Loss of CD34 Leads To Exacerbated Autoimmune Arthritis through Increased Vascular Permeability

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Loss of CD34 Leads To Exacerbated Autoimmune Arthritis through Increased Vascular Permeability

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CD34 is a cell surface sialomucin expressed by hematopoietic precursors, eosinophils, mast cells, and vascular endothelia and is suggested to play an integral role in mucosal inflammatory responses. Although CD34−/− mice have normal hematopoietic cell subsets in peripheral tissues at steady state, they exhibit a cell recruitment defect when challenged, offering a unique opportunity to distinguish between local inflammatory cell proliferation and peripheral recruitment in disease. Autoimmune arthritis is an inflammatory disease dependent on hematopoietic infiltration, and in this study, we have examined the role of CD34 in disease development and progression. Using an autoimmune serum transfer model, arthritis was induced in C57BL/6 wild-type and Cd34−/− mice. Surprisingly, we found that Cd34−/− mice were more susceptible to arthritis than wild-type mice. We examined mast cell-transplanted, eosinophil-deficient, and bone marrow-chimeric mice to determine the role of CD34 expression on disease progression. These experiments excluded CD34-deficient mast cells, eosinophils, or hematopoietic cells as the cause of the exacerbated disease. Further study demonstrated that Cd34−/− mice exhibit increased vascular leakage at onset of disease and in response to TNF, which correlated with a subsequent increase in disease severity. We conclude that loss of CD34 expression leads to increased vascular permeability in the joints at onset of disease, leading to exacerbated arthritic disease in Cd34−/− mice. The Journal of Immunology, 2010, 184: 1292–1299.

Although CD34 expression has been used extensively as a marker of stem cells for over 25 years, little is known regarding the exact functional role of this sialomucin in vivo. The known tissue distribution of CD34 has recently expanded to include a variety of mature inflammatory and structural cells including mast cells (1), eosinophils (2), fibrocytes (3) and vascular endothelia (4), hinting at a potential role in tissue inflammation. Although mice lacking CD34 expression (Cd34−/−) have regular seeding of mast cells at steady-state and normal baseline hematopoietic parameters, when challenged (e.g., by an inflammatory insult in a mouse model of asthma), these mice exhibit profound defects in mast cell and eosinophil recruitment/migration into tissues (5). These findings suggest that Cd34−/− mice could be an excellent model system to evaluate the relative importance of mast cell seeding versus mast cell recruitment in various mast cell-dependent inflammatory diseases.

Numerous diseases have been reported to be dependent on the presence of mast cells, including autoimmune arthritis. Immune complexes formed by autoantibodies comprise an important pathway leading to destruction of bone and cartilage in autoimmune arthritis (6). As the disease in humans is diagnosed in the later stages of pathogenesis, little is known about the initiation and progression of this disease in humans. For this reason, the development of mouse models of autoimmune arthritis has been extremely important in understanding the pathogenesis of this disease. The K/BxN-based mouse model is induced by transferring serum from a K/BxN mouse, containing GPI autoantibodies, into naïve recipient mice. Development of the disease in the recipient is characterized by joint inflammation and severe swelling of the distal joints (7). Intriguingly, arthritis in this model has been shown to develop independently of T cells and B cells (8), although T regulatory cells seem to play a major role in the control of disease severity. Indeed, lack of regulatory T cells leads to increased pathology (affecting joints that are usually not affected such as elbows and shoulders) and more rapid disease progression (9). Neutrophils, in contrast, have been shown to play an essential role in initiation and progression of the pathology (10) and inflammatory molecules including IL-1, TNF, and PGs, which are highly elevated in the serum of rheumatoid arthritis patients, are also associated with pathogenesis. Indeed, recent studies have confirmed that the constitutively expressed form of cyclooxygenase-1 is needed whereas cyclooxygenase-2 is dispensable for development of disease. Moreover, PGI2 (and not PGE2) was shown to contribute to development of disease via activation of its receptor IP (11). An increase in vascular permeability, which is one of the first steps in response to immune complexes in the distal joints (occurring within 5 min of i.v. injection of immune complexes and KxB/N serum), leads to the development of joint swelling, inflammation, and remodeling in autoimmune arthritis (12). This particular hallmark of the disease has been associated with mast cell and neutrophil-driven alterations in the non-hematopoietic cells of the local joint environment, in particular with the vascular endothelia (12).
A mast cell contribution has also been demonstrated in the K/BxN serum transfer model. Mast cell-deficient W/W' mice show protection from KxB/N serum-induced arthritis (13), and reconstitution of the mast cell population with C57Bl/6 bone marrow mast cells (BMMCs) rendered these mice sensitive to the normal course of disease development, confirming that mast cells are a major effector cell in autoimmune arthritis. What has not yet been explored is whether the resident mast cell population is sufficient to initiate disease or, alternatively, whether this disease is dependent on the de novo recruitment of mast cell progenitors to the joint during the inflammatory response. The answer to this question could have important implications when designing approaches to target mast cells in autoimmune diseases.

