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*J Immunol* 2005; 175:685-692; doi: 10.4049/jimmunol.175.2.685

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The Synthetic Peptide Trp-Lys-Tyr-Met-Val-D-Met Inhibits Human Monocyte-Derived Dendritic Cell Maturation via Formyl Peptide Receptor and Formyl Peptide Receptor-Like 2

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Trp-Lys-Tyr-Met-Val-D-Met (WKYMVm) has been reported to stimulate monocytes, neutrophils, and dendritic cells (DCs). However, although WKYMVm has been reported to function as a DC chemoattractant, its role on DC maturation has not been examined. In this study, we investigated the effects of WKYMVm on human DC maturation. The costimulation of DCs with WKYMVm and LPS dramatically inhibited LPS-induced IL-12 production, CD86 and HLA-DR surface expression, and DC-mediated T cell proliferation. However, DC phagocytic activity was increased by WKYMVm stimulation. These findings demonstrate that WKYMVm inhibits DC maturation by LPS. In terms of the mechanism underlying DC maturation inhibition by WKYMVm, we found that LPS-induced DC maturation was negatively regulated by WKYMVm-stimulated ERK activity. Moreover, the costimulation of DCs with WKYMVm and LPS dramatically inhibited the LPS-induced accumulations of IL-12 mRNA, thus suggesting that WKYMVm inhibits LPS-induced IL-12 production at the transcriptional level. We also found that DCs express two WKYMVm receptors, formyl peptide receptor (FPR) and FPR-like 2 (FPRL2). In addition, formyl-Met-Leu-Phe (a FPR ligand), Trp-Lys-Tyr-Met-Val-Met, Hp(2–20) peptide, and F2L (three FPRL2 ligands) inhibited LPS-induced IL-12 production in DCs. Taken together, our findings indicate that the activations of FPR and FPRL2 inhibit LPS-induced DC maturation, and suggest that these two receptors should be regarded as important potential therapeutic targets for the modulation of DC maturation. The Journal of Immunology, 2005, 175: 685–692.

Dendritic cells (DCs) play a key role in adaptive immune response. DCs uptake pathogens or cancer cells, process them, and then present processed peptides to the surface-bound MHC molecule, which is recognized by T cells (1, 2). Stimulated T cells then initiate primary Ag-specific immune responses. Once activated by either inflammatory stimuli or infectious agents, immature DCs undergo maturation, a process that involves the up-regulation of surface molecules, such as HLA-DR, CD40, CD83, and CD86 (1, 3). Mature DCs also acquire the remarkable ability to produce a broad variety of cytokines, including IL-12 (4). It has been reported that various extracellular stimuli, e.g., LPS and TNF-α, stimulate DC maturation (5–8). However, the extra-cellular signals that regulate LPS or TNF-α-induced DC maturation have not been fully identified.

Trp-Lys-Tyr-Met-Val-D-Met (WKYMVm; a synthetic peptide) was originally identified as a peptide library component that stimulated leukocyte activity (9, 10). Previous studies have demonstrated that WKYMVm induces human monocytes and neutrophils to generate cellular superoxide and to undergo chemotactic migration (11–13). Three cell surface G-protein-coupled WKYMVm receptors have been identified (14–16), namely, formyl peptide receptor (FPR), FPR-like 1 (FPRL1), and FPR-like 2 (FPRL2) (14–16). Moreover, as FPR family members play a key role in innate immune response, WKYMVm has proven useful in the study of phagocyte activation mechanisms. In terms of the functional roles of FPR ligands, it has been reported that the activation of FPR by the HIV-derived peptide T-20 suppresses IL-12 production by human monocytes (17). However, the effect of WKYMVm on adaptive immune response has not been elucidated. Recently, DCs, which play a key role in the regulation of adaptive immune responses, were also found to express FPR family receptors (18). Furthermore, WKYMVm has been reported to function as a chemoattractant for human monocyte-derived DCs (MoDCs) (18), but the roles of FPR family members and the effects of WKYMVm on DC maturation have not been determined.

In the present study, we undertook to characterize the effects of WKYMVm on LPS-induced DC maturation, and to further investigate the target receptors and signaling pathways involved in the regulation of WKYMVm-induced DC maturation.

