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CUTTING EDGE

Cutting Edge: Profile of Chemokine Receptor Expression on Human Plasma Cells Accounts for Their Efficient Recruitment to Target Tissues[1]

Takashi Nakayama, Kunio Hieshima,* Dai Izawa,* Youichi Tatsumi,† Akihisa Kanamaru,† and Osamu Yoshie[2]**

We systematically examined the repertoire of chemokine receptors expressed by human plasma cells. Fresh bone marrow plasma cells and myeloma cells consistently expressed CXCR4, CXCR6, CCR10, and CCR3. Accordingly, plasma cells responded to their respective ligands in chemotaxis and very late Ag-4-dependent cell adhesion to fibronectin. Immobilized CXC chemokine ligand (CXCL)16, a novel transmembrane-type chemokine and CXCR6 ligand, also directly induced adhesion of plasma cells without requiring $G_{\alpha i}$ signaling or divalent cations. Furthermore, we revealed consistent expression of CXCL12 (CXCR4 ligand), CXCL16 (CXCR6 ligand), and CC chemokine ligand 28 (CCR10 and CCR3 ligand) in tissues enriched with plasma cells including bone marrow, and constitutive expression of CXCL12, CXCL16, and CC chemokine ligand 28 by cultured human bone marrow stromal cells. Collectively, plasma cells are likely to be recruited to bone marrow and other target tissues via CXCR4, CXCR6, CCR10, and CCR3. CXCR6 may also contribute to tissue localization of plasma cells through its direct binding to membrane-anchored CXCL16. The Journal of Immunology,* 2003, 170: 1136–1140.

Chemokines play important roles in innate and acquired immunity by inducing directed migration of various types of leukocytes through interactions with a group of seven-transmembrane, G protein-coupled receptors (1). Accumulating evidence has demonstrated that chemokines and their receptors are crucial in trafficking and tissue microenvironmental localization of various lymphocyte classes and subsets (1). Thus, upon differentiation, maturation, and activation, cells of the lymphoid lineages dynamically change their expression profiles of chemokine receptors, leading to their specific migration programs to new sets of chemokines (1).

Plasma cells represent the end stage of B cell differentiation and function as the factories for Ab production. Plasma cells from immunized mice demonstrated up-regulation of CXCR4 and down-regulation of CXCR5 and CCR7 (2, 3). Furthermore, plasma cells in chimeric mice reconstituted with CXCR4-deficient fetal liver cells were mislocalized within the spleen, found in elevated numbers in the blood, and failed to accumulate in the bone marrow (2). Thus, CXCR4 and its ligand CXC chemokine ligand (CXCL)[3]12 play a major role in the localization of plasma cells within splenic red pulp and lymph node medullary cords as well as in the bone marrow (2). Furthermore, IgA-producing cells but not those producing IgG or IgM in mice express CCR9 and efficiently respond to its ligand CC chemokine ligand (CCL)25, which is selectively expressed by cryptic epithelial cells in the small intestine (4).

Recently, we have found that EBV-immortalized human B cells consistently up-regulate CCR6 and CCR10 and down-regulate CXCR4 and CXCR5 (5). We have further shown that the EBV-encoded latent proteins are responsible for up-regulation of CCR6 and down-regulation of CXCR4 (5). However, the up-regulation of CCR10, whose expression in normal B cells has not been reported so far (6), or the down-regulation of CXCR5 could not be explained by the effects of the EBV-encoded latent proteins (5). Because EBV-immortalized B cells resemble plasma cells, we speculated that their differentiation stages fixed by immortalization with EBV may be responsible for CCR10 up-regulation and CXCR5 down-regulation. Indeed, recent studies have consistently shown CXCR5 down-regulation in mouse plasma cells (2, 3). These considerations prompted us to examine the full repertoire of chemokine receptors expressed by human plasma cells. In this study, we report that human bone marrow plasma cells and myeloma cells selectively express CXCR4, CXCR6, CCR10, and CCR3, and that tissues known to be enriched with plasma cells as well as cultured human bone marrow stromal cells constitutively express CXCL12 (CXCR4 ligand) (7), CXCL16 (CXCR6 ligand) (8, 9), and CCL28 (CCR10 and CCR3 ligand) (10, 11).

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[3] Abbreviations used in this paper: CXCL, CXC chemokine ligand; CCL, CC chemokine ligand; CX_3CL, CX_3C chemokine ligand; VLA-4, very late Ag-4; SEAP, secreted form of placental alkaline phosphatase.

