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1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease that results in the destruction of cartilage and bone in joints. The murine Collagen-Induced Arthritis (CIA) model has been used to investigate the pathogenesis of RA representatively, because it shares many features with RA (Courtenay, et al., 1980; Luross & Williams, 2001). Susceptibility to arthritis of both CIA and RA is associated with the specific major histocompatibility complex class II allele (Gregersen, et al., 1987; Wooley, et al., 1989). In addition, autoantibodies to type II collagen (CII) have been detected from the synovial fluid of RA patients and it has an aggravating effect in both CIA mice and RA (Clague & Moore, 1984; Cook, et al., 1996; Mullazehi, et al., 2007; Tarkowski, et al., 1989). Finally, pathogenic contributions of \( \text{CD}^4^+ \) helper T (Th) cells have been reported in both CIA mice and RA (Weyand & Goronzy, 1999; Weyand, et al., 1998). More recently, the SKG mouse which carries a point mutation of the gene encoding zeta-chain-associated protein kinase 70 (ZAP-70) has been reported as a new model of RA. However, there is little information available about the similarities and differences in the pathogenesis of arthritis among these murine models and RA.

Interleukin-17 (IL-17) is a cytokine secreted by T cells, natural killer (NK) cells, and neutrophils (Ferretti, et al., 2003), and it induces IL-6, IL-8, chemokine, and metalloproteinase production by target cells (Weaver, et al., 2007). Central pathogenic roles of IL-17 in CIA have also been reported recently. For example, systemic or local IL-17 gene transfer aggravated CIA, whereas administration of an IL-17-blocking antibody ameliorated CIA even after the onset of arthritis (Lubberts, et al., 2001; Lubberts, et al., 2004) and IL-17 deficient mice also showed reduced severity of CIA (Nakae, et al., 2003). Furthermore, IL-23 deficient mice, which show impaired Th17 response, do not exhibit CIA because IL-23 is an essential factor for the maintenance of Th17 cells (Murphy, et al., 2003). Consequently, although the pathological contribution of IL-17 to CIA is evident, it remains unclear with RA.

In the present study, we analyzed the phenotypes and cytokine profiles of T cells in the joints of CIA mice kinetically, for the first time, and then analyzed those of SKG mice and RA.

2. Most of the IL-17-producing T cells in the swollen joints of CIA were gamma/delta T cells

To analyze the phenotype and cytokine profile of T cells in the joints of CIA mice, we choose foot pad injection for CII-CFA (complete Freund’s adjuvant) instead of tail base injection to
distinguish the inflammatory effect of adjuvant itself from real CIA. Each joint was thus designated as immunized joint (CII-CFA injected site), swollen joint (real CIA), or non-swollen joint (Figure 1A). First, the phenotypes and cytokine profiles of T cells in swollen joints of CIA mice were analyzed using intra-cellular cytokine staining by FACS at the peak of CIA (Figure 1B). Surprisingly, most of the IL-17-producing T cells were gamma/delta TCR+ T cells, and did not express CD4, CD8, and DX5. The remainder of the IL-17-producing cells were Th17 cells which express alpha/beta TCR+ (data not shown) and CD4, and neither CD8+ cells nor DX5+ NK cells produced IL-17.

Fig. 1. Phenotypes of IL-17 producing T cells in the swollen joints of CIA
A, Schema of analyzed joints and their DLNs of mice with CIA. B, Infiltrated cells of swollen joint of CIA mice were obtained by collagenase digestion, and stained with antibodies against CD3, CD4, CD8, DX5, and gamma/delta TCR. IL-17-producing cells were detected by intracellular cytokine staining. The percentage of cells in each region or quadrant is noted.

