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Blockade of Chemokine Receptor CXCR3 Inhibits T Cell Recruitment to Inflamed Joints and Decreases the Severity of Adjuvant Arthritis

Karkada Mohan* and Thomas B. Issekutz2*†

T lymphocytes expressing the chemokine receptors, CCR2, CCR5, CXCR3, and CXCR6 are increased in inflamed tissues in rheumatoid arthritis. The role of CXCR3 in autoimmune arthritis induced in Lewis rats was investigated. CXCR3+ T cells migrated 2- to 3-fold more than CXCR3− T cells to inflamed joints in arthritic animals. CXCR3-expressing in vivo Ag-activated T lymphoblasts and in vitro-activated lymph node cells from arthritic animals were strongly recruited to the arthritic joints, and treatment with anti-CXCR3 mAb significantly inhibited this T cell recruitment by 40–60%. Immune T cells from the spleen and lymph nodes of actively immunized arthritic donors adoptively transferred arthritis to naive rats. Treatment with anti-CXCR3 mAb delayed the onset of arthritis and significantly reduced the severity of joint inflammation with a >50% decrease in the clinical arthritis score. Blockade of CXCR3 also significantly reduced the weight loss in the arthritic animals and inhibited neutrophil accumulation in the joints by 50–60%. There was a marked reduction in the leukocyte infiltration of the synovium in the presence of CXCR3 blockade and a decrease in the loss of articular cartilage of the joints. In conclusion, CXCR3 on T cells has an essential role in T cell recruitment to inflamed joints and the development of joint inflammation in adjuvant arthritis. The Journal of Immunology, 2007, 179: 8643–8469.

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by extensive leukocyte infiltration of the joint space, synovium, and periartricular tissue eventually leading to joint destruction. The process of leukocyte infiltration of inflamed tissues is mediated in part by both cell adhesion molecules and chemokine receptors expressed by various cell types found in such inflamed tissues. Chemokines, which are induced by inflammatory cytokines in the inflamed joint tissue, facilitate the cellular influx to the joints during arthritis. T lymphocytes expressing the chemokine receptors CXCR3, CCR2, CCR4, CCR5, CXCR6, and others are present in RA joint tissue (1–6). Similarly, levels of CXC and CC chemokine ligands, such as CXCL10, CXCL11, CCL2, CCL3, CCL5, and others are found in abundance in synovial fluids of patients with RA (4, 5, 7, 8). Thus, chemokine-chemokine receptor interactions play a major role in T cell recruitment to arthritic joints. Although the notion that targeting this interaction would be an effective therapeutic strategy in preventing cellular influx and joint inflammation in arthritis is attractive, given the large number of chemokine-chemokine receptor interactions involved in cell traffic, it is important to identify specific and nonredundant interactions that are critical in cell recruitment to inflamed joints.

Adjuvant arthritis (AA) in the rat is an animal model of human arthritis in which neutrophil, monocyte, and T cell recruitment to inflamed joints can be readily quantified (9–12). Using this model, the role of several cell adhesion molecules, such as integrins and selectins, in leukocyte recruitment to inflamed joints has been extensively studied (9, 11–16). A few studies were reported that examined the effect of blockade of chemokines or chemokine receptors in animal models of arthritis. Neutralizing Abs to CCL5 and CXCL10 were able to reduce the severity of AA (17–19). In mouse type II collagen-induced arthritis (CIA), CCR5 antagonists reduced the severity of arthritis (20–22). Blockade of CCR2 also inhibited the development or severity of arthritis (23–25) and a neutralizing mAb to CCL2 resulted in reduced monocyte migration and joint swelling in rats with CIA (26). However CCR2 blockade has also been shown to aggravate some forms of arthritis in rodents.

Inflamed joints in patients with RA are infiltrated by T cells that express numerous chemokine receptors including CXCR3 (2, 3). Both normal human blood T cells and IL-2-activated T cells are highly chemotactic to the CXCR3 ligands, CXCL10 and CXCL11 (8, 27, 28). Xie et al. (29) showed that a neutralizing Ab to CXCR3 inhibited activated T cell migration to the inflamed peritoneum. We showed that blockade of CXCR3 can also result in strong and nonredundant inhibition of memory and activated T cell migration to dermal inflammation (30). However, the contribution of CXCR3 to T cell recruitment to the inflamed arthritic joint has not been examined, which is important given the contribution of memory and activated T cells in this disease. Our objective was to examine the role of CXCR3 in the migration of T cells to inflamed arthritic joints and to determine the effect of CXCR3 blockade on the induction of AA and on the severity of arthritis and joint injury. This study demonstrates that memory and activated T cells that are CXCR3+ in contrast to CXCR3− T cells preferentially migrate to inflamed joints, and that blockade of CXCR3 significantly inhibits T cell infiltration of arthritic joints, and can reduce the severity of arthritis.
Materials and Methods