Materials and Methods

Materials

RPMI 1640 medium was bought from Invitrogen Life Technologies. Dialyzed FBS and supplemented bovine calf serum were purchased from

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MoDCs were matured by stimulating them with LPS (100 ng/ml) or TNF-α and recombinant human IL-4 (10 ng/ml; Pierce Endogen). All cultures were supplemented with recombinant human GM-CSF (10 ng/ml; Pierce Endogen) complete medium (RPMI 1640 medium supplemented with 10% FCS) supplemented with HBSS (without Ca2+ and Mg2+), 10 mM HEPES, 10 mM HEPES, 10 mM sodium bicarbonate, 1.0 mM sodium pyruvate, and penicillin/streptomycin (100 U/ml each). MoDCs were differentiated from monocytes by culture in 6-well plates in 2 ml of RPMI 1640 medium containing 10% FBS and incubated for 60 min at 37°C to allow monocytes to attach to the culture dish. Attached monocytes were magnetically labeled and depleted using a mixture of CD19 and CD14 mAb against HLA-DR for 30 min, and then washed with cold PBS and incubated with PE-labeled mAb against CD86 or FITC-labeled mAb against CD86, FITC-conjugated Ab coupled to HRP.

**Generation of human MoDCs**

Peripheral blood was collected from healthy donors, and PBMCs were isolated by separation on a Histopaque-1077 gradient. After two washings with HBSS (without Ca2+ and Mg2+), PBMCs were suspended in RPMI 1640 medium containing 10% FBS and incubated for 60 min at 37°C to allow monocytes to attach to the culture dish. Attached monocytes were then collected as described previously (21, 22). Peripheral blood monocytes were differentiated to MoDCs by culture in 6-well plates in 2 ml of RPMI 1640 medium supplemented with 10% FCS and recombinant human IL-4 (10 ng/ml; Pierce Endogen), and recombinant human IL-12 (100 ng/ml; Pierce Endogen). All cultures were incubated at 37°C in 5% humidified CO2. After 7 days of culture, MoDCs were matured by stimulating them with LPS (100 ng/ml) or TNF-α (100 nm) for 48 h.

**The isolation of DCs from peripheral blood**

Peripheral blood DCs were isolated using a blood DC isolation kit II (Miltenyi Biotec; catalog no. 130-091-379). Briefly, cells were isolated using a two-step MACS separation. First, B cells and monocytes were magnetically labeled and depleted using a mixture of CD19 and CD14 MicroBeads. Nonmagnetic “flow through” cells were magnetically labeled and enriched with a mixture of Abs against the DC markers, blood DC Ag-4, blood DC Ag-3, and CD1c, according to the manufacturer’s instructions (Miltenyi Biotec).

**FACS analysis**

Cells were incubated with PE-labeled mAb against CD86 and FITC-labeled mAb against HLA-DR for 30 min, and then washed with cold PBS and analyzed using a Coulter Epics XL flow cytometer (Beckman Coulter).

**Measurement of phagocytic activity**

Phagocytosis was measured after treating DCs for 48 h with vehicle, LPS, WKYMVm plus LPS, or wkymvm plus LPS. Cells were then incubated in 0.2 ml of PBS containing 5% human serum with 1 mg/ml FITC-dextran for 30 min at 37°C, washed four times in ice-cold PBS, and analyzed using a flow cytometer. Control cells were incubated in the same PBS/human serum/FITC-dextran solution for 30 min at 4°C before analysis.

**Cytokine assays**

DCs (5 × 10^5 cells/ml) were treated with vehicle, LPS, or TNF-α in the presence or absence of the synthetic peptides WKYMVm, WKYMVM, MLF, Hp(2–20), F2L, or wkymvm for 48 h. In addition, DCs were also pretreated with PD98059 (an MEK inhibitor, 50 μM), LY294002 (a PI3K inhibitor, 50 μM), or GF109203X (a protein kinase C (PKC) inhibitor, 5 μM) before WKYMVm plus LPS stimulation for 48 h. Culture supernatants were analyzed by ELISA for IL-12 p70 or IL-1β according to the manufacturer’s instructions (BD Pharmingen).

**Measurement of allostimulatory activity**

T cells purified from human PBMCs using nylon wool columns, were used as responders (23), and DCs, which had been treated with vehicle, LPS, WKYMVm plus LPS, or wkymvm plus LPS were used as stimulator cells. A total of 1 × 10^5 allogeneic T cells were added to DCs (1 × 10^5, 3 × 10^5, 1 × 10^4, or 3 × 10^3) in 96-well tissue culture plates containing 0.2 ml of medium well. Allostimulatory activity was measured for 3 days, and cells were pulsed with 0.5 μCi of [3H]thymidine over the last 18 h. The radioactivity incorporated T cells were counted using a liquid scintillation counter (TRI-CARB 2100 TR; Packard).
We also examined the effect of WKYMVm on LPS-stimulated IL-12 production in DCs isolated from peripheral blood. Initially, we found that the stimulation of peripheral blood DCs with LPS markedly up-regulated IL-12 production (Fig. 1). Moreover, the stimulation of these DCs with WKYMVm (100 nM) and LPS (100 ng/ml) dramatically inhibited IL-12 production by LPS (Fig. 1).

