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Cutting Edge: SR-PSOX/CXC Chemokine Ligand 16 Mediates Bacterial Phagocytosis by APCs Through its Chemokine Domain¹

Takeshi Shimaoka,^{*} Takashi Nakayama,[‡] Noriaki Kume,[†] Shu Takahashi,[§] Junko Yamaguchi,[§] Manabu Minami,[†] Kazutaka Hayashida,[†] Toru Kita,[†] Jun Ohsumi,[§] Osamu Yoshie,[‡] and Shin Yonehara^{2*}

SR-PSOX and CXC chemokine ligand (CXCL)16, which were originally identified as a scavenger receptor and a transmembrane-type chemokine, respectively, are indicated to be identical. In this study, we demonstrate that membrane-bound SR-PSOX/CXCL16 mediates adhesion and phagocytosis of both Gram-negative and Gram-positive bacteria. Importantly, our prepared anti-SR-PSOX mAb, which suppressed chemotactic activity of SR-PSOX, significantly inhibited bacterial phagocytosis by human APCs including dendritic cells. Various scavenger receptor ligands inhibited the bacterial phagocytosis of SR-PSOX. In addition, the recognition specificity for bacteria was determined by only the chemokine domain of SR-PSOX/CXCL16. Thus, SR-PSOX/CXCL16 may play an important role in facilitating uptake of various pathogens and chemotaxis of T and NKT cells by APCs through its chemokine domain. The Journal of Immunology, 2003, 171: 1647–1651.

The scavenger receptor family is a highly heterogeneous group of cell surface molecules that commonly bind and uptake oxidized low density lipoprotein (OxLDL)³ (1). Currently, scavenger receptors are categorized into almost 10 classes on the basis of structure, even though there are few structural and primary amino acid similarities among the classes. Scavenger receptors have been primarily studied for their roles in foam cell formation and the pathogenesis of atherosclerosis. Some scavenger receptors have also been shown to bind a broad range of ligands including bacteria (2–5). Studies with scavenger receptor class-A (SR-A) knockout mice revealed that a deficiency of SR-A enhances sensitivities for infection of *Staphylococcus aureus* and *Listeria* (6, 7), suggesting that its function as a pattern recognition receptor plays potential roles in innate immunity and in the initiation of acquired immune responses (8).

Previously, we identified a novel scavenger receptor capable of binding and uptaking phosphatidylserine and OxLDL, and termed it SR-PSOX (scavenger receptor that binds phosphatidylserine and oxidized lipoprotein) (9). Surprisingly, SR-PSOX was indicated to be identical to CXC chemokine ligand (CXCL)16 (10, 11), which was identified as the ligand for an orphan G-protein coupled chemokine receptor Bonzo/CXCR6. CXCL16 is the second transmembrane-type chemokine with a chemokine-domain fused to a mucin-like stalk, a structure very similar to that of fractalkine/CX₃CL1 (12, 13). CXCL16 selectively expresses on APCs such as dendritic cells (DCs) and macrophages, while its receptor Bonzo/CXCR6 expresses on naive CD8 T cells, NKT cells, and type 1-polarized CD4 and CD8 T cells (10, 11, 14). Thus, SR-PSOX/CXCL16 is a multifunctional molecule that may link the family of scavenger receptors and that of chemokines.

In the present study, we have demonstrated that SR-PSOX/CXCL16 expressed by macrophages and DCs supports binding and phagocytosis of both Gram-negative and Gram-positive bacteria through the chemokine domain. SR-PSOX/CXCL16 should play a role in facilitating uptake of various pathogens and chemotaxis of T and NKT cells by professional APCs.

Materials and Methods

Cells

DCs were generated from peripheral blood monocytes isolated from human blood (a gift from Kyoto Red Cross Blood Center, Kyoto, Japan) by cultivation with 20 ng/ml IL-4 and 50 ng/ml GM-CSF (PeproTech, Rocky Hill, NJ) for 7 days. DCs were confirmed to express CD1a, CD40, CD80, HLA-DR, and HLA-ABC at high levels, and CD14 at a low level by flow cytometry. L1.2 murine pre-B cells stably expressing CXCR6 (L-CXCR6 cells) and CX₃CR1 (L-CX₃CR1 cells) were generated as described previously (15).

