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Manifestations of Inflammatory Arthritis Are Critically Dependent on LFA-1

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Leukocyte infiltration of synovial fluid and tissues is the hallmark of inflammatory arthritis. Selectins and β2 integrins have been implicated in the multistep process of leukocyte adhesion to vascular endothelium. However, previous work has revealed disparate requirements for leukocyte recruitments to specific anatomic locales. Moreover, the mechanisms regulating recruitment of leukocytes to the joint in inflammatory arthritis models are not fully understood. We hypothesized that β2 integrins, expressed on leukocytes, might play a pathogenic role in synovial inflammation. Using mice deficient in all β2 integrins (CD18 null mice), we demonstrate that expression of these heterodimeric adhesion molecules is critical for arthritis induction in the K/B × N serum transfer model. Using null-allele mice and blocking mAbs, we demonstrate specifically that CD11a/CD18 (LFA-1) is absolutely required for the development of arthritis in this model. Blocking mAbs further revealed an ongoing requirement for LFA-1 I-domain adhesive function in disease perpetuation. These findings suggest that the LFA-1 I-domain forms an attractive target for treatment of human inflammatory arthritis. The Journal of Immunology, 2005, 174: 3668–3675.
Given the acute and chronic requirement for leukocytes in the 
K/B × N arthritis model, we investigated the role of β2 integrins 
and their receptors in this model of synovial inflammation that 
results in synovitis and histopathologic joint damage resembling 
rheumatoid arthritis. We find that β2 integrin-deficient mice are 
resistant to development of arthritis and that the CD11a chain (LFA-1) is critical for this process, while the CD11b chain (Mac-1) is not. Furthermore, administration of a mAb directed 
against the LFA-1 I-domain ameliorates established disease, dem-
onstrating the ongoing requirement for leukocyte LFA-1 after ar-
thritis onset. In addition, we delineate a specific role for the LFA-1 
counterreceptors ICAM-1 (CD54) and ICAM-2 (CD102) and pro-
vide the first in vivo evidence for a role for the LFA-1 counterre-
ceptor JAM-A in synovial inflammation.

Materials and Methods

Mice
Age-matched male mice aged 6–12 wk were used in these studies. 
C57BL/6J (B6) were purchased from The Jackson Laboratory. K/B × N transgenic mice were maintained, as described (16). All other mice were 
maintained as homozygous inbred lines in the Dana-Farber Cancer Institute animal facility. Strain sources: CD18 null mice (10) (N8 backcross to B6, 
Jax 003329) were originally purchased from The Jackson Laboratory; 
CD11a null (14) (>N6 backcross to B6) and CD11b null (17) (>N6 back-
cross to B6) were obtained from C. Ballantyne (Baylor University, Hous-
ton, TX); and ICAM-1 null (18) (N8 backcross to B6), ICAM-2 null (19) 
(N5 backcross to B6), and control B6 × 129 (N5 backcross on B6) were 
obtained from Millennium Pharmaceuticals. All studies were conducted 
with Institutional Animal Care and Use Committee approval and followed 
Institutional Animal Care and Use Committee guidelines.

Abs used in vivo
mAbs were affinity purified by protein G-Sepharose chromatography from 
culture supernatants. Rat anti-mouse mAbs used for in vivo experiments in 
this study were: M17/4.4 (20) (IgG2a, anti-CD11a, ATCC TIB217; Amer-
ican Type Culture Collection), M18/2 (20) (IgG2b, anti-CD18, ATCC 
TIB218), YN1/1 (21) (IgG2b, anti-ICAM-1, ATCC CRL1878), anti-
JAM-A (22) (clone BV11, IgG2b, provided by I. Martin-Padura), and Y13-
238 (23) (IgG2a isotype control, ATCC CRL1741). A95-1 (IgG2b isotype 
control; BD Pharmingen) was purchased commercially. Purified mAbs 
were injected via i.p. route every 48 h for the study duration. For blocking 
studied, mAbs were administered 1 h before K/B × N arthritogenic serum. 
For therapy studies, Abs were injected on day 6 after initial K/B × N serum 
transfer.