WKYMVm inhibits phenotypical changes in MoDCs by LPS

To determine whether WKYMVm affects the maturation of MoDCs by LPS, we searched for phenotypic changes in WKYMVm- plus LPS-treated MoDCs by using FACS and specific Abs against MHC molecules or costimulatory molecules. Treatment with LPS (100 ng/ml) dramatically enhanced the expressions of CD86 and HLA-DR (Fig. 2A). However, WKYMVm (100 nM) plus LPS (100 ng/ml) markedly reduced mature DC surface marker expression, CD86, and HLA-DR (Fig. 2A), whereas treatment of MoDCs with wkymvm (100 nM) plus LPS (100 ng/ml) had no effect on the LPS-induced up-regulations of CD86 and HLA-DR (Fig. 2A). Moreover, the concentration-dependency of WKYMVm-induced DC marker down-regulation was found to be maximal at 100 nM (Fig. 2, B and C). Taken together, these findings indicate that WKYMVm inhibits LPS-induced MoDC maturation.

WKYMVm inhibits LPS-induced DC allostimulatory capacity

Maturred DC function can be characterized, in part, by the ability of the cell to stimulate alloreactive T cells in a MLR (26). To determine whether co-stimulation of DCs with WKYMVm plus LPS affects the allostimulatory capacity conferred by LPS, we performed an MLR assay. As shown in Fig. 3A, treatment with LPS (100 ng/ml) exhibited the allostimulatory activity, and this was reduced by treating MoDCs with WKYMVm (100 nM) plus LPS (100 ng/ml). However, treating MoDCs with wkymvm (100 nM) plus LPS (100 ng/ml) had no effect on the allostimulatory activity conferred by LPS (Fig. 3A). In addition, it was found that WKYMVm inhibited the allostimulatory activity of peripheral blood DCs (Fig. 3B). These findings also suggest that WKYMVm inhibits LPS-induced DC maturation.

WKYMVm blocks the phagocytic activity reduction induced by LPS

Immature DCs capture and process Ags as a consequence of their high endocytic activity, a feature that disappears during maturation (27, 28). Cells treated with WKYMVm plus LPS expressed lower levels of CD86 and HLA-DR than LPS-treated cells (Fig. 2). Moreover, CD86 and HLA-DR have been reported to be expressed more abundantly in mature DCs than in immature DCs (1). This finding, namely that the stimulation of MoDCs with WKYMVm plus LPS induced reductions in the expressions of CD86 and HLA-DR (Fig. 2), led us to investigate whether the treatment of MoDCs with WKYMVm plus LPS might inhibit cellular maturation by LPS. When immature MoDCs were stimulated with LPS (100 ng/ml), a significant reduction in their phagocytic activities was observed, suggesting that these cells had matured (Fig. 4). Cotreatment with WKYMVm (100 nM) plus LPS (100 ng/ml) elicited higher levels of phagocytic activity than that exhibited by cells treated with LPS alone (Fig. 4). Moreover, the treatment of MoDCs with wkymvm (100 nM) plus LPS (100 ng/ml) had no effect on their phagocytic activity (Fig. 4). These results suggest that the WKYMVm-mediated signaling pathway may involve the inhibition of DC maturation.

WKYMVm stimulates ERK activity in MoDCs

ERK has been reported to mediate extracellular signals to the nucleus in a variety of cell types (29, 30). In this study, we attempted to determine whether WKYMVm stimulates ERK activity by Western blotting with anti-phospho-specific Abs for the enzyme. When MoDCs were stimulated with WKYMVm (100 nM) for different times, ERK phosphorylation levels increased transiently, and exhibited maximal activity after 2–5 min of stimulation (Fig. 5A), which returned to baseline after 30 min of stimulation (Fig. 5A). We also examined the concentration-dependency of