Because Cd34−/− mice have normal seeding of mast cells to peripheral tissues but delayed recruitment in response to challenge (5), we have exploited them as a tool to address this question. Surprisingly, we found that mice lacking Cd34 developed much more severe disease than wild-type (wt) mice. Through the use of bone marrow chimeric mice and BMMC-reconstituted mice, we show that resident mast cells in the joints are sufficient for full induction of arthritis and, additionally, that the exacerbated disease phenotype in Cd34−/− mice is due to an increase in vascular leakage at the onset of disease in the joint, independent of Cd34 function on hematopoietic cells. This is, to our knowledge, the first study to implicate Cd34 as a regulator of vascular permeability and provides an insight into the first steps of autoimmune arthritis development.

Materials and Methods

**Mice**

Mice were maintained under specific pathogen-free conditions in The Biomedical Research Centre animal care unit and all procedures were approved by the local animal care committee. Six- to 8-wk-old male C57Bl/6 (wt) and Cd34−/− were used throughout the protocol, unless otherwise stated. Cd34−/− mice were extensively backcrossed to the C57Bl/6 mice. Mast cell deficient W/W' mice were purchased from The Jackson Laboratory (Bar Harbor, ME), and eosinophil-deficient pEpo-DTA "PHL" mice were obtained from Dr. Jamie Lee (Mayo Clinic, Scottsdale, AZ).

**Generation of bone marrow chimeric and mast cell-reconstituted mice**

To generate bone marrow chimeric mice, total bone marrow from the femur was isolated from wt Ly5.1 or Cd34−/− Ly5.2 donors, and 2 × 10^6 cells were injected into lethally irradiated Cd34−/− Ly5.2 and wt Ly5.1 recipients, respectively. Bone marrow chimerism was verified by flow cytometry staining for Ly5.1 and Ly5.2 in peripheral blood at 12 wk postreconstitution, and only mice that were >90% donor derived were used for the studies. For mast cell reconstitution, BMMCs were generated as previously published (14) by culturing wt or Cd34−/− bone marrow-isolated cells with 30 ng/ml IL-3 for 8 wk. Mast cell-deficient W/W' mice were then reconstituted with 10 × 10^6 BMMCs, and mice were used for arthritis induction 12 wk postreconstitution, as published previously (14).

**Induction of arthritis and clinical scoring**

Arthritis was induced using the K/BxN serum transfer model. Briefly, two i.p. injections of 100 μl of K/BxN serum were given on days 1 and 3. Clinical scoring was evaluated for each paw throughout days 1–11, using the following scale: 0 = no sign of swelling, 1 = minimal swelling, 2 = swelling of the paw only, 3 = swelling of the whole joint, and 4 = extensive swelling, and added together, resulting in a maximum total score of 16 for each mouse. In parallel, ankle thickness of both hind paws was measured with a manual caliper (Mitutoyo, Vancouver, British Columbia, Canada), and the mean difference in thickness from baseline was calculated for each mouse. On day 11, mice were sacrificed by overexposure to isoflurane, ankles were removed, the skin was excised and the joint exposed.

**Histology**

Joints were fixed in 10% buffered formalin, decalcified, and embedded in paraffin for histological sections. Cross sections were stained with H&E, and a histological score was blindly attributed by evaluating 1) inflammatory cell infiltration, 2) bone erosion, and 3) cartilage erosion in each sample. A score of 0–4 was given for each of these parameters in both the right and the left ankle, and added, for a maximum total possible score of 24 per mouse. Cross sections were also stained with toluidine blue for mast cells detection and counting.

