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Combined Effects of IL-12 and IL-18 on the Induction of Collagen-Induced Arthritis

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IL-18 expression has recently been detected in rheumatoid arthritis (RA) synovial membrane. We investigated the mechanisms by which IL-18-induced collagen-induced arthritis in DBA/1 mice primed intradermally with type II bovine collagen in IFA and boosted i.p. 21 days later with CII in saline. Mice were injected i.p. with rIL-12, rIL-18, or both (100 ng) during days −1 to 4 and again on days 20–24. Control mice received PBS. Mice treated with IL-12 or IL-18 alone developed significantly higher incidence and more severe disease compared with controls. These were elevated further by combination treatment with IL-12 and IL-18. The cytokine treatments led to markedly enhanced synovial hyperplasia, cellular infiltration, and cartilage erosion compared with controls. Cytokine-treated mice produced significantly more IFN-γ, TNF-α, and IL-6 than the controls. Interestingly, IL-18-treated mice produced more TNF-α and IL-6, but less IFN-γ, compared with mice treated with IL-12. Furthermore, splenic macrophages from DBA/1 mice cultured in vitro with IL-18, but not IL-12, produced substantial amounts of TNF-α. Mice treated with IL-18 or IL-18 plus IL-12 produced markedly more IgG1 and IgG2a anti-collagen Ab compared with controls, whereas IL-12 treatment alone led to an enhanced IgG2a response. Together these results demonstrate that IL-18 can promote collagen-induced inflammatory arthritis through mechanisms that may be distinct from those induced by IL-12. 

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Interleukin-18 expression within inflammatory lesions has been reported in several human diseases, including rheumatoid arthritis and inflammatory bowel disease (1–3). However, its functional role therein remains poorly understood. IL-18 is a member of the IL-1 cytokine family (4). Pro-IL-18 is cleaved by IL-1β-converting enzyme (ICE;5 caspase 1) to yield an active 18-kDa glycoprotein (5) that recognizes a heterodimeric receptor, consisting of unique α (IL-1Rrp) and nonbinding β (AcPL) signaling chains (6, 7) that are widely expressed on cells implicated in both innate and specific immune responses. The synthesis of IL-18 has been described by various cell types, including macrophages, dendritic cells, Kupffer cells, keratinocytes, articular chondrocytes, and osteoblasts (8–12), and in adrenal cortex and pituitary gland (13).

IL-18 induces the proliferation of and promotes IFN-γ, TNF-α, and GM-CSF production by Th1 clones (14). IL-18 promotes T cell and NK cell cytotoxicity and directly induces IFN-γ production by NK cells (15). Such in vitro Th1 specificity is relative. Several recent data suggest that IL-18-mediated effects on T cells, in the absence of IL-12, may extend beyond Th1 differentiation to include type 2 response activation (16, 17). Thus, IL-18 enhances IL-13 mRNA expression in Th2 and NK cells (17). The direct effects of IL-18 on macrophage function have received less attention. IL-18 and IL-12 together induce IFN-γ production by murine bone marrow-derived macrophages, whereas activation of human macrophages in PBMC cultures was effected by IL-18 through T cell- and NK cell-derived TNF-α production (18, 19).

In vivo, IL-18 exerts synergy with IL-12 to promote the development of Th1 responses. IL-18-deficient mice exhibit impaired Th1 responses to intracellular bacteria, including Propionibacterium acnes, Mycobacterium bovis, and Staphylococcus aureus and parasites, such as Leishmania major (15, 20). Such responses are further impaired in IL-12/IL-18 double-knockout mice (15). IL-18 is also implicated in protective immunity during murine Cryptococcus neoformans or Yersinia infections (21, 22). IL-18 mRNA is up-regulated in diabetic NOD mice, and the murine IL-18 gene maps to the Idd2 susceptibility locus, suggesting a potential role in the mediating autoimmune diabetes (23). However, IL-18 supplementation in nonobese diabetic (NOD) mice retarded the clinical onset of hyperglycemia and modified the transition from Th2 to Th1 cytokine mRNA expression in pancreatic islets (24). Moreover, IL-18 has also been shown to enhance Th2 cytokine production, eosinophilia, and allergic sensitization in a ragweed Ag-induced allergy model (16). Thus, commensurate with the emerging complexity of its functional effects in vitro, the role of IL-18 in murine autoimmune models is unclear.

