Bone Marrow-Derived Cells Are Responsible for the Development of Autoimmune Arthritis in Human T Cell Leukemia Virus Type I-Transgenic Mice and Those of Normal Mice Can Suppress the Disease

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Bone Marrow-Derived Cells Are Responsible for the Development of Autoimmune Arthritis in Human T Cell Leukemia Virus Type I-Transgenic Mice and Those of Normal Mice Can Suppress the Disease

Shinobu Sajiyo, Motoko Kotani, Kiyoshi Habu, Chihito Ishitsuka, Hiroaki Yamamoto, Toyozo Sekiguchi, and Yoichiro Iwakura

Previously, we reported that human T cell leukemia virus type I env-pX region-introduced transgenic (pX-Tg) mice developed an inflammatory polyarthropathy associated with a development of autoimmunity. To elucidate roles of autoimmunity in the development of arthritis, the immune cells were reciprocally replaced between pX-Tg mice and non-transgenic (Tg) mice. When bone marrow (BM) cells and spleen cells from pX-Tg mice were transferred into irradiated non-Tg mice, arthritis developed in these mice. In contrast, arthritis in pX-Tg mice was completely suppressed by non-Tg BM and spleen cells. Similar results were obtained with BM cells only. After the transplantation, T cells, B cells, and macrophages were replaced completely, whereas cells in the joints were replaced partially. In those mice, serum Ig and rheumatoid factor levels correlated with the disease development, and inflammatory cytokine expression was elevated in the arthritic joints. Furthermore, involvement of T cells in the joint lesion was suggested, because the incidence was greatly reduced in athymic nu/nu mice although small proportion of the mice still developed arthritis. These observations suggest that BM stem cells are abnormal, causing autoimmunity in pX-Tg mice, and this autoimmunity plays an important, but not absolute, role in the development of arthritis in this Tg mouse. The Journal of Immunology, 1999, 163: 5700–5707.

Rheumatoid arthritis (RA) is a systemic, chronic inflammatory disorder that mainly affects the joints. Because RA patients often develop Abs and cellular immunity against various self-substances including IgG, type II collagen (IIC), and heat shock proteins (5), immune reactions against these molecules are suspected to play important roles in the pathogenesis of the disease. However, thus far the pathogenic roles of the autoimmunity in the development of RA have not been elucidated completely.

Human T cell leukemia virus type I (HTLV-I) is the causative agent of adult T cell leukemia (6). This virus encodes a transcriptional trans-activator, Tax, in the env-pX region, that trans-activates transcription from the cognate viral promoter through the 21 bp enhancer (7). Tax also activates many cellular genes (8), including these for cytokines (9–12), cytokine receptors (13, 14), and immediate early transcriptional factors (15, 16) through activation of enhancers such as the NF-kB-dependent enhancers or serum-responsive elements (7). Previously, we found that Tg mice carrying the HTLV-I env-pX region with its own long terminal repeat (LTR) promoter developed chronic inflammatory polyarthropathy at a high incidence (17). The arthritis develops in multiple joints as early as 4 wk of age, and at 3 mo of age, 60% (BALB/cAn background) and 20% (C3H/HeN background) of the mice are affected. The histopathology is very similar to that of RA in humans, showing marked synovial and periarticular inflammation with articular erosion caused by invasion of granulation tissues. These mice develop autoimmunity with elevated levels of Abs against IgG, IIC, and heat shock proteins and show IgG hypergammaglobulinemia in which agalactosylated forms of the Ig carbohydrate chains increase (18). In this regard, we recently found that T cells from HTLV-I env-pX region-introduced transgenic (pX-Tg) mice were refractory against anti-Fas Ab treatment (19). This finding suggests that this defect may be involved in the development of autoimmunity in these mice, because Fas-mediated apoptosis of T cells is believed to be important in eliminating autoreactive T cells in the periphery (20). Furthermore, various genes including inflammatory cytokine genes such as IL-1α, IL-1β, IL-6, TNF-α, and IFN-γ genes, immediate early genes such as c-fos and c-jun, and class I and class II MHC genes are activated in the Tg joints (18, 21), probably because of the transcriptional trans-activating activity of the tax gene and also as a result of immune reactions in the affected joints in later stage. Because similar abnormalities are also found in RA patients, we think pX-Tg mice provide a good disease model for RA.