K/B × N serum transfer arthritis
To induce arthritis, arthritogenic K/B × N serum was transferred to recip-
ient mice, as described (2). Briefly, 150 μl of serum was administered via 
i.p. route on experimental days 0 and 2. Clinical index was graded as 
described at 24- to 48-h intervals (24). Briefly, each paw was scored for 
evidence of inflammation using the scale: 0 = no evidence of inflamma-
tion; 1 = subtle inflammation at one anatomic site (MTP joints, individual 
phalanx, or localized edema); 2 = easily identified swelling involving two 
anatomic regions, but not present diffusely in paw; 3 = swelling present on 
all aspects of paw. The maximum clinical score is 12.

Histology
For frozen section analyses, ankle tissues from mice were snap frozen in 
OCT (manufacturer) medium in a dry ice/isopentane bath. Nondecalcified 
5 μM cryosections were prepared using the Cryo-Jane (Instrumedics) tape 
transfer technique per manufacturer protocol. For immunofluorescence 
analyses, cryosections were stained with directly conjugated mAbs, as de-
scribed (25), using the following conjugated mAbs and reagents: CD54

FIGURE 1. β2 integrin expression in inflamed syno-
vium. Inflamed ankle tissues from 8-wk-old K/B × N mice were snap frozen and embedded in OCT medium, and 5 μM serial cryosections were prepared. PE-conju-
gugated Abs were used for direct immunofluorescence 
analysis of β2 integrin expression. Shown are: A, H&E 
stain of the ankle region used for analysis, demonstrat-
ing synovial hyperplasia surrounding an inflammatory 
synovial effusion; B, isotype control; C, anti-CD18; D, 
anti-LFA-1; and E, anti-Mac-1. Magnification = × 200. 
The hatched line in B–E outlines the synovial effusion, 
and the asterisks identify the blood vessels evident in A. 
SF = synovial fluid.
biotin (MCD5415; Calrag Laboratories), CD11a PE (RM3904; Caltag Laboratories), CD11b PE (RM2804; Caltag Laboratories), CD18 PE (RM4004; Caltag Laboratories), CD102 FITC (clone 3C4; BD Pharmingen), IgG2b biotin (R2b15; Caltag Laboratories), IgG2a PE (R2a04; Caltag Laboratories), IgG2b PE (R2b04; Caltag Laboratories), and streptavidin PE (BD Pharmingen). The JAM-A mAb (BV11) was conjugated with biotin, per manufacturer protocol (Pierce).

For histomorphologic analysis, ankle tissues were fixed for 24 h in 4% paraformaldehyde in PBS and decalcified with Kristensen’s solution for 48–72 h (26). Tissues were then dehydrated, embedded in paraffin, and sectioned at 5-μm thickness.

Statistical analysis
Student’s t test, ANOVA, and Bonferroni’s multiple comparisons calculations were performed where appropriate to assess statistical significance of clinical findings.

Results

Expression of β₂ integrins and their counterreceptors in inflamed synovial tissue

We examined the expression of the β₂ integrins LFA-1 (CD11a/CD18) and Mac-1 (CD11b/CD18) and their receptors ICAM-1 (CD54), ICAM-2 (CD102), and JAM-A in mouse inflammatory arthritis using direct and indirect immunofluorescence techniques to examine frozen nonfixed, nondecalcified inflamed synovial tissues in ankles of 8-wk-old arthritic K/B × N mice (16). We noted strong staining of both LFA-1 and Mac-1 in leukocytes within the synovial lining and within the inflammatory synovial fluid (Fig. 1). ICAM-1 staining was most striking on the vascular endothelium (Fig. 2D), and weaker staining was evident more diffusely on cells in the synovial lining and sublining. ICAM-2 staining was evident exclusively on vascular endothelium (Fig. 2G). JAM-A staining was noted on vascular endothelium with scattered rare bright cells in the synovial lining (Fig. 2C). Thus, β₂ integrins are expressed strongly by leukocytes, and their counterreceptors are expressed on vascular endothelium and some cells of the synovium under inflammatory conditions.