**Vascular leakage evaluation**

Joint vascular leakage was evaluated in wt and Cd34−/− mice as published previously (15). Briefly, mice were injected i.v. in the tail vein with 50 mg/kg Evans blue (Sigma-Aldrich, St. Louis, MO) (in PBS) on day 0, 0.5 h postserum injection, 48 h postserum injection, and days 4, 7, 9, and 11. Mice were sacrificed by overexposure to isoflurane 30 min after dye injection. The skin was excised, and the ankles were put in 1 ml of formamide for 36 h at 45°C to achieve Evans blue extraction. OD of the supernatants was read at 650 nm on a spectrophotometer. The sections were weighed, and the OD/mg tissue was calculated.

**Microvascular permeability measurement**

Microvascular permeability was measured through vascular albumin leakage from cremasteric venules of Cd34−/− and wt mice. In brief, 25 mg/kg FITC-labeled BSA (Sigma-Aldrich) was administered to the mice i.v. and FITC-derived fluorescence (excitation wavelength, 450–490 nm; emission wavelength, 520 nm) was detected using a silicon-intensified charge-coupled device camera (model C-2400-80; Hamamatsu Photonics, Hamamatsu City, Japan). Image analysis software (ImageJ, 1.38×; National Institutes of Health, Bethesda, MD) was used to determine the intensity of FITC-albumin-derived fluorescence within the lumen of the venule and in the adjacent perivascular tissue. The left scrotum was injected with 0.5 μg of recombinant mouse TNF-α (R&D Systems, Minneapolis, MN) in 200 μl of saline or saline alone 4 h prior to the exposure of the cremaster muscle. The index of vascular albumin leakage (permeability index) was determined according to the following ratio expressed as a percentage: (mean interstitial intensity – background)/(venular intensity – background).

**Ankle lavage and flow cytometry analysis of cell content**

Ankles were skinned and cut 5 mm above the joint and at the toes. The hematopoietic cell content within the ankle joint was gently washed via three injections of 100 μl of PBS using a 30-gauge needle. Analysis of cell populations was achieved by flow cytometry. Cells were stained with an anti-mouse CD45 PerCP (BD Pharmingen, San Diego, CA), and CD45+ populations was achieved by flow cytometry. Cells were further analyzed for Gr1 (anti-mouse Gr1 APC; eBioscience), Mac-1 (anti-mouse Mac-1 PE; BD Pharmingen), and B220 (anti-mouse B220 PE; BD Pharmingen) expression.

**Histamine measurement**

Blood was collected via cardiac puncture at various time points following injection of the autoimmune serum. Serum histamine was measured using an enzyme immunoassay Histamine kit (Immunotech, Marseille, France), according to the manufacturer’s instructions.

**CD34 staining of joint vasculature**

Ankle joints were harvested and fixed overnight in 10% buffered formalin and were decalcified for 2 wk with 10% EDTA. Immunostaining was performed using mAbs against CD31 (BD Pharmingen, Mississauga, Ontario, Canada) or CD34 (eBioscience). Primary Abs were detected using goat anti-rat IgG Abs conjugated to Alexa 568 (Molecular Probes, Eugene, OR). Confocal microscopy was performed using a Nikon C1 laser scanning confocal microscope.

**Statistics**

For analysis of the disease courses and ankle thickness differences, statistics were calculated using an ANOVA table followed by a Fisher’s posthoc test. For analysis of histology, cytokine response, hematopoietic cell populations, and vascular permeability, an unpaired t test was used to determine statistical significance.

**Results**

Cd34−/− mice are hypersensitive to autoimmune arthritis

Previous studies have shown that autoimmune arthritis is a mast cell-dependent disease, but it remains unclear whether this is due to activation and/or expansion of local resident mast cells or whether it requires de novo recruitment of mast cells to the joints. Because our previous studies have shown the Cd34−/− mice have normal peripheral mast cell numbers at steady state, but impaired recruitment...
in response to challenge, we examined their susceptibility to development of arthritis. Surprisingly, when arthritis was induced by injection of autoimmune serum from K/BxN mice, Cd34^2/2 mice showed exacerbated arthritis in terms of both clinical score (Fig. 1A) and ankle thickness (Fig. 1B) compared with wt control mice. This increase was observed in at least four independent experiments and confirmed when diluted amounts of the serum (1/5, 1/10, and 1/50) were administrated to the mice. In fact, Cd34^2/2 mice exhibited autoimmune disease at low Ab doses (1/50) that did not provoke any detectable disease in wt mice (Fig. 2). We conclude that Cd34^2/2 mice are hyperresponsive to induction of arthritis.