Although the pathogenesis of arthritis in this Tg mouse has not been elucidated completely, several possibilities are conceivable. One is that Tax-induced overproduction of inflammatory cytokines as well as immediate early gene products in the synovial cells may directly cause synovial cell growth and bone erosion. Actually, it
was shown that overproduction of TNF-α in the joints caused arthritis in Tg mice without involvement of immune reaction (22). IL-1α also causes arthritis when it is injected into rabbit joints (23), indicating the arthritogenic nature of these cytokines. Another possibility is that the autoimmunity that developed in these Tg mice is involved in the onset of the disease, as is suggested in RA cases (24). In this connection, it is well known that immunization of DBA1 mice with IIC causes arthritis (25). pX-Tg mice also have the Ab against IIC, and immunization with IIC augments the development of arthritis, suggesting that immune reaction against IIC may be involved in the pathogenesis (18).

In this study, the roles of the immune cells in the development of arthritis in pX-Tg mice were examined to discriminate these possibilities. For this, we conducted reciprocal replacement of the immune system between pX-Tg and normal mice. Furthermore, we examined the incidence of arthritis in athymic trangenic mice by introducing the nu gene into pX-Tg mice. The results show that immune cells, but not synovial resident cells, are primarily responsible for the development of the disease.

Materials and Methods

Animals

The original Tg mouse was produced by injecting the pX and env region of the HTLV-1 genome with its own promoter into fertilized mouse ova from C3H/HeN × C57Bl/6JF1 intercrosses (17). Then, they were backcrossed to BALB/c mice, and littermates at the age of 2–3 mo of backcross generations 8 to 11 were used for the experiments. The transgene was detected by dot blot hybridization of the tail DNA (18), and the transgene-positive and -negative mice are designated pX-Tg and non-Tg mice, respectively.

Male BALB/c-nu/nu mice were obtained from Charles River Japan (Kanagawa, Japan). They were crossed to pX-Tg females, and female progeny carrying the transgene were crossed with male nude mice again. Then, pX-positive hairless (nu/nu) and hairy (nu/+ ) mice were examined for the development of arthritis.

All the mice were kept under specific pathogen-free conditions in environmentally controlled clean rooms in the Laboratory Animal Research Center, Institute of Medical Science, University of Tokyo (Tokyo, Japan). The experiments were conducted according to the institutional ethical guidelines for animal experiments and safety guidelines for gene manipulation experiments.

BM and spleen cell transfer

old pX-Tg and non-Tg female mice, 6–8 wk old, were used as donors of BM and spleen cells. BM cells were prepared from the femurs and tibiae and were used directly (BM cells) or after treatment with mouse anti-Thy-1.2 Ab (Serotec; Oxford, U.K.) and rabbit complement (Technically, Hornby Ontario, Canada) (T cell-depleted BM cells). Age- and sex-matched recipient mice were irradiated with 7.5 Gy of gamma-rays and, after 6 h, were injected with either 10⁵ viable BM cells only or 10⁵ viable spleen cells with 10⁵ BM cells i.v.

Clinical evaluation

Arthritis was evaluated macroscopically. The joints of each paw were examined weekly for swelling and redness, and the disease severity was graded from 0 to 3 (grade 0 = no special changes; grade 1 = light swelling and/or redness of the joint; grade 2 = obvious swelling; grade 3 = fixation of the joint). The score of the four paws were totaled and used as severity score (0–12 points in individual mice).

Histopathology

All of the BM cell-transferred mice and nude mice were submitted to autopsy after inspection for the development of arthritis for 26–30 wk. The limbs were fixed in 10% neutral formalin and, after decalcification with 5% formic acid, embedded in paraffin, sectioned at 4 μm, and stained with hematoxylin and eosin.