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Materials and Methods

Cells and cytokines

RPMI8226 (JCRB0034), KMS-12BM (JCRB0429), KMS-12PE (JCRB0430), and KHM-1B (JCRB0133) were human myeloma cell lines obtained from Health Science Research Resources Bank (Sennan, Osaka, Japan). Human bone marrow irradiated stromal cells were purchased from Takara Biomedicals (Kyoto, Japan) ($n = 2$). Peripheral blood samples were obtained from healthy adult donors ($n = 3$) and patients with multiple myeloma ($n = 3$). Bone marrow samples were obtained from adult donors ($n = 7$) and also purchased from Takara Biomedicals ($n = 5$). Informed consents were obtained from all donors. Mononuclear cells were isolated by centrifugation on Ficoll-Paque (Pharmacia Biotech, Uppsala, Sweden) and stored at −80°C until use. All human recombinant cytokines were purchased from PeproTech (Rocky Hill, NJ).

RT-PCR

This was conducted as described previously (5). cDNA samples from various human tissues were purchased from Clontech (Palo Alto, CA). Primers for the chemokine receptors and G3PDH were described previously (5). Primers for chemokines were as follows: +5′-CCCTCTGTGAGATCCGTCTTTG GCCT-3′ and −5′-TCTGATTGGAACCTGAACCCCTGCTG-3′ for CXCL12; +5′-CGTCACTGGAAGTTGTTATTGTGGT-3′ and −5′-TG GTAGGAAGTAAATGCTTCTGGTG-3′ for CXCL16; +5′-ACCACC TCTCACGCCAAAGCTCACAC-3′ and −5′-CGGCACAGATATCCTT GGCCAGTTTG-3′ for CCL11; +5′-CAACCTTCTGCAGCCTCCTG-3′ and −5′-CCATTTTCCTTAGCATCCCA-3′ for CCL27; and +5′-AGAAGCCATACTTCCCATTGC-3′ and −5′-AGCTTGCACTTTCAT CCACTG-3′ for CCL28. Real-time PCR was performed using TaqMan assay and 7700 Sequence Detection System (Applied Biosystems, Foster City, CA). Conditions for PCR included 50°C for 2 min, 95°C for 10 min, and 50 cycles of 95°C for 15 s (denaturation) and 60°C for 1 min (annealing/extension). The primers for chemokines were as follows: +5′-CCATGCCGATTCTT CGAAAG-3′ and −5′-TTCAGCCGGGCTACAATCTG-3′ for CXCL12; +5′-CGCCATCGGTTCAGTTCAT-3′ and −5′-ACACACGCTCCAGG AAAGGA-3′ for CXCL16; and +5′-CAGAGAGGACTCGCCATCGT-3′ and −5′-TGTGAAACCTCCGTGCAACA-3′ for CCL28. The probes for chemokines were as follows: +5′-CATCTCAAAATTCTCAACACTCCAAACT GTGCC-3′ for CXCL12; +5′-ACCATCGGTGTCTATACTACAC GAGGTTCCAG-3′ for CXCL16; and +5′-CTTGGCTGTCTGTGCG GCCCTACAT-3′ for CCL28. The probes were labeled with reporter fluorescent dye 6-FAM at the 5′ end. Primers and fluorogenic probes for G3PDH were from TaqMan kit (Applied Biosystems). Quantification of chemokine expression was obtained using sequence detector system software (Applied Biosystems).

Flow cytometric analysis

The following murine mAbs were purchased from R&D Systems (Minneapolis, MN): anti-CXCR3 (clone 49801.111), anti-CXCR6 (clone 56811.11), anti-CCR3 (clone 444.11), anti-CCR6 (clone 53103.111), anti-CXCR4 (clone 44717.111), and anti-CXCR5 (clone 51505.111). Anti-CCR7 (2H7), PE-labeled anti-CD38 (HIT2), and Cy5-labeled CD45 (HI30) were purchased from BD Biosciences (Mountain View, CA). Rabbit anti-CCR10 was purchased from BIOCARTA (San Diego, CA). Isotype controls were purchased from DAKO (Kyoto, Japan). Cells were washed with PBS containing 2% FBS and reacted for 30 min with each mAb. After washing, cells were reacted with FITC-conjugated sheep $(F(ab')_2)$ anti-mouse IgG (Sigma-Aldrich, St. Louis, MO). In some experiments, cells were double stained with PE-labeled anti-CD38 and Cy5-labeled anti-CD45. For intracellular staining of CCR10, cells fixed and permeabilized with 2% paraformaldehyde and 0.1% Triton X-100 were indirectly stained with anti-CCR10 and FITC-labeled goat anti-rabbit IgG (Sigma-Aldrich). After staining, cells were analyzed on FACSCalibur (BD Biosciences) with appropriate gatings and quantitated in comparison with isotype control Abs. Dead cells were gated out by staining with propidium iodide.