Monoclonal anti-human SR-PSOX Abs

BALB/c female mice were immunized with SR-PSOX-Fc fusion protein produced by COS-7 cells transfected with a fusion construct consisting of the extracellular domain of human SR-PSOX (amino acids 1–206) fused at its C terminus with Fc fragment of human IgG₁. According to the method described previously (16), we generated three anti-human SR-PSOX mAbs 22-19-12, 49-36, and 28-12.

^{*}Graduate School of Biostudies and Institute for Virus Research, and [†]Department of Cardiovascular Medicine, Graduate School of Medicine, Kyoto University, Sakyo-ku, Kyoto, Japan; [‡]Department of Microbiology, Kinki University School of Medicine, Osaka-Sayama, Japan; and [§]Biomedical Research Laboratories and Molecular Biology Research Laboratories, Sankyo, Shinagawa-ku, Tokyo, Japan

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² Address correspondence and reprint requests to Dr. Shin Yonehara, Graduate School of Biostudies and Institute for Virus Research, Kyoto University, Shogoin Kawahara-cho 53, Sakyo-ku, Kyoto 606-8507, Japan. E-mail: syonehar@virus.kyoto-u.ac.jp

³ Abbreviations used in this paper: OxLDL, oxidized low-density lipoprotein; SR-A, scavenger receptor class A; CXCL, CXC chemokine ligand; DC, dendritic cell; LTA, lipoteichoic acid; LOX-1, lectin-like OxLDL receptor-1; dSR-CI, *Drosophila* scavenger receptor CI; SEAP, secreted form of placental alkaline phosphatase.

Binding and phagocytosis of bacteria

Bacterial adhesion and phagocytosis assays were conducted as described previously (5). To quantitate the phagocytosis of bacteria, COS-7 cells, PMA-stimulated THP-1 cells (PMA-THP-1 cells), or DCs (2×10^5 cells/ml) were incubated for 60 min at 37°C with FITC-labeled bacteria (3×10^6 cells/ml for COS-7 cells, and 6×10^5 cells/ml for PMA-THP-1 cells and DCs). Then cells were washed, detached with trypsin and treated with trypan blue for 10 min to quench the fluorescence of extracellular bacteria. The numbers of cells with intracellular FITC-labeled bacteria were quantified by EPICS Elite (Coulter, Hiialeah, FL). In blocking experiments, cells were preincubated with lipoteichoic acid (LTA; 500 μ g/ml), LPS (500 μ g/ml), dextran sulfate (500 μ g/ml), chondroitin sulfate (500 μ g/ml), native LDL (200 μ g/ml), OxLDL (200 μ g/ml), F(ab')₂ of monoclonal anti-SR-PSOX neutralizing mAb 22-19-12 (20 μ g/ml), F(ab')₂ of control IgG (20 μ g/ml), or cytochalasin D (2 μ M) for 30 min at 37°C. The data of bacterial phagocytosis represent the mean \pm SD from at least three independent experiments, and statistical significance was calculated by Student's *t* tests.

Results

SR-PSOX/CXCL16 mediates bacterial adhesion and phagocytosis

Scavenger receptors such as SR-A, MARCO, lectin-like OxLDL receptor 1 (LOX-1), and *Drosophila* scavenger receptor CI (dSR-CI) are known to bind and uptake bacteria (2–5). Therefore, we examined whether SR-PSOX/CXCL16 could also mediate adhesion of bacteria. COS-7 cells were transfected with expression vectors for SR-PSOX as described previously (9). As shown in Fig. 1A, SR-PSOX-transfected COS-7 cells (COS-SR-PSOX cells), but not control COS-7 cells, were found to efficiently bind FITC-labeled Gram-negative *Escherichia coli* and Gram-positive *S. aureus*. We next examined

phagocytosis of cell surface bound bacteria by COS-SR-PSOX cells under confocal microscopy. Phagocytosed *E. coli* (Fig. 1B) and *S. aureus* (data not shown) were observed in COS-SR-PSOX cells. As reported with other scavenger receptors, SR-PSOX did not mediate adhesion and phagocytosis of zymosan (data not shown) (3–5).