Monoclonal Abs

Hamster anti-rat CXCR3 mAb, XR3.1, and XR3.2 were generated in our laboratory (30). XR3.1 binds to rat CXCR3 and is weakly inhibitory, whereas XR3.2 is a potent neutralizing mAb that blocks CXCR3-induced cell adhesion, chemotaxis, and in vivo T cell recruitment to dermal inflammation. The hamster mAb 145-2C11 (anti-mouse CD3) was obtained from American Type Culture Collection, and HRL-2 (anti-rat CD62L) 2-omino-4-(thiazol-2-yl)-3-(4-methyl-5-phenyl-1H-pyrazol-3-yl)benzene sulfonamide chloroacetate, was a gift of Dr. M. Miyasaka (University of Osaka, Osaka, Japan). Both were used as negative control hamster mAbs.

Induction of AA

Arthritis was induced in 6- to 8-wk-old male Lewis rats (Charles River Breeding Laboratories), using an Institutional Animal Care and Review Committee-approved protocol, by s.c. immunization with 0.5 mg of killed Mycobacterium butyricum (Difco) in 0.05 ml mineral oil at two sites at the base of the tail. Arthritis was scored clinically from 0 to 4 per limb and the tail, based on the severity of swelling (0–2), erythema (0–1), and limitation of movement (0–1), as previously described (10). The total score was the sum of the scores in all four limbs and the tail, giving a possible maximum score of 20.

Adoptive transfer of AA

Twelve days after immunization with M. butyricum, cervical, axillary, inguinal, and popliteal lymph nodes (LN) and spleens were removed aseptically from animals with active arthritis. Cell suspensions were prepared. RBC in the spleen were lysed with 0.84% ammonium chloride. Spleen and LN lymphocytes were stimulated with 2.5 μg/ml Con A (Sigma-Aldrich) for 48 h in RPMI 1640 plus 5% FBS at 37°C in 5% CO₂, as described (9, 31). After 48 h, the lymphocytes were washed with RPMI 1640 and i.v. injected into naive animals at a dose of 4 × 10⁷ cells per 100 g of body weight. Recipients were scored daily for evidence of arthritis. Anti-CXCR3 mAb XR3.2 (2 mg) or a control hamster mAb was injected i.p. into groups of animals every other day, starting on the day of lymphocyte transfer, up to 6 or 10 days after cell transfer. The trough plasma concentration of the mAb was measured and found to be 35–70 μg/ml, which is several fold higher than the IC₅₀ (2 μg/ml) and IC₉₀ for this mAb.

Leukocyte isolation, radiolabeling, and migration

T cells were obtained from the spleen of normal animals by passage over nylon wool. CXCR3⁺ and CXCR3⁻ T cells were isolated using magnetic bead separation (Miltenyi Biotec) (30). Briefly, T cells were incubated on ice with anti-CXCR3 mAb XR3.1 followed by a biotinylated mouse-anti-hamster mAb (BD Biosciences), and then treated with streptavidin magnetic beads for 15 min at 6 to 9°C and passed through the separation column in a magnetic field. Column nonadherent cells were <1.0% CXCR3⁻ and adherent cells were >99% CXCR3⁺.

To obtain Ag-activated T lymphoblasts, animals were immunized once in each footpad with 10⁷ PFU vaccinia virus, cells were obtained 4 days later from the Ag draining LN, and the low density T lymphoblasts were isolated using a continuous Percoll gradient (32). To obtain M. butyricum-activated T cells inguinal and popliteal LNs draining arthritic joints were cultured at 5 × 10⁵ cells/ml in RPMI 1640 plus 10% FBS in the presence of 12.5 μg/ml M. butyricum Ag. On day 2 the cells were diluted to 1 × 10⁶ cells/ml, on day 4 the cells were washed, and cultured overnight without Ag at 1 × 10⁶ cells/ml and were used on day 5 after passing them through a nylon wool column. Neutrophils were isolated from blood collected after a transfusion exchange with hydroxyethyl starch (DuPont Merck), as previously described (15, 33). Leukocyte rich plasma was obtained after sedimentation of erythrocytes at 1 × g, and >98% pure neutrophils were isolated after centrifugation on discontinuous gradients of 74% and 63% Percoll.