3. Distribution and kinetics of IL-17- and IFN-gamma-producing T cells in the joints of CIA
We next analyzed the kinetics of phenotypes and cytokine profiles of infiltrated T cells in the joints of CIA mice at six distinct phases: before immunization (naïve mice), one day after immunization (day 1), before onset (day 10), onset (day 32), peak (day 42), and ankylosing phase (day 70) of arthritis. At each phase, cells were collected from the swollen joint, immunized joint and non-swollen joint, as well as the DLN and spleen (Fig. 1A).
In the swollen joints, absolute numbers of IL-17-producing gamma/delta T cells were larger than those of Th17 cells (CD4+, alpha/beta TCR+ T cells) with the maximal counts at the peak of arthritis (Fig. 2A and B). Surprisingly, neither IFN-gamma-producing CD4+ (Th1) cells nor IFN-gamma-producing gamma/delta T cells were detected at any phase analyzed in the swollen joints. In contrast, IFN-gamma-producing T cells were detected in their DLNs (Fig. 2A). In the immunized joints, IL-17-producing gamma/delta T cells and Th17 cells were already observed on Day 1, reached the first peak on day 10 after immunization, and
then reached their highest counts with the peak of arthritis. The absolute numbers of IL-17-producing gamma/delta T cells were consistently larger than those of Th17 cells at most time points analyzed. In contrast to the swollen joints, IFN-gamma-producing T cells were detected in the immunized joints after immunization (Fig. 2A and B). For both swollen and immunized joints, the percentages of IL-17-producing gamma/delta T cells among IL-17-producing cells were larger than those in their DLNs (Fig. 2A). In the non-swollen joints, both IL-17-producing T cells and IFN-gamma-producing T cells were rarely observed. In addition, IFN-gamma-producing gamma/delta T cells were a minor population in the joints of CIA (Fig. 2A). These data suggest that CIA is an IL-17-driven arthritis that is produced mainly by gamma/delta T cells, while IFN-gamma-producing T cells are probably dispensable.

Fig. 2. Distribution and kinetics of IL-17- and IFN-gamma-producing T cells in the CIA joints

A. Cells were obtained from joints, their DLNs, and the spleens of mice with CIA at the peak of arthritis. IL-17-producing T cells and IFN-gamma-producing T cells were detected by intracellular cytokine staining (top row). IL-17-producing T cells (second row) or IFN-gamma-producing T cells (bottom row) were gated and plotted by their expression of gamma/delta TCR and CD4. The absolute number and the percentage of T cells among
4. IL-23 and IL-1 beta efficiently stimulate IL-17 production by gamma/delta T cells

It is known that a subset of gamma/delta T cells already differentiate to acquire the IL-17-producing function in the thymus (Jensen, et al., 2008), and CCR6 is suggested as a specific marker of Th17 cells (Acosta-Rodriguez, et al., 2007; Annunziato, et al., 2007; Hirota, et al., 2007; Singh, et al., 2008). Therefore, the expression of CCR6 on IL-17-producing gamma/delta T cells in the thymus of naïve DBA1/J mice was evaluated. IL-17-producing, but not IFN-gamma-producing gamma/delta T cells preferentially expressed CCR6 (Fig. 3A). As it has also been reported that small numbers of gamma/delta T cells are present in the normal joints of mice (Arai, et al., 1996), we next examined whether de novo CCR6+ IL-17-producing gamma/delta T cells are present in the normal joints of naïve DBA1/J mice. Cells were collected from the normal joints of naïve mice and intracellular cytokine staining was performed. By analyzing cells from two normal paws and ankles at a time, CCR6+ IL-17-producing gamma/delta T cells could be detected (data not shown). In addition, in CIA mice, 92% of CCR6+ gamma/delta T cells produced IL-17 (Fig. 3B). Next, the signal requirements of IL-17-producing gamma/delta T cells were analyzed. Gamma/delta T cells from naïve DBA1/J mice were stimulated with cytokines in the presence or absence of anti-gamma/delta TCR activating mAb (Fig. 3C). Although small numbers of IL-17-producing gamma/delta T cells were detected by stimulations with anti-gamma/delta TCR mAb, IL-23, or IL-1 beta alone, IL-23 plus IL-1 beta induced IL-17-producing gamma/delta T cells quite efficiently without anti-gamma/delta TCR stimulation. These observations indicated that TCR signaling was not necessary to stimulate IL-17-producing gamma/delta T cells. Furthermore, a combination of IL-23 and IL-1 beta was a much more potent stimulator than TCR signaling. Similar results were obtained with gamma/delta T cells sorted from DLNs of swollen joints at the peak of CIA (Fig. 3C, right panel).