Expression of CD18 (integrin β₂ chain) is required for induction of inflammatory arthritis

To assess a requirement for β₂ integrins in induction of inflammatory arthritis, we transferred arthritogenic K/B × N serum into CD18 null (10) and control C57BL/6 (wild-type (WT)) mice. Strikingly, CD18-deficient mice were almost completely resistant

![Figure 2. LFA-1 ligands CD54 (ICAM-1), CD102 (ICAM-2), and JAM-A are expressed in inflamed synovium. Inflamed ankle tissues from 8-wk-old K/B × N mice were snap-frozen and embedded in OCT medium, and 5 μM serial cryosections were prepared for immunofluorescence analysis of CD54, CD102, and JAM-A expression. Shown are: A, H&E stain of the ankle region used for analysis, demonstrating synovial hyperplasia surrounding an inflammatory synovial effusion; B, isotype control; C, anti-JAM-A; D, anti-CD54; E, H&E stain of the ankle region used for CD102 analysis; F, isotype control; and G, anti-CD102. Magnification = ×200. The hatched line in B–D outlines the synovial effusion, and the asterisks identify the blood vessels evident in A. Similarly, the asterisks in F and G identify the blood vessels evident in E. SF = synovial fluid.](http://www.jimmunol.org/ Downloaded from)
to K/B × N serum transfer arthritis by clinical arthritis indices (Fig. 3A). To complement the clinical findings, ankle tissues from CD18 null and WT mice were examined histologically (Fig. 3, B–E). In contrast to the extensive synovial hyperplasia, synovial effusions, leukocytic infiltration of synovial fluid, and tissues and development of erosive pannus seen in WT mice, the synovia of CD18 null mice were virtually normal.

Critical role for LFA-1, but not Mac-1, in arthritis induction

Having demonstrated a requirement for $\beta_2$ integrins in the induction of inflammatory arthritis, we next assessed the role of individual $\beta_2$ integrin subfamily members in arthritis pathogenesis using mice selectively lacking the $\alpha$-chain for either LFA-1 (CD11a null) (14) or Mac-1 (CD11b null) (17). In these experiments, we observed resistance to development of arthritis in CD11a null mice, while CD11b null mice demonstrated a trend toward more intense inflammation than WT control mice (Fig. 4A). Both WT and CD11b null mice demonstrated extensive arthritic changes histologically, including synovial hyperplasia, leukocytic infiltration, joint effusions, and erosive pannus formation (Fig. 4, B, C, F, and G), while the synovia of CD11a null mice show a normal appearing synovial lining and sublining with little evidence of inflammatory change (Fig. 4, D and E).

Anti-LFA-1 I-domain mAb blocks the development and perpetuation of inflammatory arthritis

To confirm a critical role for LFA-1 in induction of inflammatory arthritis, we coadministered arthritogenic K/B × N serum and either anti-CD18, anti-CD11a (LFA-1), or isotype control mAbs to WT C57BL/6 mice. The anti-LFA-1 mAb used in these analyses, M17/4, was chosen because of its demonstrated ability to block LFA-1-mediated adhesion to ICAM-1 via interaction with the integrin I-domain in vitro and because of its ability to block leukocyte recruitment in vivo (27). The anti-LFA-1 mAb M17/4 significantly inhibited development of K/B × N-induced arthritis, compared with the isotype control mAb (Fig. 5).