T cells and neutrophils were labeled with either ⁵¹Cr or ¹¹¹In oxine (Amersham Biosciences), and their in vivo migration was measured as previously described (11, 34, 35). T lymphocytes were labeled with 5 μCi of ⁵¹Cr or ¹¹¹In oxine per 10⁶ cells for 30 min at 37°C or with 1 μg 7T15, a ⁵¹Cr-oxine per 10⁶ cells for 10 min at room temperature. Cells were washed twice and resuspended for i.v. injection. Each animal received 1–2 × 10⁸ cells carrying 1–5 × 10⁶ cpm, and T cell migration was determined after 20 h. The neutrophils were labeled with ¹¹¹In as described, washed twice, and i.v. injected. Each animal received 10⁷ neutrophils carrying 2–5 × 10⁶ cpm and migration was determined after 2 h. In some experiments, 2 mg of control mAb or anti-CXCR3 mAb XR3.2 was given i.v. immediately before the injection of labeled T cells. Animals were sacrificed, and cardiac blood was obtained to measure the leukocyte- and plasma-associated radioactivity. Joints were dissected and segments of limbs sectioned to include carpal, metacarpal, talar, and metatarsal joints for analysis as previously described (11). ¹¹¹In and ⁵¹Cr content of joints as well as internal organs such as spleen, liver, lung, and LNs was determined by gamma counting with spectral spillover correction. Accumulated isotope in the tissue is expressed as cpm per 10⁶ cpm injected.

Histology

Joints were fixed in 10% phosphate-buffered formalin, decalcified in formic acid, and embedded in paraffin. Sections were stained with H&E and cartilage proteoglycan on serial sections was stained for 1 min with safranin O (Difco) as previously described (13).

Statistical analysis

Data are expressed as mean ± SEM of multiple experiments. ANOVA and Student’s unpaired t test were used for statistical analysis. A value for p < 0.05 was considered significant.

Results

Migration of CXCR3⁺ and CXCR3⁻ T cells to inflamed joints

The ability of CXCR3⁺ and CXCR3⁻ T cells to migrate to inflamed joints in animals with AA was determined. CXCR3⁺ and CXCR3⁻ T cells were isolated, radiolabeled, and injected i.v. into arthritic animals at the height of the disease, 13 days after immunization with Mycobacterium. The accumulation of the labeled cells in the joints and in inflammatory lesions induced in the skin (as control sites) was determined (Fig. 1). CXCR3⁺ T cells...
preferentially migrated to arthritic joints compared with cells lacking CXCR3 expression. Nearly 2.5-fold more CXCR3+ T cells than CXCR3- T cells were recruited to the inflamed joints (p < 0.001 for carpal and talon joint, hindpaw, and tail; p < 0.01 for forepaw). CXCR3+ T cells migrated 6- to 7-fold more to dermal inflammation induced by cytokines and polyinosinic polycytidylic acid (p < 0.001) and 4- to 5-fold more to purified protein derivative of Mycobacterium and LPS induced dermal inflammation (p < 0.01), as compared with CXCR3- T cells (Fig. 1B). Levels of both CXCR3+ and CXCR3- T cells found in the blood were similar (Fig. 1C). However, significantly fewer CXCR3+ T cells migrated to the LNs (p < 0.001) and significantly more to spleen (p < 0.01), compared with CXCR3- T cells.

**Effect of CXCR3 blockade on in vivo activated LN T lymphoblast migration to inflamed joints**

The effect of blocking CXCR3 using anti-CXCR3 mAb on the ability of Ag-activated LNs T lymphoblasts to migrate to inflamed joints in AA rats was tested. Nearly 60% of CD4+CD45RC- T lymphoblasts and 80% of CD8+CD45RC- express CXCR3 (30 and our unpublished observations). Anti-CXCR3 mAb treatment significantly inhibited T lymphoblast recruitment to all of the joint tissues examined (Fig. 2A). Cell migration was inhibited by 65% to carpal joints (p < 0.01); 42–62% to talar joints and hind paws (p < 0.05); and 87% to articular joints of the tail (p < 0.05). In addition, nearly 75% of T lymphoblast migration to the synovial tissue obtained from the talon joints was inhibited (p < 0.01) in anti-CXCR3-treated animals. Marked inhibition (75–88%) of cell recruitment to dermal inflammatory sites was also seen in animals receiving anti-CXCR3 mAb (Fig. 2B). However, the extent of labeled cells in the blood, the plasma, various lymphoid organs, the liver and the lung were not significantly different between the control and anti-CXCR3-treated animals, indicating that the T lymphoblasts were not cleared from the blood (Fig. 2C).