Chemotaxis assay

All recombinant chemokines were purchased from R&D Systems. Migration assays for fresh human bone marrow mononuclear cells were conducted using Transwell plates with 8-μm pore size (Corning, Corning, NY) as described previously (5).

Cell adhesion assays

Cell adhesion to immobilized fibronectin was determined as described previously (12). The extracellular domain of human CXCL16/SR-PSOX (13) was subcloned into pDREF-SEAP $(His)_6$-Hyg expression vector (14), and CXCL16 fused at the C terminus with secreted form of placental alkaline phosphatase (SEAP), or CXCL16-SEAP, was generated by transfection to HEK293 cells. Cell adhesion to immobilized CXCL16 was determined essentially as described previously (14).

ELISA

Human bone marrow stromal cells were seeded in 24-well plates at a density of 1×10^5 cells/well and cultured without or with 10 ng/ml IL-1β. Measurement of CXCL12 and CCL28 in the culture supernatants was conducted using ELISA kits purchased from R&D Systems. For standardization of assay, serially diluted recombinant CXCL12 or CCL28 was included in each ELISA plate.

Results

Consistent expression of CXCR4, CXCR6, CCR10, and CCR3 in plasma cells and myeloma cells

To gain an insight into the full repertoire of chemokine receptors expressed by human plasma cells, we first examined chemokine receptor expression in a panel of four human myeloma cell lines. RT-PCR analysis using specific primer sets for all known 18 chemokine receptors (CXCR1∼6, CCR1∼10, XCR1, and CX_3CR1) (1) revealed that the myeloma cell lines were consistently positive for CXCR4, CXCR6, CCR10, and CCR3. Staining of these myeloma cell lines with specific Abs for various chemokine receptors and flow cytometric analysis verified the RT-PCR results (data not shown).

After getting a consensus profile of chemokine receptor expression in human myeloma cell lines, we proceeded to examine the expression of selected chemokine receptors on human bone marrow plasma cells. Plasma cells in bone marrow mononuclear cells could be identified by the expression of high levels of CD38 on their surface (15, 16). We confirmed that $CD38^{high}$ cells sorted from bone marrow mononuclear cells had the typical plasma cell morphology (Fig. 1*a*). As shown in Fig. 1*a*, plasma cells in the bone marrow expressed CXCR4 and CXCR6 at high levels, CCR10 at intermediate levels, CCR3 at low levels, and CXCR5, CCR6, and CCR7 at marginal levels. We found no significant differences in the expression levels of these chemokine receptors between $CD38^{high}CD45^{+}$ immature and $CD38^{high}CD45^{-}$ mature plasma cells (15, 16) (data not shown).

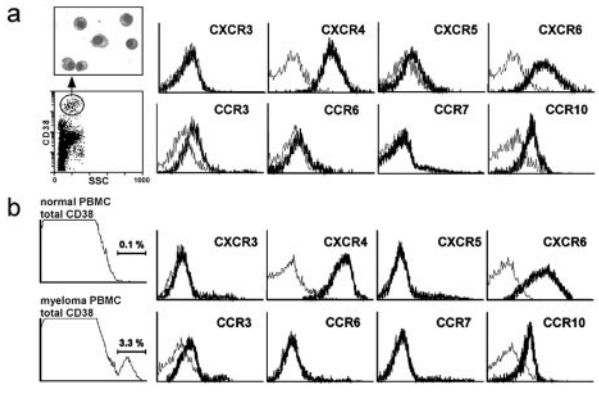

FIGURE 1. Flow cytometric analysis for expression of chemokine receptors in fresh plasma cells and myeloma cells. *a*, Bone marrow mononuclear cells obtained from adult donors were triple stained for CD38, CD45, and indicated chemokine receptors, and analyzed by flow cytometry. Representative results from three donors are shown. May-Giemsa staining of $CD38^{high}$ cells sorted from bone marrow mononuclear cells was also shown. *b*, PBMC obtained from healthy adult donors and myeloma patients were double stained for CD38 and indicated chemokine receptors, and analyzed by flow cytometry. Representative results from three patients with multiple myeloma are shown.