Ab titration

Serum levels of IgG rheumatoid factor (RF) were determined by ELISA as previously described (18). Briefly, polyvinyl microtiter plates (Falcon Micro Test III, Becton Dickinson, Tokyo, Japan) were coated with 50 μl heat-denatured rabbit IgG (10 μg/ml) in PBS overnight at 4°C. For total IgG and total IgM, the plates were coated with anti-mouse Ig (DAKO, Kyoto, Japan; 1/10,000 dilution). After a washing with TBS (25 mM Tris-HCl and 140 mM NaCl, pH 7.4), the plates were blocked with 1% skim milk (Difco), 5 mM EDTA, 0.02% NaN₃, TBS (blocking buffer) for 1 h at room temperature. Then, 50 μl blocking buffer-diluted mouse serum were added to each well and incubated for 1 h at room temperature followed by washing with 0.05% Tween 20-TBS. Fifty microliters of alkaline phosphatase-conjugated goat anti-mouse IgG or IgM (Zymed; 1/500 dilution) in the blocking buffer was added as the second Ab and incubated at room temperature for 1 h. After a washing with Tween 20-TBS, 100 μl of 1 mg/ml p-nitrophenylphosphate (Sigma, St. Louis, MO) in 50 mM NaHCO₃, 5 mM MgCl₂ (pH 9.5) was added, and the optical density at 415 nm was measured by an ELISA microreader (MTP-120, Colona, Tokyo, Japan) after incubation at 37°C for 1 h. The Ab levels were calculated with the use of standard positive controls.

Northern blot hybridization and RNase protection assay

Macrophages were collected from the peritoneum after injection with 2% thioglycolate, and T cells were purified from the spleen cells with a nylon wool column. B cells were purified from adherent cell-removed spleen cells by depleting T cells with mouse anti-Thy-1.2 Ab (Serotec) and rabbit complement (Technically, Joint preparation contained the knees, ankles, and the digits from which the skin and the muscle were removed. Then, total RNA was prepared by the acid-phenol-extracted chloroform method (26). Cytokine mRNA was analyzed by Northern blot hybridization using oligo(dT) column-purified poly(A)+ RNA (18). The pX mRNA was measured by RNase protection assay using the total RNA (17). The intensity of the bands on the autoradiograph was estimated by the BAS 2000 system (Fuji-film, Kanagawa, Japan).

Probes

Mouse IL-1α and IL-1β cDNA (CDMIL-1α and CDMIL-1β, respectively) were provided by Dr. Tetsumi Sudo (27, 28), and the XhoI fragments (2.0 and 1.3 kb) were used as probes. Mouse IL-6 (moll-6) and TNF-α (moTNF-α) DNA were kindly gifted from Dr. Takashi Yokota (29, 30), digested with BamHI (1.2 kb) and BglI-BglII (0.7 kb), respectively, and used as probes.

Results

Chronic polyarthritis was induced in non-Tg mice by transferring Tg BM cells

Previously, we reported that pX-Tg mice develop arthritis spontaneously. Those mice began to develop arthritis around 4 wk of age, and the incidence at 30 wk of age was ~80% (Fig. 1). To elucidate the roles of autoimmunity in the development of arthritis, we conducted reciprocal reconstitution of the immune system between pX-Tg and non-Tg mice. As shown in Fig. 1A, irradiated non-Tg mice transferred with T cell-depleted pX-Tg BM cells (Tg→non-Tg) mice developed arthritis 16 wk after the transplantation, and 50% of the mice were affected after 30 wk. Transfer of the pX-Tg spleen cells together with the BM cells or T cell-undepleted BM cells also showed similar results, suggesting that BM cells, but not T cells or B cells, are responsible for the development of this arthritis. The average severity score of the affected joints 30 wk after the transplantation was comparable with that of untreated pX-Tg mice (Fig. 1B). No remarkable changes were found in the BM cell populations expressing either CD11b, Gr1, B220, or Thy-1.2 Ags between pX-Tg mice and wild-type mice as analyzed by FACs, excluding a possibility that cell composition is abnormal in Tg mice (data not shown). Thus, these results indicate that BM stem cells are abnormal in pX-Tg mice.

The development of arthritis was confirmed microscopically (Fig. 2 and Table I). Bone and cartilage erosion caused by invasion of granuloma-like cells was seen in the affected joints of the [Tg→non-Tg] mice (Fig. 2, A–C). Overgrowth of the synovial cells and infiltration of inflammatory cells consisting of neutrophils, lymphocytes, and plasma cells were marked in the joints and periarticular space (Table I). Exfoliation of the synovial lining cells was also observed in some mice. These histopathological findings are consistent with those described in RA patients.
observations were very similar to those seen in spontaneously developed arthritic joints and show that pX-Tg mouse BM-derived cells are abnormal and are responsible for the development of the disease.