Collagen-induced arthritis (CIA) represents an ideal opportunity to explore the diverse inflammatory effects of IL-18 in an inducible, autoimmune model. CIA has proven a useful surrogate in which to investigate the role of cytokines in RA, particularly in defining key roles for TNF-α and IL-1. Considerable data implicate Th1 responses in the pathogenesis of CIA (25). Thus, the incidence and severity of CIA are reduced in IL-12-deficient mice (26). Neutralizing anti-IL-12 Abs ameliorate the onset and progression of disease (27–29), particularly in synergy with anti-TNF-α Abs (29). However, IL-12 probably has a biphasic role, such that low dose, early administration of IL-12 is proinflammatory, whereas high dose or chronic administration may be anti-inflammatory through an IL-10-dependent mechanism (30).
recently detected IL-18 in RA synovial membrane and demonstrated that rIL-18 together with type II collagen can promote clinically detectable, inflammatory arthritis in DBA/1 mice. Moreover, synovial macrophages expressed IL-18R and produced TNF-α in direct response to IL-18 in vitro (1). In the present study we have extended these observations to compare the capacities of IL-18, IL-12, and their combination to promote CIA, and thereafter, we have defined mechanisms by which such arthritis is induced. Our data demonstrate that IL-18 can promote erosive CIA, which is histologically indistinguishable from that induced by collagen in CFA. The mechanisms implicated differ significantly from those induced by IL-12. These data identify IL-18 as a potential proinflammatory cytokine in inflammatory arthritis.

Materials and Methods

Animals and reagents

Male DBA/1 mice obtained from Harlan Olac (Bicester, U.K.) were used at 8–10 wk of age. Murine rIL-12 was provided by Genetics Institute (Cambridge, MA). rIL-18 used in our experiments was generated as described previously (31). Total RNA was extracted from 3774 cells stimulated for 18 h with 100 U/ml IFN-γ (provided by Dr. G. A. Adler, Bender Wien, Austria) and LPS (1 μg/ml; Sigma, Poole, U.K.) using the Trizol reagent (Life Technologies, Paisley, U.K.). RNA was transcribed into cDNA using SuperScript II reverse transcriptase (Life Technologies) according to a standard protocol. Primers were designed from murine IL-18 sequence data were used to clone IL-18 from the cDNA (sense, GACCACATGGGCGACTCTACTGTACAAACGCG; antisense, CCTAAAGATCTATGTAAGTTAGTGAGATGTCAGAC; Genosys, Cambs, U.K.). The PCR product was confirmed by sequencing, cloned into the pQE-30 expression vector (Qiagen, Dorking, U.K.), and expressed in Escherichia coli M15 (Qiagen). Following induction with isopropyl-β-D-thiogalactoside (BioLine, London, U.K.), IL-18 was extracted under native conditions and purified as a 6× histidine-tagged fusion protein using a nickel agarose purification system (Qiagen) according to the manufacturer’s recommendations. Purity was analyzed by SDS-PAGE and Coomassie blue staining, which showed a single protein band coinciding with the manufacturer’s recommendations. Purity was analyzed by SDS-PAGE and Coomassie blue staining, which showed a single protein band coinciding with the manufacturer’s recommendations.

Cytokine treatment was scheduled 1 day before the primary and secondary immunizations with collagen (days 1–2 and days 20–24). The IL-12 dose was determined based on previous studies that documented biphasic effects of IL-12, such that higher doses could exert anti-inflammatory effects through IL-10 induction (30).