**Effect of CXCR3 blockade on Mycobacterium restimulated AA LN T cell migration to joints**

The effect of CXCR3 blockade on the ability of in vitro mycobacterial Ag-activated LNs T cells from arthritic animals to arthritic joints was tested (Fig. 3A). Anti-CXCR3 mAb treatment inhibited migration by >50% to carpal joints (p < 0.01), ~90% to the forepaws (p < 0.05), 35% to talar joints (p < 0.01), 45% to hindpaw (p < 0.01), and 72% to articular joints of the tail (p < 0.05). Mycobacterial Ag-activated T cell migration to the synovial tissue was strongly inhibited by 66% (p < 0.001). Marked inhibition (64–81%) of activated T cell recruitment to dermal inflammatory sites was also observed in animals receiving anti-CXCR3 mAb (Fig. 3B). The migration of labeled cells in the blood and in various lymphoid organs was not affected by mAb treatment (data not shown).

**Effect of anti-CXCR3 mAb treatment on the severity of adoptively transferred arthritis**

To examine the role of CXCR3 in mediating joint inflammation in arthritis, the effect of blocking CXCR3 on joint inflammation and
the severity of disease was examined (Fig. 4). T cells from the LN and spleen of arthritic animals were isolated, activated in vitro with Con A, and transferred to naive animals to induce arthritis. In untreated or control mAb-treated animals, joint inflammation began 5 days after T cell transfer, reached a maximum at day 12–13, and remained at that level.

As shown in Fig. 4, A and B, carpal and talar joints in control mAb-treated animals developed a progressively increasing severity of arthritis beginning 5 days after T cell transfer. Severity reached a score of 2 ± 0.3 and 4 ± 0.01, respectively, at 12 days. Anti-CXCR3 mAb-treated animals had milder disease with scores of 0.6 ± 0.1 (*p < 0.001) and 1.6 ± 0.4 (**p < 0.001) in carpal and talar joints, respectively, i.e., a 60–70% decrease in disease severity. Similarly, articular joints of the tail showed a 68% inhibition in joint inflammation in anti-CXCR3 mAb-treated animals (score of 0.5 ± 0.01 vs 1.6 ± 0.2 in controls; **p < 0.001) (Fig. 4C). Taken together, total arthritic score in anti-CXCR3 mAb-treated animals was significantly lower (4.9 ± 1.0) than the total in the control mAb-treated group (13.5 ± 0.6), representing a 64% inhibition (**p < 0.001) (Fig. 4D).

**Effect of anti-CXCR3 mAb treatment on the weight loss of arthritic animals**

Animals developing arthritis following adoptive T cell transfer lose weight as the disease progresses, which is another feature of this autoimmune inflammation. The effect of blocking CXCR3 on weight loss in animals with arthritis was investigated (Fig. 4E). During the first 5 days after immune T cell transfer, animals gained weight, but thereafter, control Ab-treated animals lost significantly more body weight than anti-CXCR3-treated animals. By day 14, mean body weight of control animals was even lower than on day 0. In contrast, animals treated with anti-CXCR3 mAb kept gaining weight until day 9 post transfer of T cells, and any weight loss observed thereafter was significantly less than loss observed in the controls (**p < 0.001).
Effect of anti-CXCR3 mAb treatment on neutrophil migration to inflamed joints

Neutrophils migrate avidly to arthritic joints during arthritis as a result of ongoing inflammation at these sites and there is a strong correlation between neutrophil recruitment to the inflamed joints and the severity of the disease (15). Blood neutrophil migration in 2 h to joints in control mAb-treated and anti-CXCR3 mAb-treated animals was examined 9 days after adoptive transfer of T cells. Neutrophil migration was significantly higher ($p < 0.05$) to the joints of animals that received control mAb compared with the joints of those injected with anti-CXCR3 mAb while inducing arthritis (Fig. 4F). Migration of neutrophils to carpal, talar, and tail joints was 50–60% less in anti-CXCR3 mAb-treated animals than in control mAb-treated animals.