**Development of arthritis in pX-Tg mice was suppressed by the introduction of non-Tg BM cells**

Next, we examined whether replacement of the immune cells can prevent development of the disease in pX-Tg mice. As shown in Fig. 1, C and D, when BM cells from non-Tg mice were transferred into irradiated Tg mice, the development of arthritis was completely suppressed. The presence of T cells did not affect the results; BM transplantation with spleen cells or T cell-undepleted BM cells transplantation gave the similar results, although the efficiency of the suppression appeared better in BM plus spleen cell transfer. Interestingly, the swelling and redness of the joint became resolved in three of six mice that had already developed arthritis after transplantation of BM plus spleen cells. Under these conditions, the Tg mice that were transplanted with Tg BM plus spleen cells or only BM cells developed arthritis 100%.

**Joints had no remarkable histological changes in most [non-Tg→Tg] mice (Fig. 2, D and E), in support of the macroscopic observation. However, proliferation of the synovial lining cells as well as fibroblastic cells of the periarticular tissues were observed in some of the [non-Tg→Tg] mice (Fig. 2F and Table I). This incomplete suppression of the disease was observed more frequently in BM cell-transferred mice than in BM plus spleen cell-transferred mice (Table I). Collectively, these results established the primary role of the BM-derived cells in the pathogenesis of arthritis in pX-Tg mice.**

The pX transgene was strongly expressed in lymphatic organs, but only weakly in the joints, after transplantation of Tg BM cells

The transgene is expressed in many organs including the joints, spleen, thymus, and muscle in the original pX-Tg mice (17). We examined the expression of the transgene 6 mo after the transplantation of the Tg BM cells into irradiated non-Tg mice to survey the fate of the transferred cells. As shown in Fig. 3, the transgene was strongly expressed in T cells including the thymocytes and splenic
T cells of [Tg→non-Tg] mice, but the expression was not detected in those of [non-Tg→Tg] mice. Thus, most of the T cells seemed to be replaced by those from donor mice. Transgene expression in macrophages was similarly observed in [Tg→non-Tg] mice but not in [non-Tg→Tg] mice, indicating that this population was also replaced. Transgene expression in B cells was also observed in [Tg→non-Tg] mice, but not in [non-Tg→Tg] mice. In contrast, replacement of the synovial cells in the joints seemed to occur only partially, because the pX expression was still observed in [non-Tg→Tg] mouse joints and that in [Tg→non-Tg] mouse joints was lower than that of Tg mice (Fig. 3). These observations suggest that BM-derived cells such as T cells, B cells, or macrophages are responsible for the development of arthritis, but resident cells in the joint are not directly involved.

**RF and Ig levels in the circulation and the expression of cytokine genes in the joints increased in mice transferred with Tg immune cells**

Because high levels of serum Ig and RF relevant to autoimmunity are characteristic of pX-Tg mice, these autoimmune parameters were determined. Total IgG levels (Fig. 4A), total IgM levels (Fig. 4B), and IgG class RF levels (Fig. 4C) in [Tg→non-Tg] mice were significantly higher than those in non-Tg control mice. In contrast,

Table I.  **Pathologic score in transferred mice**

<table>
<thead>
<tr>
<th>Transfer</th>
<th>RA score</th>
<th>Degeneration</th>
<th>Proliferation</th>
<th>Cell infiltration</th>
<th>Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Edem</td>
<td>Nec</td>
<td>C exf</td>
<td>Lining</td>
</tr>
<tr>
<td>BM cells + Spleen cells</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Tg → WT</td>
<td>9/12</td>
<td>+</td>
<td>–</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>2. Non-Tg → Tg</td>
<td>0/12</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>3. Tg → Tg</td>
<td>9/12</td>
<td>–</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>BM cells</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Tg → WT</td>
<td>8/12</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>5. Non-Tg → Tg</td>
<td>2/12</td>
<td>–</td>
<td>+</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>6. Tg → Tg</td>
<td>10/12</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>