Administration of cytokines

Mice received daily i.p. injections of IL-12, IL-18, or both (all at 100 ng) diluted in PBS supplemented with 0.1% BSA for 5 consecutive days, while control mice received PBS/0.1% BSA only. Cytokine treatment was scheduled 1 day before the primary and secondary immunizations with collagen (days 1 to 4 and days 20–24). The IL-12 dose was determined based on previous studies that documented biphasic effects of IL-12, such that higher doses could exert anti-inflammatory effects through IL-10 induction (30).

Collagen-specific in vitro culture

Spleens and draining lymph nodes were removed on days 24, 42, and 73 after primary immunization. Single-cell suspensions were prepared and cultured in triplicate at 2 × 10^5 cells/ml in RPMI 1640 supplement with 100 IU/ml penicillin, 100 μg/ml streptomycin, 25 mM HEPES buffer, and 10% FCS (all from Life Technologies) at 37°C in 5% CO₂. Cells were stimulated with graded concentrations of type II collagen in flat-bottom 96-well plates (Nunc, Roskilde, Denmark). Supernatants were collected after 48 or 72 h and stored at −20°C until assay for cytokine concentration. Proliferation assays were performed in parallel cultures in U-bottom 96-well plates (Nunc) for 96 h and were pulsed with [³H]thymidine (Amer sham, Aylesbury, U.K.) during the last 6 h of culture. Plates were then harvested and measured for incorporation of radioactivity as previously described (33).

Measurement of cytokines and serum anti-collagen Ab levels

All cytokines and anti-collagen Ab levels were detected by ELISA as described previously (31). The Ab pairs were as follows: TNF-α, IFN-γ (Genzyme, Cambridge, MA), IL-4, IL-5, IL-6, and IL-10 (PharMingen, San Diego, CA), and assays were performed according to the manufacturers’ instructions. Detection limits were as follows: IL-4, IL-5, IL-6, and TNF-α, 10 pg/ml; and IL-10 and IFN-γ, 40 pg/ml. Serum anti-collagen II Ab titers in pooled sera (n = 5) were detected with biotin-conjugated anti-mouse IgG1 or IgG2a (PharMingen) followed by conjugated avidin peroxidase (Sigma) and developed with tetramethylbenzidine substrate (Kirkegaard & Perry, Gaithersburg, MD).

Spleen macrophage culture and FACS analysis

Spleen macrophages were enriched by adherence as described previously (34). Additional characterization by FACS was conducted on enriched spleen macrophages using FITC-conjugated anti-CD4, anti-CD8 (both from Sigma), anti-CD19, and anti-NK (both from PharMingen) Abs to confirm the purity of the enriched macrophage population. Cells were <2% CD4⁺, CD8⁺, or CD19⁻ and <1% NK⁻. Enriched macrophages were cultured in supplemented RPMI 1640 medium at 2 × 10^6 cells/ml in flat-bottom 96-well plates (Nunc) in the presence of either IL-12 or IL-18 (both at 100 ng/ml) for 48 h, and supernatants were stored at −20°C until assay of cytokines. For intracellular staining, enriched macrophages were suspended at 2 × 10^5 cells/ml and stimulated with IL-12 or IL-18 (100 ng/ml) in the presence of brefeldin A (Sigma) for 4 h. Cells were then washed, fixed with 2% paraformaldehyde, permeabilized with 0.5% saponin (both Sigma), stained with PE-conjugated anti-mouse TNF-α or PE-conjugated rat anti-mouse IgG1 isotype control (both from PharMingen), and analyzed on a FACScaliber flow cytometer (Becton Dickinson, Mountain View, CA).

Statistical analysis

Statistical analysis was performed using Minitab software (State Collage, PA) for Macintosh. Clinical and histologic scores were analyzed with the nonparametric Mann-Whitney U test. Differences between cumulative incidences at a given time point were analyzed by the log rank contingency analysis. Cytokine and collagen-specific IgG levels were compared using Student’s t test. Bonferroni’s correction for multiple comparison was applied as appropriate.