A, Thymocytes from naïve mice were stimulated with PMA and ionomycin for 4 h. Gamma/delta TCR+ cells were gated and CCR6+ cells among IL-17-producing or IFN-gamma-producing gamma/delta T cells were detected. The percentages of cells in each quadrant are indicated. B, Cells were collected from DLNs of swollen joints of CIA mice. IL-17-producing cells were detected by intracellular cytokine staining. CCR6+ cells were gated and IL-17-producing cells were analyzed. The percentage of IL-17-producing cells among CCR6+ gamma/delta T cells is noted. C, Gamma/delta T cells were sorted from peripheral lymph nodes of naïve DBA1/J mice (upper panel) or DLNs of swollen joints of CIA mice at the peak of arthritis (lower panel) and stimulated with cytokines, activating anti-gamma/delta TCR antibodies, and anti-CD28 antibodies for 24 h. By intracellular cytokine staining, the percentages of IL-17-producing cells among gamma/delta T cells were determined. Mean ± SEM is shown from three different mice.
5. IL-17-producing gamma/delta T cells were maintained by IL-23 but not by CII in vitro and induced by IFA in vivo

Since IL-23 plays important roles in the maintenance of Th17 cells (Bettelli, et al., 2006; Harrington, et al., 2005; Infante-Duarte, et al., 2000; Mangan, et al., 2006; Park, et al., 2005; Veldhoen, et al., 2006), we next analyzed the maintaining effect of IL-23 or CII on IL-17-producing gamma/delta T cells. To test this, cells from DLNs of swollen joints of CIA mice were cultured with IL-23, CII, or medium alone (Fig. 4A). Both IL-17-producing gamma/delta T cells and Th17 cells were maintained by the presence of IL-23. However, IL-17-producing gamma/delta T cells were not maintained by the presence of CII, and Th17 cells showed CII-dependency. To further investigate the factors that enhance the accumulation of IL-17-producing gamma/delta T cells in the inflamed joints, the numbers of IL-17-producing gamma/delta T cells were counted in the joints of differently-immunized mice on day 10. Mice were immunized with PBS, IFA+solution (0.05 mM of acetic acid for CII solvent), IFA+CII, or CFA+CII (Fig. 4B). The numbers of IL-17-producing gamma/delta T cells were not significantly different between mice immunized with IFA+solution, IFA+CII, or CFA+CII. In contrast, the numbers of IL-17-producing gamma/delta T cells were significantly smaller in mice immunized with PBS than in the other three conditions, while the numbers of Th17 cells were significantly larger in mice immunized with IFA+CII than those in mice treated with IFA+solution. These data suggested that IL-17-producing
gamma/delta T cells do not specifically respond to CII and may just respond to adjuvant (IFA+solution) or adjuvant-induced IL-23.

6. IL-17-producing gamma/delta T cells did not induce but amplified CIA

Next, the pathogenic roles of IL-17-producing gamma/delta T cells in CIA were evaluated. Because we found that CCR6 is an exclusive marker for IL-17-producing T cell even in the case of gamma/delta T cells, CCR6+ gamma/delta T cells were sorted from DLN of the swollen joints of CIA mice as the source of IL-17-producing gamma/delta T cells (data not shown). When CCR6+ gamma/delta T cells were transferred to the joints of naïve mice, arthritis was not induced. However, when it was transferred to the joints of mice immunized with CII+CFA, it significantly worsened the arthritis score compared with PBS (Fig. 4C). The arthritis-exacerbating effect of CCR6+ gamma/delta T cells from swollen joints was equivalent to CCR6+ gamma/delta T cells from DLNs of swollen joints (data not shown).

Fig. 4. IL-17-producing gamma/delta T cells were maintained by IL-23, and did not induce but amplified CIA

A. Cells were prepared from the DLNs of swollen joints and cultured for 7 days in the presence of IL-23, CII, or medium alone. IL-17-producing T cells were detected using FACS analysis. The ratio of the numbers of IL-17-producing T cells in the presence of IL-23 or CII to those in medium alone was calculated. Mean ± SEM is shown from at least three different experiments.

B. Various combinations of substances were administered into the footpads of DBA1/J mice. Ten days later, the absolute numbers of IL-17-producing cells were counted by FACS analysis. Mean ± SEM is shown from at least three different mice. * = P < 0.05.

C. CCR6+ gamma/delta T cells were sorted from DLNs of swollen joints of CIA mice, then those cells or PBS alone were injected to unimmunized wrists or ankles of mice immunized with CII+CFA.
two weeks before. For naïve mice, CCR6+ gamma/delta T cells, naïve CD4+ T cells, or PBS alone were injected. Mean ± SEM of the arthritis score of affected joints is shown. * = P < 0.05.