To further quantitate cells phagocytosing bacteria, cells incubated with FITC-labeled bacteria were analyzed by flow cytometry after washing and quenching of surface fluorescence of extracellular bacteria with trypan blue. COS-SR-PSOX cells, but not COS-control or fractalkine-transfected COS-7 cells (COS-fractalkine cells), were indeed found to efficiently phagocytose both *E. coli* and *S. aureus* (Fig. 1C) in the condition that expression levels of the transfected SR-PSOX and fractalkine were almost the same (see Fig. 3, B–D). The level of bacterial phagocytosis by COS-SR-PSOX cells was almost comparable to that by COS-7 cells expressing other scavenger receptors such as SR-A and LOX-1 which were reported to have bacterial phagocytosis activity (2, 5). Furthermore, COS-SR-PSOX cells efficiently phagocytosed *E. coli* and *S. aureus* in serum-free medium as well as in serum-containing medium (Fig. 1C). Bacterial phagocytosis was effectively suppressed by an actin-depolymerizing agent, cytochalasin D (Fig. 1C). Collectively, these findings clearly demonstrate that serum factors are not required for SR-PSOX-mediated bacterial phagocytosis, and the actin cytoskeleton is necessary for SR-PSOX-mediated bacterial firm adhesion and/or phagocytosis.

Role of SR-PSOX/CXCL16 in bacterial adhesion and phagocytosis by professional APCs

We generated novel anti-human SR-PSOX mAbs, 22-19-12 and 28-12, which recognize the chemokine and mucin domain of SR-PSOX, respectively. To examine inhibitory activity of the mAbs for chemotactic activity of SR-PSOX/CXCL16, we generated soluble SR-PSOX as a fusion protein consisting of the extracellular domain of SR-PSOX (amino acids 1–206) fused at its C terminus with the secreted form of placental alkaline phosphatase (SEAP). SEAP was used for quantification of SR-PSOX-SEAP by ELISA with anti-SEAP mAb, and the fused SEAP was shown not to significantly affect the chemotactic activity of SR-PSOX (data not shown). mAb 22-19-12 was shown to inhibit chemotactic activity to CXCR6-expressing cells by soluble SR-PSOX, while mAb 28-12 did not show the inhibitory activity (Fig. 2B).

The phagocytosis of bacteria is a necessary step for the presentation of bacterial Ags by professional APCs (17, 18), which were reported to express SR-PSOX/CXCL16 (9–11). Therefore, we examined whether SR-PSOX plays a role in bacterial phagocytosis by macrophage-like cells and DCs. We confirmed the expression of SR-PSOX in PMA-THP-1 cells and monocyte-derived DCs by RT-PCR (data not shown) and flow cytometry (Fig. 2A). We then analyzed the effects of F(ab')₂ of anti-SR-PSOX mAb 22-19-12 on bacterial phagocytosis by SR-PSOX-expressing cells. Anti-SR-PSOX 22-19-12 F(ab')₂ was clearly shown to inhibit bacterial phagocytosis by COS-SR-PSOX cells (Fig. 2C). In PMA-THP-1 cells, 30–40% of the phagocytosis of both *E. coli* and *S. aureus* were specifically inhibited by F(ab')₂ of the mAb (Fig. 2D). In DCs, F(ab')₂ inhibited 60% of phagocytosis of *E. coli*, while it did not significantly inhibit phagocytosis of *S. aureus* (Fig. 2E). These results indicate that SR-PSOX/CXCL16 plays an important role in