To support the hypothesis that M17/4 anti-LFA-1 prevented arthritis by blocking LFA-1-mediated adhesion, rather than by another mechanism such as cross-linking LFA-1 and thereby altering leukocyte function, we tested mAb M18/2 (20). This mAb binds the CD18 subunit of $\beta_2$ integrins, but does not interfere with LFA-1 binding to ICAM-1 or block T cell cytotoxicity. In the serum transfer model of arthritis in C57BL/6 mice, treatment of the mice with M18/2 mAb had no effect on the time course or severity of arthritis compared with the isotype control mAb (Fig. 6). Thus, we conclude that LFA-1-mediated adhesion to one or more of its counterreceptors may be important for the development of arthritis in this model.

To investigate an ongoing requirement for LFA-1 in the process of inflammatory arthritis, we induced K/B × N serum transfer arthritis in C57BL/6 mice and allowed 6 days for development of significant inflammatory activity before administration of anti-LFA-1 mAb M17/4 or isotype control mAb. Administration of anti-LFA-1 mAb significantly ameliorated development of K/B × N-induced arthritis, as established (Fig. 5).

Role of LFA-1 ligands ICAM-1 and ICAM-2 in inflammatory arthritis

Having observed a critical requirement for LFA-1 in the induction of inflammatory arthritis, we next sought to examine the role of its counterreceptors in this process. We compared arthritic responses in mice genetically deficient in either ICAM-1 (CD54 null) or ICAM-2 (CD102 null) and found a delay in disease onset and initial severity in ICAM-1 null mice, while the ICAM-2 null mice demonstrated no observable difference in their arthritic response (Fig. 7A). Previous analyses have suggested that ICAM-1 null mice are, in fact, not a true null allele, but display circulating leukocyte ICAM-1 (28). Thus, in a further series of experiments, we administered blocking anti-ICAM-1 mAb YN1/1 (21, 29–31) to WT mice. Mice administered anti-ICAM-1 mAb displayed a delay in arthritis onset with a partial amelioration of the arthritic response similar to that seen in ICAM-1-deficient mice (Fig. 7B). Because ICAM-1 and ICAM-2 may provide complementary or overlapping functions for LFA-1-mediated inflammatory responses, we administered anti-ICAM-1 mAb to ICAM-2-deficient mice and assessed the response to K/B × N serum transfer arthritis (Fig. 7A). We found that functional blockade of both ICAM-1 and ICAM-2 provides further, but still incomplete, amelioration of induction of inflammatory arthritis when compared with ICAM-1 deficiency alone.

Role of the LFA-A ligand JAM-A in inflammatory arthritis

The ability of both ICAM-1 and ICAM-2 to only partially prevent induction of inflammatory arthritis suggested the possibility of at
least one additional functional LFA-1 counterreceptor participating in arthritis induction. In mice, JAM-A also has been found to bind to LFA-1 in vitro studies, although no role in inflammation has been ascribed to this ligand (22) (reviewed in Ref. 32). Thus, we explored its possible functional role in synovial inflammation. For these analyses, C57BL/6 mice were coadministered K/B × N serum and their clinical arthritis response was monitored (A). B–G, Representative H&E tissue sections from decalcified, paraffin-embedded ankle tissues from control (B and C), CD11a null (D and E), and CD11b null (F and G) mice. Open arrowhead, bone erosion; filled arrowhead, cartilage erosion (magnification = 25 (B, D, and F) and 200 (C, E, and G)). n = 4 mice/group; p < 0.001. Data are representative of 11 mice (CD11a) and 8 mice (CD11b) in three or two independent experiments, respectively.

FIGURE 4. β2 integrin α-chain CD11a (LFA-1)-, but not CD11b (Mac-1)-deficient mice are resistant to arthritis. CD11a null, CD11b null, and C57BL/6 (B6) control mice were administered arthritogenic K/B × N serum, and their clinical arthritic response was monitored (A). B–G, Representative H&E tissue sections from decalcified, paraffin-embedded ankle tissues from control (B and C), CD11a null (D and E), and CD11b null (F and G) mice. Open arrowhead, bone erosion; filled arrowhead, cartilage erosion (magnification = 25 (B, D, and F) and 200 (C, E, and G)). n = 4 mice/group; p < 0.001. Data are representative of 11 mice (CD11a) and 8 mice (CD11b) in three or two independent experiments, respectively.