7. IL-17-producing gamma/delta T cells were not detected in the swollen joints of SKG mice

To elucidate the pathological differences from other murine arthritis models, the same analysis was performed using SKG mice (Sakaguchi, et al., 2003). SKG mice carry a point mutation of the gene encoding zeta-chain-associated protein kinase 70 (ZAP-70), and homozygous mice show IL-17-dependent arthritis resembling RA. Although the present study could detect only a few IL-17-producing gamma/delta T cells in the DLNs of swollen joints, surprisingly almost all of the IL-17-producing cells were Th17 cells and the numbers of IL-17-producing gamma/delta T cells were negligible in the swollen joints of SKG mice (Fig. 5A). As SKG is a BALB/c-background strain, and SKG arthritis is induced by zymosan as an adjuvant (Sakaguchi, et al., 2003; Yoshitomi, et al., 2005), the possibility that IL-17-producing gamma/delta T cells are absent in the joints of SKG arthritis should be excluded because of the differences in strain or adjuvant from CIA. Thus we counted the absolute numbers of cell subsets from joints immunized with CFA+CII of SKG or BALB/c mice. Even in this condition, IL-17-producing gamma/delta T cells were not detected in SKG mice, whereas IL-17-producing gamma/delta T cells were more abundant than Th17 cells in BALB/c (Fig. 5B). These data suggested that SKG mice have some impairment of development or maintenance in IL-17-producing gamma/delta T cells.

Fig. 5. IL-17-producing gamma/delta T cells were not detected in swollen joints of SKG mice
A. Cells were collected from an ankle with maximum arthritis and its DLNs of SKG mice treated with zymosan 7 weeks previously. IL-17-producing cells and IFN-gamma-producing cells were detected by intracellular cytokine staining (left column). IL-17-producing IFN-gamma-negative cells (middle column) or IFN-gamma-producing IL-17-negative cells (right column) were gated and plotted by their expressions of gamma/delta TCR and CD4. The absolute numbers and percentages of CD4\(^+\) cells and gamma/delta TCR\(^+\) cells are indicated.

B. SKG or BALB/c mice were immunized with CFA+CII and cells in their immunized joints were collected 10 days later. Absolute numbers of cells were counted by FACS analysis. Mean ± SEM is shown from three different mice.

8. In RA affected joints, IL-17-producing gamma/delta T cells were not detected, and IFN-gamma-producing T cells were dominant

Finally, cells in synovial tissues or fluids with RA patients were analyzed to determine the presence of IL-17-producing gamma/delta T cells, Th17 and Th1 cells. In contrast to CIA, IL-17-producing gamma/delta T cells could not be detected in either synovial tissues or synovial fluids of the affected joints with RA, whereas a small number of IFN-gamma-producing gamma/delta T cells were present in synovial tissues (Fig. 6A). Among the CD4\(^+\) T cells in both synovial tissues and synovial fluids, IL-17-producing cells were rarely present, and IFN-gamma-producing T cells were clearly dominant in the affected joints of RA patients (Fig. 6A and B). Although this finding is consistent with a previous report (Yamada, et al., 2007), we confirmed it in both synovial tissues and fluids of RA patients.

Fig. 6. IL-17-producing gamma/delta T cells were not detected, and IFN-gamma-producing T cells were dominant in the affected joints of RA

Cells in synovial tissues (n=4) or synovial fluids (n=7) of RA were isolated and stained with antibodies against CD4, gamma/delta TCR, IL-17, and IFN-gamma after stimulation by PMA/ionomycin for 6 hours. The percentages of cells out of the total of gamma/delta T cells plus CD4\(^+\) T cells were determined. Mean ± SEM is shown.
9. Conclusion

This study initially focused on IL-17-producing T cells in the swollen joints of CIA. We found that gamma/delta T cells were the predominant source of IL-17 and were more abundant than Th17 cells, and DX5+ NK cells did not secrete IL-17 in swollen joints of CIA mice. Although it is known that gamma/delta T cells are dispensable for the induction of CIA, because gamma/delta TCR deficient mice can mount CIA (Corthay, et al., 1999), the present findings in the kinetic study and adoptive transfer experiments, together with previous reports (Arai, et al., 1996; Peterman, et al., 1993; Roark, et al., 2007), suggest that not only Th17 cells but also IL-17-producing gamma/delta T cells contribute to the exacerbation of CIA. On the other hand, alpha/beta T cells, especially Th17 cells, are essential for the induction of CIA because alpha/beta TCR deficient mice cannot mount CIA (Corthay, et al., 1999). In addition, IL-17-producing iNKT cells in CIA have been reported recently (Yoshiga, et al., 2008), but these cells were not analyzed in this study.