**FIGURE 1.** WKYMVm inhibits IL-12 production by LPS- or by TNF-α-matured DCs. MoDCs were stimulated with several concentrations of WKYMVm or wkymvm in the presence of LPS (100 ng/ml) (A) or TNF-α (100 nM) (B), for 48 h. MoDCs (C) or peripheral blood DCs (D) were either stimulated with vehicle, WKYMVm, or wkymvm (100 nM) in the absence or presence of LPS (100 ng/ml) for 48 h. Supernatants were harvested from cultures and evaluated for IL-12 p70 (A, B, and D) or IL-1β (C) production by ELISA. Data are presented as means ± SE of three independent experiments performed in duplicate.
WKYMVm-induced ERK phosphorylation. Treating MoDCs with different concentrations of WKYMVm for 5 min caused ERK phosphorylation, and this activity was at a maximum at a WKYMVm concentration of 100 nM (Fig. 5A). However, when MoDCs were stimulated with wkymvm (100 nM), no significant ERK phosphorylation was induced (data not shown). Previous studies have demonstrated that the stimulation of DCs with LPS is accompanied by ERK activation (31, 32), and we too found that LPS (100 ng/ml) stimulated ERK phosphorylation at 5–30 min (Fig. 5B). We then investigated the effects of WKYMVm on LPS-induced ERK activation, by costimulating MoDCs with WKYMVm plus LPS. As shown in Fig. 5B, treatment with WKYMVm (100 nM) plus LPS (100 ng/ml) induced a more vigorous activation of ERK, as compared with the LPS only-treated control. Moreover, treating MoDCs with increasing concentrations of WKYMVm plus LPS for 10 min induced a gradual increase in ERK phosphorylation vs the LPS-treated control, and showed maximal activity at 100-1000 nM (Fig. 5C). We also compared PI3K-mediated Akt activation as induced by LPS vs WKYMVm plus LPS in MoDCs. Akt phosphorylation level was higher in WKYMVm plus LPS stimulated MoDCs than in cells stimulated with LPS alone (data not shown).

ERK activity is involved in the WKYMVm-induced inhibition of MoDC maturation by LPS

We observed that WKYMVm dramatically inhibited IL-12 secretion by LPS-treated DCs (Fig. 1). To elucidate the intracellular pathways involved in the inhibition of IL-12 secretion in WKYMVm- plus LPS-treated MoDCs, we assessed IL-12 production by ELISA in cells treated with an ERK pathway inhibitor (PD98059), which prevents the activation of MEK1/2, an upstream activator of ERK 1/2. PD98059 was found to have no effect on IL-12 production and release by LPS-treated MoDCs (Fig. 6A), although PD98059 treatment did lead to recovery from WKYMVm-induced IL-12 down-regulation (Fig. 6A). This latter finding suggests that the PD98059-inhibitable MAPK pathway may negatively modulate WKYMVm-induced IL-12 production in LPS-stimulated MoDCs. IL-12 secretion by LPS-treated MoDCs did not appear to be significantly affected by LY294002 or GF109203X (Fig. 6A). However, LY294002 or GF109203X recovered the WKYMVm-induced down-regulation of IL-12 production by LPS (Fig. 6A).

We also examined the effects of the ERK, PI3K, and PKC pathways on the inhibitory effect of WKYMVm on LPS-stimulated DC marker expression. As shown in Fig. 6B, pretreatment of MoDCs with PD98059 (50 μM), LY294002 (50 μM), or GF109203X (5 μM) for 1 h (15 min for GF109203X) before treating with WKYMVm plus LPS blocked the inhibitory effect of WKYMVm on MoDC HLA-DR expression induced by LPS. Pretreatment of MoDCs with PD98059 (50 μM), LY294002 (50 μM), or GF109203X (5 μM) for 1 h (15 min for GF109203X) before adding WKYMVm plus LPS also blocked the inhibitory effect of WKYMVm on MLR activity induced by MoDC (data not shown). Taken together, these results suggest that the ERK, PI3K, and PKC pathways exert a strong negative effect on LPS-induced MoDC maturation, possibly due to their influence on WKYMVm.