Results

Cytokine-mediated onset of CIA

To determine whether IL-18 might promote collagen-specific articular immunopathology, we administered rIL-18 immediately before and during initial collagen priming (days 0–4) and challenge (days 20–24). In the absence of cytokine administration (saline recipients, n = 29), male DBA/1 mice primed with type II bovine collagen in IFA developed only low levels of arthritis (Fig. 1). In contrast, mice that received IL-18 (n = 38) developed severe inflammatory, polyarticular arthritis onset from day 29, involving up to 87% of animals by day 69. The incidence of arthritis was comparable to that achieved by administration of IL-12 (n = 27) in a similar regimen. Combination of IL-12 and IL-18 (n = 27) did not significantly enhance the incidence of arthritis (Fig. 1A). The severity of arthritis was measured by sequential estimation of the articular index and was compared for involved animals within each group. Disease severity was higher throughout in all cytokine-treated groups compared with saline-treated collagen/IFA controls (p < 0.05; Fig. 1B). Moreover, IL-12/IL-18 induced significantly more severe arthritis than did IL-12 alone. Disease severity after IL-18 administration was intermediate between that in IL-12- and IL-12/IL-18-treated groups (Fig. 1B). By day 73 the incidence and
severity of CIA in all cytokine-treated groups were equivalent to those observed in positive control mice primed with collagen in CFA on day 1 (n = 16; data not shown).

To determine whether cytokine administration with collagen induced erosive articular disease, histological examination of arthritic joints was performed on day 42. Whereas little inflammatory change was observed in saline-treated, collagen/IFA-immunized mice, IL-18-treated mice exhibited an extensive inflammatory infiltrate, consisting of mononuclear cells with synovial hypertrophy, and evidence of cartilage erosion (Fig. 2). Significantly higher levels of inflammation, synovial hypertrophy, and cartilage erosion were evident in IL-12/IL-18 than in IL-12 recipients, comparable to those seen in positive control mice, which were primed with collagen/CFA. Changes in IL-18-treated mice were again intermediate. Together, these data clearly indicate that IL-18 alone is sufficient to induce inflammatory arthritis in IFA/collagen-primed mice. Furthermore, IL-18 significantly enhanced the efficacy of IL-12 administration in vivo.

**Modified Ag-driven cytokine responses ex vivo**

Th1 and Th2 cytokine expression was first assessed in serum and thereafter in vitro. To compare the sequential expressions of cytokines in serum, arthritic mice of equivalent articular index (between groups) were selected from each treatment group during the acute (day 29) and established (day 42) phases of disease. IL-4, IL-5, and IL-10 were not detected throughout, confirming the expected absence of a significant Th2 response. In contrast, during

the acute phase, elevated levels of IFN-γ were present in sera in IL-12- and IL-18-treated mice. These levels were further enhanced in the IL-12/IL-18 recipients. Of interest, IL-12 treatment induced higher levels of IFN-γ than did IL-18 administration alone (Fig. 3A). These high levels of IFN-γ expression were maintained into the chronic phase, by which time levels in IL-18 recipients were similar to those in IL-12-treated mice, although levels in the IL-12/IL-18 group remained significantly higher (Fig. 3B). Since the above observations were made without further exogenous cytokine administration, it seemed likely that the long term polarity of Ag-specific responses had been modified by transient cytokine treatment during Ag exposure. We therefore characterized collagen-specific responses in draining lymph node cultures (LNC) prepared from mice with equivalent articular indexes on day 24 (before disease onset), day 42, and day 74. Immediately
following cytokine administration, but before disease onset (day 24), collagen-specific IFN-γ production by LNC was significantly elevated in IL-12- and IL-12/IL-18-treated, but not IL-18-treated, mice (Fig. 4). However, by day 42 levels of IFN-γ production in response to collagen in IL-18-treated mice were equivalent to those in IL-12/IL-18- and IL-12-treated mice. These data reflected the expression of IFN-γ detected in sera (Fig. 3, A and B). Collagen-driven cellular proliferation was equivalent in all cytokine-treated groups (Fig. 4). Together, these data show that IL-18 administration facilitated the development of a Th1 response to collagen, although the kinetics were apparently delayed in comparison with IL-12 and IL-12/IL-18 recipient groups. This did not, however, correlate with a delay in clinical disease onset, suggesting that IL-18-mediated effects beyond Th1 cell induction.