In addition, the average weight of the joint tissues was also significantly higher (~30%) in control animals (data not shown) than in the anti-CXCR3-treated animals, suggesting greater swelling and edema during the development of arthritis.

Effect of anti-CXCR3 mAb treatment on joint histology

Talar joints were taken for histology from arthritic animals and treated with either control mAb or anti-CXCR3 mAb 18 days after T cell transfer. As shown in Fig. 5, A–D, talar joints from control mAb-treated animals showed synovial expansion and extensive leukocyte infiltration. In contrast, sections of joints from anti-CXCR3 mAb-treated animals showed a marked decrease in the synovial infiltration of leukocytes, indicative of less severe joint inflammation. To examine the articular surface of the joints, sections were also stained with safranin O for cartilage proteoglycan. As shown in Fig. 5, E and F, in control arthritic rats, there was a marked decrease in safranin O staining, indicating a loss of cartilage proteoglycan. In addition, the synovial infiltrate was adhering and extending into the eroding cartilage within the joint. In contrast, joints from animals that received anti-CXCR3 mAb during the development of arthritis (Fig. 5, G and H) had more proteoglycan staining, indicating minimal loss of cartilage and better preservation of joint architecture.

Discussion

The recruitment of leukocytes into sites of inflammation is crucial for the pathogenesis of arthritis and other inflammatory conditions (36, 37). Previous studies in patients with RA and juvenile idiopathic arthritis have reported the presence of T cells expressing
CXCR3 and CCR5 in synovial tissues (2, 3, 38, 39), and the presence of CC and CXC chemokines in synovial fluid (5, 7, 8, 40). AA in the rat, used as a model for arthritic diseases in humans, has been useful to help understand the role of cell adhesion molecules in leukocyte migration in the pathogenesis of joint injury (9, 11, 12, 16). In the present study, we examined the role of CXCR3 in the pathogenesis of AA. This study demonstrates for the first time that CXCR3 plays a nonredundant role in the recruitment of T cells to inflamed joints in AA, and that blockade of CXCR3 ameliorates the severity of AA induced by adoptive transfer of sensitized T cells. CXCR3 blockade leads to a decrease in joint inflammation as demonstrated by lower clinical scores, decreased neutrophil migration to the joints, decreased systemic effects of arthritis as reflected by a reduction in weight loss, and improved histology with preservation of the articular cartilage and joint architecture.

Although studies in human arthritis have shown the presence of CXCR3+ T cells in joint tissues, the contribution of CXCR3 to the recruitment of T cells to these inflamed tissues is not well established. It is unclear whether most T cells that have accumulated in the joint are induced to express CXCR3 in the cytokine microenvironment of the synovial tissue, whether CXCR3 is coexpressed along with other chemokine receptors on the cells that are recruited and not required for infiltration of the joint, or whether CXCR3 is essential for migration to this inflamed tissue. Previous studies had shown that most of the T cells seen in inflamed arthritic joints are of the memory phenotype (2, 3, 41). Our results show that cells expressing CXCR3 migrated to the inflamed joints in a much larger number than T cells lacking this chemokine receptor. This result is not merely a reflection of the expression of CXCR3 on memory T cells because most memory T cells in the spleen (85%) are CXCR3+ (30). Thus, this preferential accumulation of CXCR3+ cells suggests that CXCR3+ T memory cells lack the ability to migrate to these inflamed tissues.

CXCR3+ T cells also usually coexpress chemokine receptors, such as CCR2, CCR5, CXCR6, and others. These receptors may also mediate T cell migration to inflamed joints independent of or together with CXCR3 given the abundant chemokines in the joints (5, 7, 8, 40). Our results show that in vivo-activated memory T cells, many of which express CXCR3 together with other chemokine receptors, efficiently migrate to arthritic joints, and blockade of CXCR3 significantly inhibits their recruitment to these joints. Moreover, the migration to inflamed joints of in vitro Mycobacterium-activated memory T cells from LN draining arthritic joints was also markedly reduced by CXCR3 blockade. These findings provide direct evidence that CXCR3 mediates T cell recruitment from the blood to inflamed joints in arthritis and, hence, has a major role in inflammation of arthritic joints.