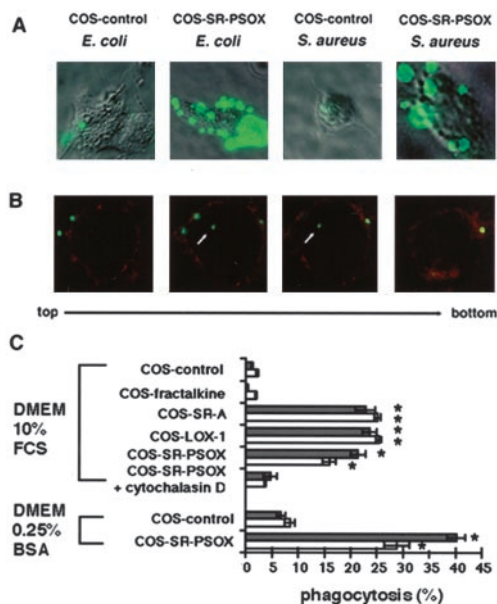


FIGURE 1. Adhesion and phagocytosis of *E. coli* and *S. aureus* mediated by SR-PSOX/CXCL16. *A*, COS-control and COS-SR-PSOX cells were incubated with FITC-labeled *E. coli* and *S. aureus* in the presence of 10% FCS for 1 h at 37°C. After washing, cells were observed under fluorescence microscopy. *B*, COS-SR-PSOX cells were incubated with FITC-labeled *E. coli* for 1 h at 37°C. After washing, cell surface labeling was performed with rhodamine-Con A at 4°C. After another wash, cells were observed under confocal microscopy. Arrows indicate internalized bacteria. *C*, COS-control cells, COS-SR-PSOX cells, COS-fractalkine cells, COS-SR-A cells, and COS-LOX-1 cells were incubated with FITC-labeled *E. coli* (■) or *S. aureus* (□) for 1 h at 37°C with or without cytochalasin D or in the medium without serum. Cells that internalized FITC-labeled bacteria were quantified by flow cytometry and expressed as a percentage of total COS-7 cells. *, *p* < 0.01.

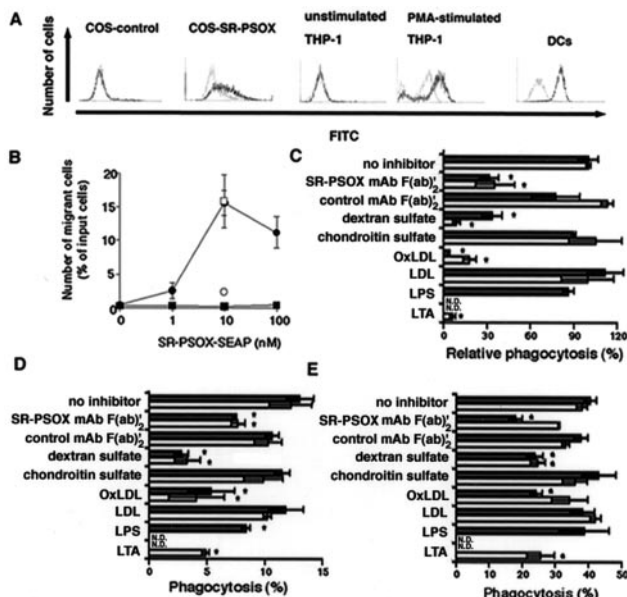


FIGURE 2. Role of SR-PSOX/CXCL16 in bacterial adhesion and phagocytosis by professional APCs. *A*, Surface expression of SR-PSOX on indicated cells was determined by flow cytometry after staining with anti-SR-PSOX mAb 22-19-12 (bold line) or control IgG (dotted line). *B*, Soluble SR-PSOX, which was generated as a fusion construct consisting of the extracellular domain of SR-PSOX (amino acids 1–206) fused at its C terminus with SEAP, was examined for its chemotactic activity against CXCR6-expressing L1.2 cells (L-CXCR6 cells) (●) and control L1.2 cells (■) by standard Transwell assays (21). Effects of 5 μ g/ml anti-human SR-PSOX mAbs 22-19-12 (○) and 28-12 (□) were also analyzed. The number of cells that migrated into bottom wells was expressed as a percentage of input cells. The data shown represent the mean \pm SD from at least three independent experiments. *C–E*, COS-SR-PSOX cells (*C*), PMA-THP-1 cells (*D*), and human peripheral monocyte-derived DCs (*E*) were incubated with FITC-labeled *E. coli* (■) or *S. aureus* (□) for 1 h at 37°C with or without various inhibitors as described in *Materials and Methods*. Levels of phagocytosis were quantified by flow cytometry. *, $p < 0.01$.

bacterial phagocytosis by professional APCs including DCs and activated macrophages, although other cell surface molecules must be also involved.