*The severity of arthritis was graded as – to ++ +++, and the average score is presented. Number of mice examined: 1, 3 mice; 2, 12 mice; 3, 2 mice; 4, 3 mice; 5, 10 mice; and 6, 2 mice. Nec, necrosis; C exf, synovial lining cell exfoliation; lining, synovial lining cell overgrowth; fibro, fibrosis; pannus, pannus formation; PMC, polymorphocyte; Plasm, plasma cell; Lymp, lymphoid cell.
these Ig levels in [non-Tg→Tg] mice significantly reduced compared with those in arthritic Tg mice, being nearly equal to the levels in nonarthritic Tg mice. These serological data suggest involvement of autoimmunity in the development of arthritis in [Tg→non-Tg] mice.

Various proinflammatory cytokines are abundantly expressed in the affected joints of RA patients, and the same kinds of gene are also activated in the joints of pX-Tg mice. These proinflammatory genes, especially IL-1β, IL-6, and TNF-α genes, were activated in the affected joints of [Tg→non-Tg] and [Tg→Tg] mice as in arthritic Tg mice (18), compared with the nonarthritic joints of [non-Tg→Tg] and non-Tg mice (Fig. 5). However, their expression in the spleen was not correlated to the arthritis. The expression of these cytokines in the nonarthritic joints of [non-Tg(BM)→Tg] mice was not augmented (Fig. 5), in spite of the pX expression in the joints of these mice (Fig. 3). Thus, it was suggested that pX-gene expression in the resident cells in the joints is not directly involved in the activation of cytokine expression in the affected joints.

Development of arthritis greatly reduced in nu/nu-pX-Tg mice

To elucidate roles of T cells in the development of arthritis in pX-Tg mice, the incidence and severity of the disease were compared between nu/nu (athymic)- and nu/+ (euthymic)-pX-Tg mice. As shown in Table II, the incidence of arthritis was clearly lower in homozygous nude mice than in heterozygous ones. The histology of the nonarthritic joints was normal when examined by a microscope (Fig. 6A). The incidence in heterozygous mice was not significantly different between female and male mice. Although only female nu/nu mice developed arthritis, the difference is statistically not significant. The average incidences in heterozygous and homozygous mice including both female and male were 56.2 and 4.3% at 3 mo and 84.2 and 13.6% at 5 mo of age, respectively. The severity scores were also low in nude mice compared with euthyemic mice, because fewer paws were affected in those mice. These results suggest that T cell immunity plays a crucial role in the development of arthritis in pX-Tg mice.

Small but significant numbers of nu/nu mice developed arthritis in which erosion of the articular cartilage, proliferation of synovial cells, and infiltration of neutrophils were observed in the joints (Fig. 6, B and C). In this respect, we found that many CD3+ T cells was present in nu/nu mouse lymph nodes at the age of 5 mo; ~30% of the lymph node cells were T cells in nu/nu mice, in contrast to 60% in wild-type mice. However, the RF levels in nu/nu-pX-Tg mice were not elevated even after development of arthritis (Fig. 7). These observations indicate that RF is not necessarily required for the development of arthritis in these mice.
Discussion

In this study, to investigate the etiopathogenesis of the arthritis in pX-Tg mice, we have conducted reciprocal replacement of the immune cells between pX-Tg and normal mice and found that transplantation of BM cells from pX-Tg mice into lethally irradiated non-Tg mice caused autoimmunity and arthritis, and conversely, introduction of non-Tg mouse BM cells suppressed the onset of the disease completely. These findings showed that BM cells and their derivatives are abnormal in pX-Tg mice and that these cells are enough to cause autoimmunity and arthritis in these mice.

The arthritis was not caused by the T cells that were contaminated in BM cell preparations, because we depleted T cells by treating BM cells with anti-Thy-1.2 Ab and complement before transfer of the cells. Moreover, addition of spleen cells in which large amounts of T cells were present to the BM preparation did not increase the incidence of arthritis. We also tried to induce arthritis by transferring spleen cells into nude mice, but we have never succeeded (data not shown). Thus, these observations suggest that the disease is not caused by the abnormal education of T cells in the periphery but by the disorder in the stem cells.