Previous studies showed that by neutralizing several different chemokines or using chemokine receptor antagonists in AA or mouse type II CIA, the severity of inflammation and joint swelling can be reduced. Neutralizing Abs to CCL5 and naked DNA vaccines encoding CCL2, CCL3, CCL4, CCL5, and CXCL10 reduced the severity of AA (17–19). A CXCL4 octapeptide prevented development of disease in CIA (42). Met-RANTES, which inhibits CCR1 and CCR5 function, and two different nonpeptide CCR5 antagonists reduced the severity of CIA and reduced leukocyte accumulation assessed histologically (20–22). Although two CCR2 antagonists and an anti-CCR2 mAb inhibited arthritis, a neutralizing mAb to CCL2 inhibited joint swelling in rat CIA by 30% (23, 24–26). However, CCR2 blockade or CCR2 deletion has also been reported to aggravate the severity of CIA (25, 43, 44). Thus, these studies implicate numerous chemokines and chemokine receptors in the pathogenesis of experimental arthritis in rodents. Our findings extend these studies by demonstrating that CXCR3 is also important in the development of arthritis, and that blockade of CXCR3 inhibits several aspects of joint injury.

Most previous reports have primarily examined the severity of arthritis using joint swelling and histology. In this study, we broaden the research of arthritis to include the effects of CXCR3 inhibition on neutrophil migration to the joints and on the systemic effects of the disease. Neutrophil migration to the joints in anti-CXCR3-treated animals was markedly decreased. Rat blood neutrophils do not express CXCR3, and the migration of neutrophils to T cell-independent dermal inflammatory sites in these animals was not altered by CXCR3 blockade (data not shown), indicating that the anti-CXCR3 mAb inhibition was not a direct effect on the neutrophils. It is likely that the decreased neutrophil migration to the joints was due to the reduction in the ability of the adoptively transferred T cells to induce joint inflammation, including diminished production of inflammatory cytokines and chemokines in the joint tissues.

Animals with AA become cachetic with a marked loss of weight, and develop a generalized vasculitis. CXCR3 blockade inhibited this weight loss and inhibited the migration of memory T cells to dermal inflammatory sites in these arthritic animals. Thus, there was a profound reduction in memory T cell migration to several types of inflammation when CXCR3 was blocked. Our studies directly show that CXCR3 blockade inhibits T cell migration to actively inflamed joints, suggesting that this mechanism may be critical and could be targeted to reduce joint inflammation. Although it is attractive to postulate that blockade of CXCR3 on T cells is responsible for the inhibition observed, the mAb may also be working through effects on the endothelium in the arthritic joints, which can express CXCR3 as well, and to which our mAb also binds as determined by immunohistochemistry (data not shown). Angiogenesis is a component of the inflammatory changes in arthritis. CXCR3 ligands are angiostatic (45), but it is not known whether blockade of CXCR3 would increase angiogenesis (46), and whether this increase may aggravate the inflammation.

In our model of AA, joint inflammation begins on day 5 after adoptive transfer, and the disease progresses rapidly over the next 5–7 days to reach a maximum arthritis score. The results show that treatment with anti-CXCR3 mAb not only reduces the severity of disease but also delays onset of inflammation. Increasing the dose of mAb had no effect on further inhibiting the disease or T cell migration to inflamed joints. This observation strongly suggests that CXCR3 is not absolutely essential for the development of arthritis but that other CXCR3-independent pathways also can mediate recruitment, as suggested by the migration studies discussed. Taken together current data suggests that CCR2, CCR5, and CXCR3 all contribute to the recruitment of T cells to the joint and promote the development of arthritis. Because activated T cells may express all three receptors, it is possible that the combination of these receptors is required for proper recruitment and positioning of the cells to promote arthritis. Further studies are needed to determine which of these chemokine receptor acts in concert with CXCR3 to mediate T cell infiltration in AA.

Previously, treatment with anti-CD49d/CD29 mAb was shown to reduce the clinical score in AA by 55% and reduce joint injury assessed histologically (9). Because IFN-γ is a potent inducer of both the CD49d/CD29 ligand VCAM-1 and the CXCR3 ligands CXCL9, CXCL10, and CXCL11, a common pathway involving CXCR3+ T cell binding to VCAM-1 on the endothelium may underlie the similar degree of reduction in arthritis observed by CD49d/CD29 and CXCR3 blockade.

In conclusion, this study directly demonstrates an important role for CXCR3 in T cell recruitment from blood to inflamed joints in...
AA, and that CXCR3 blockade dramatically reduces the severity and inflammatory reaction in AA.

Disclosures

The authors have no financial conflict of interest.

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