Effects of various scavenger receptor ligands on binding of SR-PSOX to bacteria

We further examined the effects of scavenger receptor ligands on phagocytosis of bacteria by COS-SR-PSOX cells (Fig. 2*C*). OxLDL and dextran sulfate were used as scavenger receptor ligands because they can inhibit uptake of 1,1'-diiodo-3,3,3',3'-tetra-methylindocarbocyanin perchlorate (DiI)-labeled OxLDL by SR-PSOX-expressing cells (9). Dextran sulfate and OxLDL inhibited bacterial phagocytosis by COS-SR-PSOX cells, while chondroitin sulfate and native LDL showed very weak or undetectable inhibitory effects. In the presence of LTA, the cell wall component of Gram-positive bacteria reported to be recognized by another scavenger receptor SR-A (2), the phagocytosis of *S. aureus* by COS-SR-PSOX cells, PMA-THP-1 cells, and DCs were clearly inhibited (Fig. 2, *C–E*). In contrast, LPS, the cell wall component of Gram-negative bacteria reported to be recognized by SR-A (19), slightly inhibited the phagocytosis of *E. coli* by PMA-THP-1 cells and did not inhibit it by COS-SR-PSOX cells and DCs (Fig. 2, *C–E*). Phagocytosis of both *E. coli* and *S. aureus* by PMA-THP-1 cells was specifically inhibited by 70–80% by

dextran sulfate and OxLDL, while neither chondroitin sulfate nor native LDL inhibited it (Fig. 2*D*). In DCs, the inhibitory activities of phagocytosis of *E. coli* by dextran sulfate and OxLDL were lower, but significant, than those in PMA-THP-1 cells (Fig. 2*E*).

Domain analysis of SR-PSOX/CXCL16

In the extracellular domain of SR-PSOX/CXCL16 and fractalkine, there are two distinct domains, namely the chemokine domain and the mucin domain. Chemotaxis of CXCR6-expressing cells was induced by only the chemokine domain of SR-PSOX (data not shown). To clarify the binding domain of SR-PSOX for bacteria, we generated SR-PSOX/CXCL16-fractalkine hybrid molecules by shuffling the chemokine domains and mucin domains of SR-PSOX and fractalkine (Fig. 3*A*). COS-7 cells were transfected with expression vectors for hybrid molecules and similar levels of cell surface expression were confirmed among these hybrid proteins on the transfected COS-7 cells by flow cytometry using anti-human SR-PSOX/CXCL16 mAbs 49-36 (Fig. 3*B*) and 28-12 (Fig. 3*C*) that recognize the chemokine and mucin domains of SR-PSOX/CXCL16, respectively, or the anti-human fractalkine mAb (Fig. 3*D*) that recognizes the chemokine domain of fractalkine. COS-7 cells expressing a hybrid molecule with a chemokine domain of SR-PSOX/CXCL16 and a mucin domain of fractalkine showed significant bacterial phagocytosis (Fig. 3*E*), while COS-7 cells expressing a hybrid molecule with a chemokine domain of fractalkine and a mucin domain of SR-PSOX/CXCL16 did not show these activities. Interestingly, COS-7 cells expressing SR-PSOX without its mucin domain impaired the activity (Fig. 3*E*) although the cell surface expression was confirmed by flow cytometry (Fig. 3*B*). All the data indicate that the recognition specificity for CXCR6 and bacteria is determined by only the chemokine domain of SR-PSOX/CXCL16, while the mucin domain of SR-PSOX/CXCL16 is necessary for other activities of SR-PSOX, including efficient recognition and/or uptake of bacteria.