The higher susceptibility of Cd34^-/- mice was further confirmed by pathology score analysis of histological sections (Fig. 3A). Both left and right ankles were scored on a scale of 0–4 for 1) degree of inflammation, 2) bone erosion, and 3) cartilage erosion to give a maximum possible total score of 24. Following induction of arthritis with K/BxN serum, Cd34^-/- mice consistently demonstrated higher histological scores compared with wt mice, and the difference in histological damage between wt and Cd34^-/- mice was even more striking when samples from mice injected with diluted amounts of K/BxN serum (1/50) were analyzed for bone erosion, cell infiltration, and cartilage erosion (Fig. 3A, 3B). Some of the Cd34^-/- samples even revealed a complete destruction of the bones indicative of extremely severe arthritis pathology.

To determine whether seeding of mast cells alone was enough to induce a response to the K/BxN serum, toluidine blue-stained sections (Fig. 4A) were analyzed for mast cell numbers. Consistent with previous reports, mast cell numbers were equivalent in wt and Cd34^-/- naive mice at baseline (data not shown). At day 11 after disease induction, there was an overall increase from baseline in the total number of mast cells in the joints, but no statistically significant difference between wt and Cd34^-/- mice (Fig. 4B). We conclude that the lack of CD34 expression on mast cells in the joints does not seem to affect development of disease.

Increased disease is due to lack of CD34 on nonhematopoietic cells

Although the data suggest the resident mast cell population in the joints of Cd34^-/- mice is sufficient to promote arthritis, they fail to explain the exacerbated disease in these mice. To differentiate whether this exacerbation was due to a lack of CD34 expression on the hematopoietic compartment (hematopoietic stem cell, mast cells, and eosinophils) or on the nonhematopoietic cells in the joint microenvironment (vascular endothelia), bone marrow chimeric mice were generated. Briefly, wt recipients were lethally irradiated and reconstituted with Cd34^-/- bone marrow to generate mice lacking CD34 exclusively on hematopoietic cells, and irradiated Cd34^-/- recipients were reconstituted with wt bone marrow to
generate mice lacking CD34 exclusively on nonhematopoietic cells. 

Wt mice reconstituted with wt bone marrow cells were used as controls for an influence of irradiation on the disease course. Peripheral blood chimerism was assessed 8 wk posttransplant using allotypic markers to ensure that the reconstituted mice contained >90% donor peripheral blood cells prior to arthritis induction. After arthritis induction, analysis of clinical scores (Fig. 5A) and the increased ankle thickness (Fig. 5B) revealed that Cd34−/− hosts reconstituted with wt bone marrow developed significantly worse disease than the controls in which wt mice were reconstituted with wt bone marrow (p < 0.05; n = 6 per group). Correspondingly, wt mice reconstituted with Cd34−/− bone marrow developed similar disease severity compared with control mice. These data suggest that the increase in disease severity in the Cd34−/− mice is likely because of the lack of CD34 on nonhematopoietic cells within the afflicted joints.

FIGURE 3. A, Histological sections of H&E stained joints from naive and K/BxN-injected (undiluted and 1/50) wt and Cd34−/− mice. b, bone; c, cartilage; i, inflammatory infiltrate; s, synovium. Ankle samples were taken on day 11 postserum injection (original magnification ×100). B, Histological scores were attributed through evaluation of inflammatory infiltrate, bone erosion and cartilage erosion in each of the sections (n = 4 mice/group). I, undiluted serum; II, 1/50 diluted serum.

FIGURE 4. A, Histological sections of Toluidine blue stained joints from K/BxN-injected wt and Cd34−/− mice, day 11 postserum injection. Mast cells were identified as dark purple granular cells (arrows; original magnification ×400). B, Mast cells were counted in whole sections and the left and right paw were averaged.