WKYMVm inhibits LPS-induced IL-12 mRNA induction

We investigated the effect of WKYMVm on LPS-induced IL-12 mRNA accumulation by RT-PCR. The stimulation of MoDCs with 100 ng/ml LPS elicited IL-12 p40 mRNA accumulation in a time-dependent manner, and showed maximal activity 4–6 h after stimulation (Fig. 7A). And the stimulation of MoDCs with WKYMVm (100 nM) for 1, 2, 4, or 6 h did not affect IL-12 p40 mRNA accumulation (Fig. 7B and data not shown). However, costimulation with WKYMVm (100 nM) plus LPS (100 ng/ml) for 4 h almost completely blocked IL-12 p40 mRNA accumulation (Fig. 7B), indicating that WKYMVm inhibits LPS-induced IL-12 production at a transcriptional level.
Both FPR and FPRL2 are involved in the WKYMVm-induced inhibition of MoDC maturation

Previous studies have demonstrated that WKYMVm binds to at least three different cell surface receptors, i.e., FPR, FPRL1, and FPRL2 (14–16). Because we observed that WKYMVm inhibits LPS-induced DC maturation, we undertook, using receptor-selective agonists, to identify the receptor participating in this inhibition. Initially, we evaluated the expression patterns of FPR family members in MoDCs by RT-PCR. As shown in Fig. 8A, MoDCs were found to express FPR and FPRL2, but not FPRL1. Moreover, fMLF and WKYMVM have been reported to bind FPR and FPRL2, respectively (16, 33). The costimulation of MoDCs with fMLF (1 μM) plus LPS (100 ng/ml) significantly inhibited IL-12 production by LPS (Fig. 8B). And, treatment with WKYMVM (1 μM) plus LPS (100 ng/ml) also partially inhibited IL-12 production by LPS (Fig. 8B). In addition, we examined the effect of fMLF plus WKYMVM on IL-12 production by LPS in MoDCs. The treatment of MoDCs with fMLF (1 μM) plus WKYMVM (1 μM) plus LPS (100 ng/ml) was found to dramatically inhibit IL-12 production by LPS (Fig. 8B), thus suggesting that FPR and FPRL2 are engaged in the WKYMVm-induced inhibition of IL-12 production by LPS in MoDCs.

Helicobacter pylori-derived peptide Hp(2–20) binds FPRL2 and activates monocytes, and thus induces lymphocyte dysfunction and apoptosis (34). Thus we attempted to investigate whether a pathogen-derived FPRL2 agonist would also inhibit LPS-induced MoDC maturation. To assess the effect of Hp(2–20) on LPS-induced DC maturation, we examined the effect of Hp(2–20) on LPS-induced IL-12 production in DCs. As shown in Fig. 8B, treatment of MoDCs with Hp(2–20) (50 μM) plus LPS (100 ng/ml) inhibited IL-12 production by DCs, suggesting that LPS-induced MoDC maturation is inhibited by Hp(2–20) treatment, and that the activation of FPRL2 by Hp(2–20) inhibits LPS-induced MoDC maturation. More recently, the FPRL2-selective peptide ligand, F2L, was reported to be a natural DC chemoattractant (20). We also found that treatment with F2L (100 nM) plus LPS (100 ng/ml) significantly inhibited IL-12 production by LPS (Fig. 8B), supporting the notion that FPRL2 participates in the inhibition of MoDC maturation by LPS. We also examined the effect of pertussis toxin on the WKYMVm-induced inhibition of IL-12 by LPS. MoDC pretreatment with pertussis toxin (100 ng/ml) prior to WKYMVm (100 nM) treatment, almost completely blocked the WKYMVm-induced inhibition of IL-12 production by LPS (data not shown). The result strongly suggests that Gαi-coupled receptors (FPR and FPRL2) participate in the WKYMVm-induced inhibition of IL-12 production by LPS.

Discussion

In this study, we investigated the effects of WKYMVm on DC maturation induced by LPS. The costimulation of MoDCs with WKYMVm plus LPS inhibited LPS-induced IL-12 production, CD86 and HLA-DR expression, and the allostimulatory activity of
DCs (Figs. 1–3). Taken together, DC stimulation by WKYMVm elicits signaling pathways that inhibit DC maturation.