We also conducted flow cytometric analysis on the expression of chemokine receptors on myeloma cells present in the peripheral blood of patient with multiple myeloma. As shown in Fig. 1*b*, PBMC from patients with multiple myeloma but not those from healthy adult donors contained a substantial fraction of cells expressing CD38 at high levels. We confirmed that these cells were also positive for another plasma cell marker CD138 (data not shown) (15, 16). These cells that represented floating myeloma cells in PBMC of myeloma patients also consistently expressed CXCR4 and CXCR6 at high levels, CCR10 at intermediate levels, and CCR3 at low levels (Fig. 1*b*).

Responses of plasma cells to the ligands of CXCR4, CXCR6, CCR10, and CCR3

We next examined chemotactic responses of bone marrow plasma cells to CXCL12 (CXCR4 ligand), CXCL13 (CXCR5 ligand), CXCL16 (CXCR6 ligand), CCL11 (CCR3 ligand), CCL27 (CCR10 ligand), and CCL28 (CCR10 and CCR3 ligand) (1). As shown in Fig. 2*a*, CXCL12, CXCL16, and CCL28 induced migration of plasma cells with similar potencies and efficiencies. CCL11 and CCL27 also induced modest migratory responses, while CXCL13 induced only marginal responses. The chemotactic responses of plasma cells to CCL28, which signals via both CCR10 and CCR3 (10, 11), were roughly about the summation of those to CCL27 and CCL11, the specific ligands of CCR10 and CCR3, respectively (1). These results were in good accordance with the expression profile of chemokine receptors on plasma cells (Fig. 1).

Previously, CXCL12 was shown to induce transient adhesion of fresh myeloma cells to fibronectin and VCAM-1 via activation of very late Ag-4 (VLA-4) (12). Therefore, we examined whether CXCL16 and CCL28 were also capable of inducing adhesion of plasma cells to fibronectin. As shown in Fig. 2*b*, not only CXCL12 but also CXCL16 and CCL28 efficiently induced adhesion of bone marrow plasma cells to fibronectin. The adhesion responses were rapid and transient, reaching the maximal levels within 5 min and returning to basal levels by 30 min (12), and also VLA-4 dependent as shown by the ability of anti-α_4 integrin mAb to block cell adhesion to fibronectin.

Direct adhesion of plasma cells to immobilized CXCL16

CXCL16, the ligand of CXCR6, is a novel transmembrane-type chemokine whose structure is very similar to that of another transmembrane chemokine fractalkine/CX_3C chemokine ligand (CX_3CL)1 (8, 9). Previously, we have shown that immobilized CX_3CL1 induces firm adhesion of CX_3CR1-expressing cells via its chemokine domain in both static and flow conditions without requiring signaling via $G_{\alpha i}$ or divalent cations (14, 17). The structural similarity of CXCL16 to CX_3CL1 prompted us to examine whether immobilized CXCL16 was also capable of inducing direct adhesion of plasma cells expressing CXCR6. As shown in Fig. 2*c*, CXCL16-SEAP immobilized to the plastic surface efficiently induced adhesion of plasma cells, which was effectively blocked by anti-CXCR6 but not by control Ab. Furthermore, pretreatment of plasma cells with pertussis toxin or presence of EGTA during the binding assay did not affect the levels of adhesion. Collectively, immobilized CXCL16 was indeed capable of inducing adhesion of plasma cells via CXCR6 without requiring signaling via $G_{\alpha i}$ or divalent cations (integrins).