FIGURE 5. Clinical scores (A) and difference in ankle thickness from baseline (B) in bone marrow chimeric mice. *p < 0.05 compared with the wt into wt group; n = 6–8 mice/group.
One potential caveat to the interpretation of these results is that previous reports have indicated that some subsets of resting mast cells are resistant to irradiation. Thus, it remains a formal possibility that some of the mast cells in bone marrow chimeric mice were host derived. To exclude this possibility, we performed mast cell transplantsations into mast cell-deficient mice that lack any resident mast cells and therefore could obscure this interpretation. Mast cell-deficient W/Wv mice were reconstituted with wt or Cd34^−/− BMMCs, and arthritis was induced 12 wk postreconstitution as published previously (13). This ensured that the only difference between the two cohorts was the expression of Cd34 on mast cells. Results are presented in Fig. 6A for clinical scores and Fig. 6B for the increase in ankle thickness. As previously reported (13), W/Wv mice were protected from arthritis compared with their wt, mast cell containing littermates (W/Wv controls). Reconstitution of W/Wv mice with wt BMMCs 12 wk prior to disease induction led to fully restored disease susceptibility. Reconstitution of W/Wv mice with Cd34^−/− BMMCs also led to regular restoration of disease susceptibility, which further supports that loss of Cd34 on mast cells is not the cause of exacerbated disease.

A second hematopoietic inflammatory cell subset expressing Cd34 is eosinophils and their precursors (2). To rule out eosinophils as an important cell type that could positively or negatively influence the development of arthritis in Cd34^−/− mice, we induced arthritis in “PHIL” mice. These mice express the diphtheria toxin A chain under the control of the eosinophil peroxidase promoter, which renders them completely eosinophil deficient. We found that transfer of K/BxN serum resulted in normal development of arthritis in these mice when compared with their wt littermates (Fig. 6C, 6D). Indeed, the clinical scores and the increase in ankle thickness from baseline showed no statistically significant differences between the PHIL mice and their wt littermates. Thus, neither Cd34 expression on eosinophils nor eosinophils themselves appear to play a major role in the induction, progression, or pathogenesis of autoimmune arthritis.

Cd34^−/− mice exhibit increased vascular permeability in the joints at onset of disease

Previous studies using the K/BxN serum transfer model have also shown that increased vascular permeability (12) is a major hallmark of this mouse model of arthritis. Because Cd34 is prominently expressed on the vascular endothelia and particularly on the microvasculature, we evaluated vascular permeability in the joints of wt and Cd34^−/− mice treated with K/BxN serum by measuring vascular leakage of injected Evans blue dye. Staining for Cd34 on the joint blood vessels (CD31-positive) is presented in Fig. 7A. Results of the permeability assay are presented in Fig. 7B as a representative of three independent experiments. At 48 h after injection of arthriogenic K/BxN serum and prior to onset of clinical manifestations of disease, Cd34^−/− mice have clear increase in vascular permeability compared with wt mice as shown by Evans blue extravasation. This increased vascular permeability preceded the first signs of inflammatory cell infiltration into arthritic joints. Vascular permeability in Cd34^−/− mice was further evaluated in a parallel study using intravital microscopy. Vascular leakage of FITC-albumin was measured in the cremaster of TNF-injected mice, and is presented in Fig. 7C. We observed an increase in vascular permeability in response to TNF in wt mice, which was significantly exaggerated in Cd34^−/− mice, further confirming that these mice show an increase in vascular permeability in the response to inflammatory stimuli. Thus, our data suggest that Cd34 plays an important role in regulating vascular integrity at the onset of disease and prior to inflammatory cell infiltration and that it could contribute to the increase in disease severity observed in Cd34^−/− mice.

Finally, since joint and peripheral mast cells are involved in development of arthritis and release histamine upon stimulation, and since histamine was shown to be involved in the rapid vascular permeability induced in this model, we evaluated whether lack of Cd34 could lead to differences in histamine production in response to the autoimmune serum. We observed no statistically significant differences (n = 6 mice/group) in serum histamine content 48 h after arthritis induction (Fig. 7D) between the two genotypes, confirming that the increase in vascular permeability observed at 48 h postserum injection in Cd34^−/− mice is due to an intrinsic defect in the response of the Cd34^−/− vasculature to inflammatory stimuli.