FIGURE 5. Anti-LFA-1 Abs ameliorate arthritis. C57BL/6 mice were coadministered arthritogenic K/B × N serum and either isotype control (rat IgG2a; ■) or anti-LFA-1 mAbs (M17/4; □). The mAbs were dosed at 100 μg/injection every 48 h throughout the experiment (open arrow labels initiation of therapy). Separately, C57BL/6 mice were administered arthritogenic K/B × N serum, and arthritis was allowed to progress for 6 days. The mice were then administered either isotype control (■) or anti-LFA-1 (□) mAbs at 100 μg/injection every 48 h throughout the remainder of experiment (shaded arrow labels initiation of therapy). The clinical course of arthritis was monitored by assessing clinical index (A). Mice were then sacrificed, and joint tissues were fixed, decalcified, and paraffin-embedded. Shown are representative 5 μM H&E sections of mice administered isotype control (B and C) pretreatment with anti-LFA-1 (D and E) and treatment after 6 days with anti-LFA-1 (F and G). Note the absence of synovial hyperplasia, leukocytic infiltrate, pannus formation, and joint erosions in anti-LFA-1-pretreated mice and the decreased inflammatory infiltrate in synovial tissues in anti-LFA-1-treated mice. Open arrowhead, bone erosion; filled arrowhead, cartilage erosion (magnification = 25 (B, D, and F) and 200 (C, E, and G)). n = 5 mice/group; p < 0.001 in pretreated mice and p < 0.01 in the mice treated beginning on day 6. Data are representative of two independent experiments.
Our findings demonstrate a critical role for one specific $\beta_2$ integrin, LFA-1 (CD11a/CD18), both in the induction and in the perpetuation of K/B $\times$ N serum transfer arthritis. Analysis of mice lacking CD18 (all $\beta_2$ integrins) demonstrated this family of adhesion molecules is required for the development of arthritis. Subsequent studies of mice singly deficient in distinct $\beta_2$ integrin $\alpha$-chains demonstrate a striking dependence on LFA-1, but not Mac-1, for arthritis induction and an ongoing requirement for LFA-1 in arthritis perpetuation. The overlapping arthritis phenotypes of the CD18 null and CD11a null mice suggest that the requirement for $\beta_2$ integrin expression in arthritis induction resides entirely in the LFA-1 species. This finding contrasts with previous analyses of peritoneal inflammation in CD18- and CD11a-deficient mice in which mice lacking CD11a demonstrated a marked reduction in acute leukocyte recruitment, while leukocyte recruitment was intact in mice lacking CD18 (12). This difference suggests that the mechanisms of CD18-independent peritoneal leukocyte recruitment operative in CD18-deficient mice are not at play in synovial inflammatory processes in the K/B $\times$ N model.

The dependence on CD18 seen in this study is also consistent with the previous demonstration of decreased neutrophil recruitment to inflamed synovial tissue when CD18-blocking mAbs were administered in a rat model of adjuvant arthritis (33). However, in the same rat adjuvant arthritis experiments, blockade of individual $\beta_2$ integrin species was ineffective; blocking Abs to both LFA-1 and Mac-1 were required to decrease neutrophil trafficking to the inflamed joint, and significant synovial neutrophil accumulation persisted with all Abs used. The clinical effect of Ab administered to arthritic rats in those studies was not documented. The differential functional requirement for Mac-1 in the rat adjuvant arthritis model and K/B $\times$ N serum transfer arthritis is intriguing and could suggest either species-specific redundant functional activity for LFA-1 and Mac-1 in rats or, because Mac-1 is a complement C3b receptor, a functional role for complement opsonin in rat adjuvant-induced arthritis not present in K/B $\times$ N serum transfer arthritis.