The origin and functions of IL-17-producing gamma/delta T cells in physiological and pathological conditions have been elucidated recently. It was reported that a subset of gamma/delta T cells acquired IL-17-producing function in the thymus (Jensen, et al., 2008) and produced cytokines immediately responding to the initial stimulation. In various murine infectious disease models, these gamma/delta T cells predominantly produce IL-17 and eradicate pathogens (Lockhart, et al., 2006; Romani, et al., 2008; Shibata, et al., 2007; Umemura, et al., 2007). Although IL-23 is known to be a sufficient stimulant of IL-17-production by gamma/delta T cells in naïve mice (Shibata, et al., 2007), the precise requirements of IL-17 production by gamma/delta T cells especially in CIA are unknown. We herein demonstrated that the combination of IL-23 and IL-1 beta synergistically stimulated IL-17 production, but stimulation via gamma/delta TCR had a limited effect. Given the enhanced expression of IL-1 beta and IL-23 in inflamed joints of CIA (Kim, et al., 2007; Weiss, et al., 2005), these findings suggest that IL-17-production by gamma/delta T cells in CIA might mainly be an inflammatory cytokine-driven, and not a TCR-signal-driven process.

The present study showed that IL-17-producing gamma/delta T cells were CCR6 positive, and CCR6 was already expressed on IL-17-producing gamma/delta T cells in the thymus of naïve mice. CC chemokine ligand 20 (CCL20), the only chemokine known to interact with CCR6, is physiologically expressed at epithelial surfaces (Schuttyser, et al., 2003) and fibroblast-like synoviocytes (Hirota, et al., 2007), and is upregulated in inflammatory conditions (Hirota, et al., 2007; Schuttyser, et al., 2003). These findings suggest that CCR6 might have some role in determining the physiological distribution of IL-17-producing gamma/delta T cells. In fact, it was found that a small number of CCR6+ IL-17-producing gamma/delta T cells were present in the joints of naïve mice. Next, the differences between IL-17-producing gamma/delta T cells and Th17 cells were focused upon. IL-17-producing gamma/delta T cells are maintained by IL-23 but not by a specific antigen (CII, in this case). In contrast, Th17 cells responded to both CII and IL-23. Furthermore, IL-17-producing gamma/delta T cells were induced equivalently in response to stimulation by IFA+solution in the absence of CII. Together with the previous study demonstrating that IL-17-producing gamma/delta T cells are induced equally by CFA+CII and CFA (Roark, et al., 2007), the present data suggest that IL-17-producing
gamma/delta T cells do not recognize the specific antigen (CII) but rather proliferate in response to IL-23, which may be produced locally by synovial cells (Kim, et al., 2007). The ligands of gamma/delta T cells are largely unknown and further analysis of possible antigens of IL-17-producing gamma/delta T cells in CIA could be difficult (Konigshofer & Chien, 2006). However, we confirmed the diverse usage of gamma/delta TCR in IL-17-producing gamma/delta T cells in CIA (Ito, et al., 2009), which supported the present conclusion that IL-17-producing gamma/delta T cells are antigen-independently induced by inflammatory cytokines.

In summary, the sequence of pathology of CIA is speculated to be as follows. First, CII-specific Th17 cells are induced by CII+CFA, which then infiltrate into the joints and cause primary inflammation. Although antigen-independent IL-17-producing gamma/delta T cells could be induced simultaneously by CFA, they are dispensable for the induction of arthritis. Next, primary inflammation induces local production of IL-23 from synoviocytes and increases the expression of IL-1 beta in the joint cartilage and pannus (Weiss, et al., 2005). Locally-produced IL-23 induces the proliferation of resident IL-17-producing gamma/delta T cells. These gamma/delta T cells, stimulated by IL-1 beta and IL-23, produce enhanced amounts of IL-17 and exacerbate the arthritis of CIA. Another, but not mutually exclusive, possibility is that primary inflammation enhances CCL20 expression in vascular endothelial cells and fibroblast-like synoviocytes (Hirota, et al., 2007) in inflamed joints, and recruits CCR6+ IL-17-producing cells. In the ankylosing phase, the burned out tissue does not produce inflammatory cytokines, and then the activities and the number of IL-17-producing gamma/delta T cells decrease to the basal level.