Discussion

SR-PSOX/CXCL16 is a recently identified molecule with distinct dual biological functions. We and others independently identified this molecule as a novel class of scavenger receptor capable of uptaking OxLDL (9) and as a transmembrane-type chemokine capable of recruiting cells expressing CXCR6 (10, 11), respectively. Importantly, we have demonstrated here for the first time that SR-PSOX/CXCL16 is capable of mediating bacterial phagocytosis. This activity of SR-PSOX/CXCL16 is shared with several other scavenger receptors but not with another transmembrane chemokine, fractalkine/CX₃CL1 (Fig. 1). Furthermore, we demonstrated that the recognition specificity for bacteria is determined by only the chemokine domain of SR-PSOX/CXCL16 (Fig. 3).

We have also shown that SR-PSOX/CXCL16, which is expressed on macrophages and DCs, plays an important role in bacterial phagocytosis by these APCs (Fig. 2). Thus, SR-PSOX/CXCL16 has unique characteristics as a transmembrane chemokine by providing another set of multiple functions for professional APCs, i.e., recruitment of CXCR6-expressing cells such as activated T and NKT cells and also uptake of bacteria for Ag presentation.

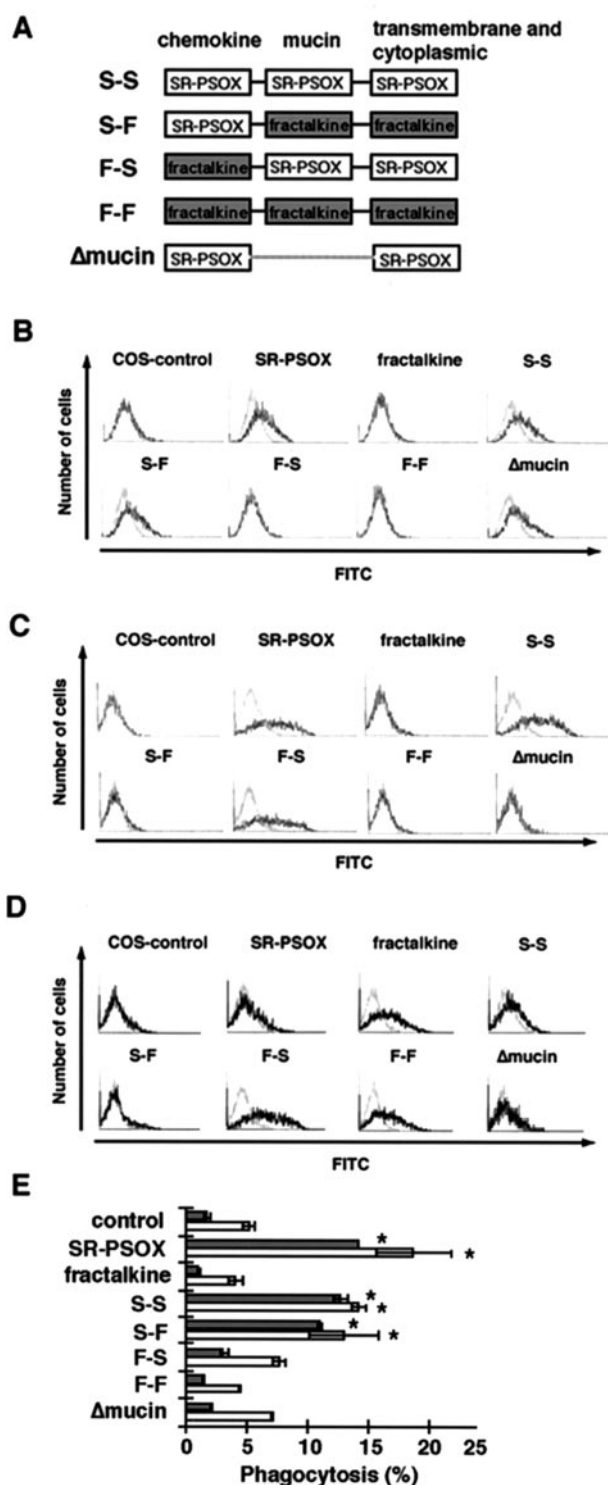


FIGURE 3. Domain analyses of SR-PSOX/CXCL16 to bind bacteria. *A*, Schematic illustration of SR-PSOX/CXCL16-fractalkine hybrid molecules. Δ Mucin construct shows SR-PSOX without mucin domain. *B–D*, Flow cytometric analysis. COS-7 cells were transiently transfected with each SR-PSOX/CXCL16-fractalkine hybrid molecules schematically shown in *A*. Surface expression of human SR-PSOX-fractalkine hybrid molecules was analyzed by flow cytometry after staining with anti-human SR-PSOX mAb (*B*) 49-36 (bold line) which recognize chemokine domain or (*C*) 28-12 (bold line) which recognize the mucin domain of SR-PSOX or with anti-human fractalkine mAb, (*D*) 51637.11 (bold line) which recognize the chemokine domain of fractalkine or (*B–D*) control IgG (dotted line) and thereafter anti-mouse IgG-FITC. *E*, COS-7 cells transfected with the indicated SR-PSOX/CXCL16-fractalkine hybrid molecules were incubated with the indicated FITC-labeled *E. coli* (■) or *S. aureus* (□) for 1 h at 37°C. Cells internalizing FITC-labeled bacteria were enumerated by flow cytometry. *, $p < 0.01$.