Under our conditions, pX gene expression was observed in Tg cells, B cells, and macrophages when BM cells from Tg mice were transplanted into lethally irradiated non-Tg mice. However, the expression disappeared completely both in T cells, B cells, and macrophages after transfer with non-Tg mouse BM cells into irradiated Tg mice. These results indicate that the immune system of the recipient mice was completely substituted with the donor cell-derived population. Suppression of arthritis was better in [non-Tg (BM + S)→Tg] mice than in [non-Tg (BM)→Tg] mice, probably because the immune system could be reconstituted earlier by the presence of spleen cells. In this connection, it is known that presence of T cells in donor bone marrow inocula leads to predominant repopulation with donor lymphocytes in recipient mice (31).

In contrast, the pX gene expression was still observed in Tg mouse joints transferred with non-Tg mouse BM cells. Because the

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Table II. Incidence of arthritis in athymic nu/nu pX-Tg mice

<table>
<thead>
<tr>
<th></th>
<th>Incidence</th>
<th>Severity Score*</th>
<th>Incidence</th>
<th>Severity Score*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 mo</td>
<td>5 mo</td>
<td>3 mo</td>
<td>5 mo</td>
</tr>
<tr>
<td>pX-nu/+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>14/26 (53.8%)</td>
<td>21/26 (80.8%)</td>
<td>8.5 ± 2.3</td>
<td>9.3 ± 2.2</td>
</tr>
<tr>
<td>Female</td>
<td>16/31 (51.0%)</td>
<td>27/31 (87.1%)</td>
<td>8.1 ± 2.0</td>
<td>8.3 ± 2.0</td>
</tr>
<tr>
<td>pX-nu/nu</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0/8a (0.8%)</td>
<td>0/7b (0.0%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Female</td>
<td>1/15a (6.7%)</td>
<td>3/15b (20.0%)</td>
<td>3.0 ± 0</td>
<td>5.0 ± 1.4</td>
</tr>
</tbody>
</table>

*Average of arthritic score and SD of the affected mice.

b p < 0.01, compared with euthymic pX-nu/+ mice by χ2 analysis.
pX gene is expressed in cells other than immune cells, including muscle and synovial cells in pX-Tg mice (17), this residual expression of the pX gene is considered to be originated from the resident cells in the joints. This pX gene expression in the joints did not cause arthritis providing the BM-derived cells were normal. Not only the histology but also the autoantibody levels and cytokine production in the joints were normal in these normal BM cell-transferred Tg mice. These findings indicate that synovial cell overgrowth in the affected joints is not the direct effect of the pX gene expression in the synovial cells. Cytokine overproduction also seems not to be caused by the resident cells in the joints, although it is quite possible that BM-derived cells such as macrophages, or type A cells in the synovial tissues participate in the production of inflammatory cytokines (32).

Accordingly, these findings, together with the observations that 1) a considerably long time (>15 wk), i.e., enough to replace the production of inflammatory cytokines (32), and 2) acceleration of the cytokine overproduction in the joints may trigger the inflammation in the joints caused joint destruction without infiltration of immune cells (22). Thus, the arthritis seems to be induced by two steps: 1) the triggering by the cytokine overproduction; and 2) acceleration by the autoimmune reaction against synovial components. Cytokine overproduction may also contribute to the development of autoimmunity by enhancing recruitment of immune cells, augmenting expression of MHC genes, and activating T cells in anergy (37). These mechanisms may also explain why these mice develop such a tissue-specific autoimmunity.

Our study shows that T cell-dependent autoimmunity plays crucially important roles in manifesting symptoms of arthritis. We are now examining the roles of cytokines and autoimmunity in the development of arthritis by producing cytokine knockout mice and tissue-specific tax-Tg mice.

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References

FIGURE 7. Serum RF levels in nu/nu-pX-Tg mice. ATg, arthritic Tg mice; NTg, nonarthritic Tg mice; non-Tg, non-Tg mice. Columns indicate the means, bars indicate the SD, and circles indicate individual values. ○, nonarthritic mice; ●, arthritic mice. The mice were sacrificed at the age of 5 mo. **, p < 0.01, compared with non-Tg mice by F test.