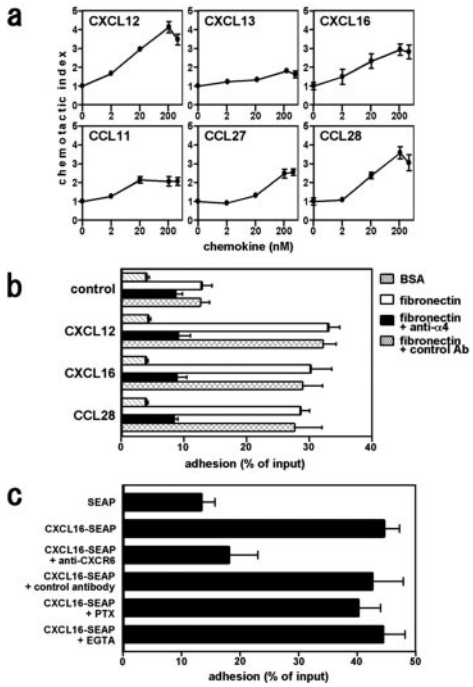

FIGURE 2. Chemotactic and adhesion responses of plasma cells. *a*, Migratory responses of human bone marrow plasma cells to indicated chemokines were determined in Transwell plates. After incubation for 2 h at 37°C, input cells and cells migrated into lower wells were double stained with PE-labeled anti-CD38 and Cy5-labeled anti-CD45, and measured by flow cytometry. All assays were done in duplicate. Chemotaxis index = migration in response to chemokine/background migration. Representative results of $CD38^{high}CD45^{low}$ mature plasma cells from five donors are shown. Each point represents mean ± SEM from three separate experiments. *b*, Bone marrow mononuclear cells were resuspended without or with chemokines at 200 nM and immediately added in triplicate to 96-well plates coated with BSA or fibronectin. After washing, bound cells were harvested and stained with PE-labeled anti-CD38. Plasma cells in original and bound populations were counted by flow cytometry. For blocking experiments, cells were pretreated for 20 min with 10 μg/ml anti-integrin α_4 (HP1/2) before treatment with chemokines. Representative results from three donors are shown. Each point represents mean ± SEM from three separate experiments. *c*, Bone marrow mononuclear cells obtained from adult donors ($n = 3$) were seeded in triplicate into 96-well microtest plates coated with CXCL16-SEAP or SEAP and incubated for 30 min at room temperature. In some experiments, cells were pretreated with 30 μg/ml anti-CXCR6 or 500 ng/ml pertussis toxin (PTX; Invitrogen) for 30 min, or the assay was conducted with adhesion buffer containing 5 mM EGTA. After gentle washing, original cell populations and adherent cells were stained with PE-labeled anti-CD38, and $CD38^{high}$ plasma cells were counted by flow cytometry. Representative results from three donors are shown. Each point represents mean ± SEM from three separate experiments.

Expression of CXCL12, CXCL16, and CCL28 by human bone marrow stromal cells

The selective expression of CXCR4, CXCR6, CCR10, and CCR3 by bone marrow plasma cells suggests that their respective chemokine ligands may be involved in the homing and tissue microenvironmental localization of plasma cells in the bone marrow and other target tissues. However, except for CXCL12 (CXCR4 ligand) (7), expression of these chemokines in the bone marrow has not been reported. Therefore, we conducted RT-PCR analysis for expression of these chemokines in bone marrow and other human tissues known to be enriched with plasma cells. As shown in Fig. 3*a*, all the tissues examined including bone marrow expressed CXCL12 (CXCR4 ligand),

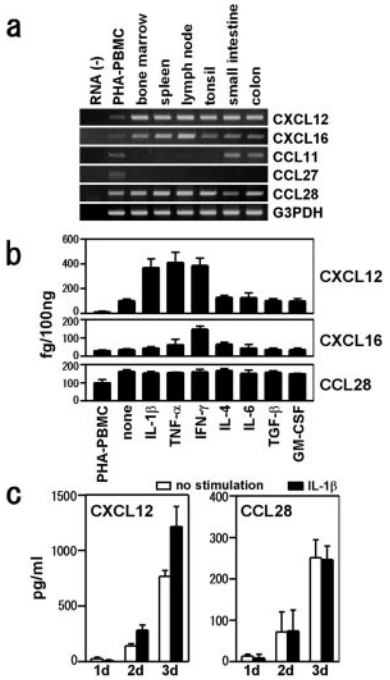

FIGURE 3. Expression of CXCL12, CXCL16, and CCL28 in human bone marrow tissue and stromal cells. *a*, cDNA samples from PHA-stimulated PBMC (positive control), human bone marrow, spleen, lymph node, tonsil, small intestine, and colon were analyzed for expression of CXCL12, CXCL16, CCL11, CCL27, CCL28, and G3PDH by PCR. Representative results from two separate experiments are shown. *b*, cDNA samples from PHA-stimulated PBMC (positive control) and human bone marrow stromal cells treated without or with 10 ng/ml IL-1β, 50 ng/ml TNF-α, 100 ng/ml IFN-γ, 10 ng/ml IL-4, 10 ng/ml IL-6, 10 ng/ml TGF-β, and 10 ng/ml GM-CSF for 24 h were analyzed for expression of CXCL12, CXCL16, CCL28, and G3PDH by real-time PCR. Representative results from two separate experiments are shown. *c*, Bone marrow stromal cells were seeded in triplicate in 24-well plates and cultured without or with 10 ng/ml IL-1β. At indicated time points, CXCL12 and CCL28 in the culture supernatants were measured by using ELISA. Each point represents mean ± SEM. Representative results from two separate experiments are shown.