Recently, some chemokines were reported to have killing activity against bacteria, which is similar to that of antimicrobial peptides such as β -defensin (20). We have confirmed not only direct binding of soluble SR-PSOX/CXCL16 to bacteria, but also its killing activity against bacteria (data not shown). However, higher concentrations of SR-PSOX/CXCL16 were necessary to kill bacteria than those of other antimicrobial chemokines previously reported (20). The previous report and our data suggest that innate immune activity as well as chemotactic activity may be evolutionary conserved in the chemokine superfamily, and some chemokines may be a new class of pattern recognition receptor for bacteria.

Gram-positive and Gram-negative bacteria have different cell wall components. LPS and LTA are the cell wall components of Gram-negative and Gram-positive bacteria, respectively. Because SR-PSOX/CXCL16 can recognize negative-charged molecules such as OxLDL and dextran sulfate, SR-PSOX/CXCL16 may recognize common and/or different negative-charged molecules on these bacterial cell walls. LTA with negative charge is a candidate on Gram-positive bacteria recognized by SR-PSOX/CXCL16, while that on Gram-negative bacteria remains to be identified (Fig. 2*C*).

DCs play an important role in providing a link between the innate and adaptive immune systems by phagocytosing pathogens, presenting Ag, and triggering T cell activation (21). Though scavenger receptor family members, such as mammalian SR-A, MARCO, and LOX-1 as well as *Drosophila* dSR-CI, were reported to be involved in phagocytosis of Gram-negative and Gram-positive bacteria by mammalian macrophages and endothelial cells as well as *Drosophila* macrophages (2–5), it remains to be determined which kinds of scavenger receptors on DCs are involved in the phagocytosis of bacteria. In this study, we showed that SR-PSOX/CXCL16 plays a role in the phagocytosis of bacteria in monocyte-derived DCs, while SR-A, LOX-1 and/or other scavenger receptors may be also involved in bacterial phagocytosis in other-type DCs. After phagocytosing bacteria, DCs possibly present bacterial peptide epitopes and glycolipids together with self histocompatibility Ags to T cells and NKT cells, respectively. In contrast, the soluble form of SR-PSOX/CXCL16, released by DCs, can recruit activated T cells and NKT cells expressing CXCR6 by its chemotactic activity in cooperation with other chemokines.

In conclusion, SR-PSOX/CXCL16, which is a unique class of transmembrane molecule with multiple biological activities as a scavenger receptor and chemokine through the same chemokine domain, is likely to play important roles in host defense by mediating innate and adaptive immunity. Future studies using SR-PSOX/CXCL16 gene-disrupted and CXCR6 gene-disrupted mice will no doubt clarify the physiological roles of SR-PSOX/CXCL16 in innate and acquired immunity.

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