Using mAb administered to WT mice, we confirmed the critical requirement for LFA-1 in induction of inflammatory arthritis and extended these findings to show an ongoing requirement for LFA-1 in perpetuation of arthritis. In LFA-1-deficient mice, it is possible that the developmental lack of LFA-1 could impart leukocyte deficits independent of those required locally for synovial inflammatory processes.

Among the outstanding questions in our understanding of the pathogenesis of inflammatory arthritis are the mechanisms by which leukocytes are recruited to the synovium for disease induction and perpetuation. The multistep process of leukocyte recruitment to sites of inflammation involves the coordinated interaction of adhesion molecules expressed by leukocytes and the inflamed tissue. This highly regulated process involves initial leukocyte interactions with the vascular endothelium, which progress from cellular rolling to firm attachment to transmigration through the vascular endothelium and into the tissue parenchyma (reviewed in Ref. 7). Multiple adhesion molecule families are involved in this process, including selectins, Ig superfamily members (cell adhesion molecules), and integrins.

**FIGURE 7.** Participation of LFA-1 ligands ICAM-1 ICAM-2 and JAM-A in inflammatory arthritis. A, Clinical arthritic response in ICAM-1 null (△), ICAM-2 null (○), and control mice (■) coadministered arthritogenic K/B $\times$ N serum and isotype control Ab (IgG2b) (open arrows). Concurrently, ICAM-2 null mice (hatch symbol) were coadministered arthritogenic K/B $\times$ N serum and anti-ICAM-1 mAbs. The mAbs were dosed at 100 $\mu$g/injection every 48 h throughout the experiment (n = 4 mice/group; data are representative of n = 14 mice (ICAM-1 null), n = 8 mice (ICAM-2 null), and n = 8 mice (ICAM-2 null plus anti-ICAM-1)), $p < 0.05$ for ICAM-1; $p < 0.001$ for ICAM-2 + anti-ICAM-1; and $p = \text{NS}$ for ICAM-2 alone. B, Clinical arthritic response in C57BL/6 mice coadministered arthritogenic K/B $\times$ N serum and isotype control (■), anti-ICAM-1 (○), or anti-JAM-A (△) Abs. The mAbs were dosed at 200 $\mu$g/injection every 48 h throughout the experiment (open arrows). n = 5 mice/group. Data are representative of nine mice/group studied in independent experiments ($p < 0.001$).
induction of inflammation. Indeed, discrepancies between Ab-blocking studies and β₂ integrin-deficient mice have been described in pulmonary and peritoneal inflammation models (30). The ability of an LFA-1 I-domain adhesion-blocking mAb to reproduce the blockade of arthritis induction seen in LFA-1-deficient mice provides independent evidence for the importance of LFA-1 function in arthritis induction. Furthermore, analyses of LFA-1-deficient mice are inherently limited by an inability to assess the role of LFA-1 in perpetuation of established arthritis. Administration of blocking anti-LFA-1 mAb after establishment of arthritis allowed us to define an ongoing need for LFA-1 function in inflammatory arthritis. This ongoing requirement for LFA-1 function contrasts with that seen in Ab-mediated blockade of peritoneal leukocyte recruitment in rabbits, which demonstrates a requirement for β₂ integrin function initially, but not after 24 h (34), and has particular relevance for treatment considerations in established human inflammatory arthritis.