With regard to immune response, IL-12 functions as a link between the innate and adaptive immune systems (35, 36). In addition, IL-12 polarizes the immune system toward a primary Th-1 response (37). Thus, IL-12 production by DCs has a key role in the determination of subsequent immune responses. In this study, we investigated IL-12 production by DCs, and found that IL-12 levels decreased dramatically 48 h after exposure to WKYMVm plus LPS (Fig. 1A). As the levels of other cytokines, including IL-1 and TNF-α, were not affected by WKYMVm plus LPS (Fig. 1C and data not shown), we focused on IL-12 production. Previous studies have demonstrated that WKYMVm stimulates a variety of intracellular signaling molecules, and perhaps its best-characterized function in this respect is its role in the ERK pathway (38). To identify the pathway that leads to the inhibition of IL-12 production in WKYMVm- plus LPS-treated DCs, we treated MoDCs with a MAPK inhibitor, a PI3K inhibitor, or a PKC inhibitor, and then assessed the amount of IL-12 produced by LPS. Unlike the results obtained in vehicle (DMSO)-pretreated controls, IL-12 production by WKYMVm- plus LPS-treated MoDCs after PD98059 or LY294002 pretreatment was similar to that in LPS only-treated cells (Fig. 6A). Furthermore, we found that MoDC stimulation with WKYMVm elicited ERK phosphorylation in a time-dependent manner, and that this activity peaked after 5 min of stimulation (Fig. 5A). In addition, LPS was found to induce ERK phosphorylation in MoDCs (Fig. 5B). When MoDCs were treated with WKYMVm plus LPS, ERK phosphorylation increased dramatically (Fig. 5B and C), suggesting that WKYMVm participates in the negative effects of the ERK or PI3K signaling pathways on LPS-induced IL-12 production in MoDCs. Previous reports demonstrated that ERK and PI3K negatively regulate the phenotypic and functional maturation of human MoDCs (39–42). It had been demonstrated that the inhibition of ERK or PI3K by selective inhibitors (PD98059 or LY294002) significantly enhanced the phenotypic and functional maturation of human MoDCs. These reports support our notion regarding the negative effects of the ERK and PI3K signaling pathways on DC maturation (39, 40). We also examined the effect of WKYMVm on the expressions of the LPS receptors TLR4 and TLR2 by using FACS. However, the stimulation of MoDCs with WKYMVm did not affect on the membrane expressions of TLR4 and TLR2 (data not shown).

The FPR family is considered to contain an important set of chemoattractant receptors for several human phagocytic cells, e.g., monocytes, neutrophils, and DCs (18, 43, 44). During the differentiation of human monocytes into DCs, FPRL1 was found to be
...down-regulated, and DCs were found not to express FPRL1 (45), in fact DCs have been reported to express only FPR and FPRL2 (18). However, the functional roles of FPR and FPRL2 on DC maturation had not been previously determined. In this study, we confirmed that MoDCs express FPR and FPRL2, but not FPRL1 (Fig. 8A), and found that the activations of FPR and FPRL2 by WKYMVM inhibit the LPS-induced maturation of MoDCs. The inhibitory effect of WKYMVM on DC maturation was confirmed by its inhibition of IL-12 production, CD86 and HLA-DR expression, the allostimulatory activity of DCs, and by retention of phagocytic activity. As both FPR and FPRL2 are classical chemotactic receptors, and because both play crucial roles in the chemotactic migration of DCs, the notion that FPR and FPRL2 may be involved in the inhibition of DC maturation is somewhat surprising. A previous study demonstrated that the stimulation of FPR by T-20 (a HIV-derived peptide) suppresses IL-12 production by human monocytes (17). This result is consistent with our idea that FPR suppresses IL-12 production in parallel with DC maturation inhibition. A number of pathogen-derived peptides have been recently reported to be agonists of FPR and FPRL2. These include T-20 for FPR (46) and the H. pylori-derived peptide Hp(2–20) for FPRL2 (35). Pathogens have notorious abilities to subvert the host immune system (47) and the chemotactic system, which is one of the most important targets of this modulation of host immune response by pathogens. Several viruses have been demonstrated to inhibit host immune responses by producing proteins that interact with target receptors in the host (47). Some viral chemokine homologues bind to chemokine or chemotactic receptors, alter receptor activation properties, and inhibit the proper functioning of receptor-mediated immune responses (47). Because HIV T-20 peptide and H. pylori Hp(2–20) peptide are ligands of FPR and FPRL2, respectively, it appears that these pathogen-derived agonists suppress DC-mediated immune responses by activating FPR or FPRL2.

In conclusion, our findings indicate that two important chemotactic receptors, namely FPR and FPRL2, can be activated by several specific ligands, including pathogen-derived peptide species. Moreover, these processes also inhibit DC maturation by LPS. Our findings provide a new perspective on the roles of FPR and FPRL2 in the regulation of immune responses, via their inhibitory effects on DC maturation. Furthermore, these findings indicate that FPR and FPRL2 should be regarded as important chemotherapeutic targets with respect to the modulation of DC maturation.

Disclosures
The authors have no financial conflict of interest.

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