CXCL16 (CXCR6 ligand), and CCL28 (CCR10 and CCR3 ligand) at high levels. Thus, these chemokines can be collectively involved in the homing and localization of plasma cells in the bone marrow and other target tissues. In contrast, CCL11 (CCR3 ligand) or CCL27 (CCR10 ligand) was hardly expressed in the bone marrow.

CXCL12 was originally identified as a secretory product of a mouse bone marrow stromal cell line (7). Therefore, we next examined expression of CXCL12, CXCL16, and CCL28 by human primary bone marrow stromal cells. We confirmed that stromal cells were $CD10^+$ and $CD34^{low}$ (data not shown) (18). As shown in Fig. 3*b*, real-time RT-PCR revealed that stromal cells indeed constitutively expressed CXCL12, CXCL16, and CCL28 at high levels. The expression of CXCL12 was enhanced by treatment with IL-1β, TNF-α, or IFN-γ, while that of CXCL16 was enhanced by IFN-γ. In contrast, the expression of CCL28 was hardly affected by any cytokines. We also examined secretion of CXCL12 and CCL28 by bone marrow stromal cells. As shown in Fig. 3*c*, stromal cells indeed secreted copious amounts of CXCL12 and CCL28 in the culture supernatants. Consistent with the results from RT-PCR (Fig. 3*b*), treatment of stromal cells with IL-1β significantly enhanced secretion of CXCL12 ($p < 0.05$) but not that of CCL28.

Discussion

We have demonstrated that human bone marrow plasma cells as well as myeloma cells consistently express CXCR4, CXCR6, CCR10, and CCR3 (Fig. 1). Accordingly, CXCL12 (CXCR4 ligand) (7), CXCL16 (CXCR6 ligand) (8, 9), and CCL28 (CCR10 and CCR3 ligand) (10, 11) efficiently induced chemotactic responses and VLA-4-dependent transient adhesion to fibronectin in plasma cells (Fig. 2). Importantly, we have also shown that human bone marrow and other tissues known to be enriched with plasma cells contain transcripts of CXCL12, CXCL16, and CCL28 at high levels (Fig. 3). Furthermore, we have shown that cultured human bone marrow stromal cells constitutively express CXCL12, CXCL16, and CCL28 at high levels (Fig. 3). Collectively, our results support the roles of CXCR4, CXCR6, CCR10, and CCR3 and their respective chemokine ligands in the migration and tissue localization of human plasma cells in bone marrow and other tissues known to be enriched with plasma cells.

CXCL16 is a novel transmembrane-type chemokine (8, 9), which was also identified as a novel scavenger receptor for oxidized low density lipoprotein (13). In the present study, we have shown that immobilized CXCL16 is capable of inducing adhesion of plasma cells expressing CXCR6 without requiring $G_{\alpha i}$-mediated signaling or divalent cations (Fig. 2), an observation quite similar to that of another transmembrane-type chemokine CX_3CL1 (14, 17). Thus, like CX_3CL1, CXCL16 may function as a chemoattractant in its soluble form and a cell adhesion molecule in its membrane-anchored form. This may allow CXCL16 to contribute to plasma cell localization in the bone marrow and other target tissues not only by its chemotactic activity but also by its direct cell adhering activity.

In conclusion, we have shown for the first time that human bone marrow plasma cells and myeloma cells consistently express CXCR6, CCR10, and CCR3 besides CXCR4. The important role of CXCR4 in migration and tissue localization of plasma cells has been reported previously (2). Thus, the exact roles of CXCR6, CCR10, and CCR3 in the migration and tissue localization of plasma cells remain to be seen. It also remains to be seen whether human plasma cells producing different Ig isotypes express a different set of chemokine receptors to migrate to different anatomical sites as mouse plasma cells do (4).

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