Mechanistically, K/B × N serum transfer arthritis is strikingly similar to the immune complex-driven cutaneous reverse Arthus reaction that displays a codominant role for both FcγRIII and CD88 and a cellular requirement for both mast cells and neutrophils (35). These pathogenic similarities notwithstanding, our findings show that the β₂ integrin and ICAM-1 involvement in these models of inflammation differ dramatically. Despite a dominant role for ICAM-1 and a codominant requirement for Mac-1 and LFA-1 in the cutaneous reverse Arthus reaction (36), the K/B × N serum transfer model of autoantibody-induced synovial inflammation displays only partial dependence on ICAM-1 and no dependence on Mac-1 for disease induction. Indeed, the dependence on LFA-1 in the K/B × N serum transfer model is more similar to that reported in the MRL/MpJ-Fas(+/−) immune complex-dependent model of lupus, which demonstrates attenuated nephritis with decreased renal neutrophil accumulation in LFA-1 null mice (37). These differences highlight the anatomic specificity for β₂ integrins and their ligands in distinct immune complex-mediated diseases.

Our findings confirmed a lack of a requirement for Mac-1 in the development of K/B × N arthritis in an independent strain of Mac-1-deficient mice (1). Previous studies have shown increased peritoneal neutrophil accumulation in response to inflammatory signals in Mac-1-deficient mice, a finding thought to result from decreased apoptosis in Mac-1-deficient neutrophils (38). We observed a trend toward increased inflammation in CD11b null mice, which may be a result of such previously noted mechanisms.

These studies also demonstrate expression of, and suggest a role for, all three known LFA-1 counterreceptors expressed on vascular endothelium: ICAM-1, ICAM-2, and JAM-A. The decrease in K/B × N serum transfer arthritis severity observed in ICAM-1 null mice, or in WT mice treated with ICAM-1-blocking Abs, is similar to the observed reduction in arthritis in the collagen-induced arthritis model (39). This partial blockade is also similar to that noted in leukocyte recruitment during peritoneal inflammation (40). Our inability to detect a decline in inflammation in the ICAM-2-deficient mice coupled with the partial amelioration of disease severity seen in the ICAM-1-deficient mice suggested a partial functional redundancy in the LFA-1 ligands expressed in synovial tissue. Consistent with this hypothesis, mAb blockade of ICAM-1 in ICAM-2 null mice resulted in additive reduction in arthritis severity. However, the failure to fully ameliorate arthritis with interruption of ICAM-1 and ICAM-2 function, suggesting yet another functional ligand for LFA-1, might be operational in inflammatory arthritis.

Our findings demonstrate that JAM-A (22), a recently described counterreceptor for LFA-1, participates functionally in the arthritic response to K/B × N serum. JAM-A is expressed primarily on vascular endothelium; based on the in vivo inhibition obtained with Abs against JAM-A, the contribution of JAM-A to the inflammatory response appears to be as important as that provided by ICAM-1. In vitro studies have suggested that ICAM-1 may function most prominently in leukocyte:endothelial cell adhesion at the luminal surface required for neutrophil arrest under flow conditions, while JAM-A may function in mediating leukocyte transmigration through the endothelial lining at the interface between endothelial cells (22, 41). These in vitro analyses also suggest ICAM-1 and JAM-A provide complementary functions. This could explain the partial amelioration of inflammation seen in single molecule interruption in the K/B × N serum transfer arthritis model.

The leukocyte adhesion deficiency-I phenotype in humans and cattle (8, 9, 42–44), as well as the defective T cell function and spontaneous skin ulceration seen in CD18 null mice emphasize that β₂ integrins are critically important for host defense. Although LFA-1-deficient mice have deficits in experimental tumor models and increased mortality to gram (+) sepsis with Streptococcus pneumoniae, they exist without apparent spontaneous illness in conventional mouse housing facilities (45, 46). Our findings point toward several therapeutic implications. First, the LFA-1-specific nature of the β₂ integrin-dependent development of arthritis provides a more selective therapeutic target than the general blockade of all β₂ integrins. Second, the apparent redundancy in LFA-1 ligand functions also highlights a likely therapeutic challenge in targeting these counterreceptors in inflammatory arthritis. Furthermore, our Ab-blocking studies suggest that the integrin I-domain mediates a functionally critical interaction for synovial inflammation, providing a focused target on the LFA-1 α-chain I-domain for therapeutic intervention in inflammatory arthritis.

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Disclosures

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