Cd34^−/− mice do not demonstrate differences in joint hematopoietic cell populations in response to K/BxN serum

To evaluate whether differences in the frequency of resident/infiltrating hematopoietic cells subsets in the joint of Cd34^−/− mice could account for the aggravated development of arthritis in these mice, we analyzed the cell populations found in the joints prior to
and following K/BxN serum injection via FACS analysis of ankle lavage samples. Briefly, ankles were lavaged with $3 \times 10^3$ µl PBS, and the total lavage was analyzed for CD45 expression (Fig. 8A). The CD45$^+$ population was then further evaluated for expression of Cd11b (macrophages), Gr1 (granulocytes), and B220 (B cells). An example of stains and gating is shown in Fig. 8A. Neither T cells (CD3$^+$) nor mast cells (C-Kit$^+$) were found in significant numbers in the hematopoietic content of the ankle lavage. All hematopoietic cells were negative for CD34 expression (data not shown), ensuring that no local joint bone marrow

**FIGURE 7.** A, Immunofluorescence showing CD31 expression (vascular endothelia) and CD34 expression on an ankle joint blood vessel in naïve mice (original magnification $\times 100$). B, Vascular permeability readout using Evans blue leakage in the joint. Results are expressed as percentage of OD of the Cd34$^-$/ Cd34$^+$ extract/tissue mass compared with wt at each time point. C, FITC-albumin vascular leakage in response to TNF stimuli as measured by intravital microscopy. Results are expressed as percentage of vascular leakage, which represents the index of interstitial intensity/venular intensity of the FITC-labeled albumin. D, Histamine serum levels at baseline and 48 h post-K/BxN serum injection. *p < 0.05; **p < 0.01; ***p < 0.001; n = 3–4 mice/group.

**FIGURE 8.** A, Example of gating and stains for the evaluation of hematopoietic cell content of the ankle lavage at 48 h post-K/BxN serum injection. Total cells were stained for CD45, and the CD45$^+$ population was further tested for expression of B220, Cd11b and Gr1. BI and BII, Compilation of percentages of both hematopoietic cell populations found in the ankle lavage at different time points postserum injection.
hematopoietic precursors were contaminating the samples. As shown in Fig. 8Bf and 8BII, the results revealed a steady increase in Gr1+/Cd11b+ cells (macrophages) following serum injection, which correlated with a decrease in B220+ cells (B cells). No major differences were found in the percentages of these two populations between wt and Cd34+/− mice following serum injection that could account for the increased vascular permeability observed previously.

Discussion

In previous studies, we showed that although Cd34+/− mice have normal seeding of inflammatory cells and their precursors at steady state, these mice display a clear impairment in the recruitment of these cell types if challenged in inflammatory models. Thus, CD34 state, these mice display a clear impairment in the recruitment of normal seeding of inflammatory cells and their precursors at steady state (Wsh/Wsh) in an anticollagen/LPS mouse model of arthritis. Sufficient strain (Wsh/Wsh) in an anticollagen/LPS mouse model of arthritis may develop arthritic symptoms in the K/BxN autoimmune serum reconstitution of W/Wv mice results in development of arthritis-like symptoms in the reconstituted joints (19). Mechanistically, it is open question that requires further study. However, because Cd34+/− mice did not show any differences in hematopoietic cell populations in the joint and in the light of the bone marrow transplantation results, the increase in permeability observed at the onset of disease is likely because of changes at the vascular level specifically. Because CD34 is well-known to mediate both adhesion (21) and antiadhesive/invasiveness functions (18, 22), it would be well-positioned to modulate the integrity/stability of endothelial cell contacts. Despite this fact, we and others have not previously detected obvious vascular defects in Cd34-deficient animals at steady state. We have, however, noted previously that deletion of the gene encoding podocalyxin, a close relative of Cd34, leads to embryonic edema. It is also noteworthy that, in perinatal podocalyxin-deficient animals, we observed a compensatory increase in Cd34 expression (23). Finally, we have noted a clear delay in lumen formation in the aorta of podocalyxin-deficient mice, suggesting a role for this family in timely vessel formation (24). Thus, there is a precedent to suggest that this family of molecules may regulate vascular integrity and, to a certain extent, can compensate for each others loss. Additional experiments will be needed to better clarify the precise defect leading to increased permeability in Cd34+/− mice, and a further evaluation of how this phenomenon contributes to the different phenotypes observed in inflammatory diseases in this mouse strain will be of great interest.

In light of these results, we can conclude that Cd34 plays a role in vascular integrity in development of autoimmune arthritis in this model and that lack of Cd34 leads to an exacerbated disease.

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Disclosures

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