cells into tumor tissue is in a CRAMP-dependent manner. The peptide expressed by myeloid cells promotes CS-induced lung tumor growth by further recruiting inflammatory cells [61]. It is therefore important to note that further studies are needed to determine the transcriptomic patterns of particular cathelicidins in particular time points of infection or cancer progression to unravel their roles. There is also a need to develop disease models with genetically engineered animals to fully establish the role of anti-microbial peptides in pathophysiological conditions and their potential in translational medicine.

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Conflict of Interest

The authors declare that they have no conflicts of interest with the contents of this article.

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