The cytokine profiles of T cells were compared in the inflamed joints of SKG mice and RA with those of CIA mice. In contrast to CIA, IL-17-producing gamma/delta T cells were not detected in the swollen joints of SKG mice. A lack of IL-17-producing gamma/delta T cells in SKG mice was not caused by the differences in strain or adjuvant. It was also found that IL-17-producing gamma/delta T cells are hardly induced, not only in immunized joints but also in their DLNs and the spleens of SKG mice by immunization with CFA+CII (data not shown). Given that the TCR signals in SKG mice are attenuated because of a point mutation in ZAP-70 (Sakaguchi, et al., 2003) and differentiation of gamma/delta T cells requires a strong signal via TCR (Haks, et al., 2005; Hayes, et al., 2005), there may be some defects in the gamma/delta T cell differentiation in SKG mice. This speculation was supported by the data of impaired development of specific subsets of gamma/delta T cells in ZAP-70 knockout mice (Kadlecek, et al., 1998). Therefore, it is true that both murine RA models share the property of IL-17-driven arthritis, and IFN-gamma-producing Th1 cells seem dispensable in these models. However, there is also a significant dissimilarity in their pathogeneses. CIA mice appear to be an arthritis model that is driven by innate factor, because the major population of swollen joints was antigen-independent gamma/delta T cell. In contrast, SKG arthritis seems to be a pure Th17-driven arthritis (Fig 7). However, the target antigen of Th17 cells in the affected joint of SKG mice is still unknown.

Contrary to the findings of murine RA models, there are big differences in the phenotypes and the cytokine profiles in the affected joints of RA patients. IL-17-production from gamma/delta T cells in synovial tissues of RA was negligible, and a small number of IFN-gamma-producing gamma/delta T cells were present in RA synovium. Furthermore, the
most notable difference was predominance of Th1 cells (IFN-gamma-producing Th cell) rather than Th17 cells in the joints of RA, and this observation is consistent with a previous report (Yamada, et al., 2007). This discrepancy could be explained by some artifacts. For example, the synovium samples of RA available are not from an early phase but a relatively late phase. In fact, Leipe et al. (2011) reported recently that the percentages of Th17 cells correlate strongly with the activity of RA using very early active and naïve RA patients, and concluded that Th17 cells play an important role in human RA. However, their data also indicated that IFN-gamma-producing T cells were dominant even in those cases. This discrepancy may also be explained by the differences between mice and humans. Alternatively, IL-17-producing T cells may play important roles in RA as well, but are suppressed by the effects of medicines. In conclusion, we have to wait for the results of clinical trials of IL-17 blocking agents in RA patients to further understand the true roles of Th17 cells in RA.

Fig. 7. A schema of cytokine profiles and T cell phenotype of two murine arthritis models and RA

10. Acknowledgment
This work was mainly conducted by Dr. Ito Yoshinaga (Ito, et al., 2009).

11. References


Cytokine Profile of T Cells in the Joints of Rheumatoid Arthritis and Its Murine Models


reduces joint inflammation, cartilage destruction, and bone erosion. *Arthritis Rheum*, Vol.50, No.2, pp.650-659, ISSN 0004-3591


The purpose of this book is to provide up-to-date, interesting, and thought-provoking perspectives on various aspects of research into current and potential treatments for rheumatoid arthritis (RA). This book features 16 chapters, with contributions from numerous countries (e.g. UK, USA, Japan, Sweden, Spain, Ireland, Poland, Norway), including chapters from internationally recognized leaders in rheumatology research. It is anticipated that Rheumatoid Arthritis - Etiology, Consequences and Co-Morbidities will provide both a useful reference and source of potential areas of investigation for research scientists working in the field of RA and other inflammatory arthropathies.

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