We therefore investigated the effects of cytokine treatment on monokine expression. During acute phase disease, TNF-α was easily detected in sera of IL-18-treated mice (Fig. 3C), whereas lower levels were present in IL-12 recipients. Synergistic enhancement of serum TNF-α levels was evident in IL-12/IL-18-treated mice. In chronic phase, TNF-α levels in IL-18-treated mice were further enhanced, comparable by then with those in IL-12/IL-18 recipients (Fig. 3D). However, TNF-α levels remained significantly lower in IL-12 recipients. The pattern of serum IL-6 expression was similar to that of TNF-α, with significantly lower levels detected in IL-12-treated mice compared with IL-18 and IL-12/IL-18 recipients at both time points (Fig. 3, E and F). IL-12 (p70) was not detected in sera from any group. We next investigated monokine production in vitro by lymph node cells. On day 24, higher levels of spontaneous and collagen-inducible TNF-α and IL-6 production by LNC were evident from IL-12/IL-18-treated mice compared with IL-18 and IL-12/IL-18 recipients at both time points (Fig. 5). Paradoxically, although TNF-α was produced in response to collagen in both IL-12 and IL-18 recipients, higher levels of TNF-α were produced in the former. Because higher levels of serum TNF-α and IL-6 were evident on day 29 in IL-18

![FIGURE 3. Serum cytokine concentrations in mice. Sera were obtained from mice in groups treated as indicated at the time points shown, and cytokine concentrations were measured by ELISA. Results are the mean ± SEM (three mice per group). *, p < 0.05; **, p < 0.01 (vs IL-12/IL-18 treated mice, by Student’s t test). ND, nondetectable.](http://www.jimmunol.org/)
recipients compared with IL-12-treated mice (Fig. 3, C and E), this observation probably reflects the high levels of IFN-γ induced in vitro in LNC from the IL-12-treated mice (Fig. 4). By day 42, IL-18-treated mice exhibited high levels of TNF-α and IL-6 production, which were by then comparable with those in IL-12/IL-18- and IL-12-treated mice. In vitro cytokine production was

**FIGURE 4.** Comparison of IFN-γ levels and proliferative responses to collagen in vitro. Lymph node cells were collected at the time points indicated (three mice per group) and cultured with type II collagen. Cytokine levels in the culture supernatant at 72 h were measured by ELISA. For proliferation, lymph node cells were incubated with 50 µg/ml of collagen or medium and measured as [3H]thymidine incorporation at 96 h. IL-4, IL-5, or IL-10 was not detected. Data are the mean ± SEM of triplicate cultures.

**FIGURE 5.** TNF-α and IL-6 produced by lymph node cells in vitro. Cells were cultured as described in Fig. 4, and the production of TNF-α and IL-6 at 72 h was measured by ELISA (three mice per group). Data are the mean ± SEM of triplicate cultures.
greater in all cytokine-treated mice than in saline-treated IFA/collagen controls. By day 74, IL-6 and TNF-α production was reduced and equivalent to that in collagen/IFA controls (Fig. 5). These data together indicate that IL-12 and IL-18 induced differential cytokine production by monocyte populations, suggesting again that their functional activities in vivo may not be identical.

We next investigated whether differential direct effects of IL-18 and IL-12 on monocyte cytokine production could explain the discrepancy between IFN-γ and TNF-α expression in vivo. Membrane-bound and intracellular TNF-α expression in macrophage-enriched spleen cell populations from DBA/1 mice was determined by FACS analysis after stimulation for 4 h with 100 ng/ml of either IL-12 or IL-18 in the presence of brefeldin A to prevent secreted cytokine-mediated interactions. TNF-α expression was significantly enhanced by the presence of IL-18, but not IL-12 (Fig. 6A). In parallel cultures maintained without brefeldin A, secreted TNF-α was higher in IL-18-treated than in IL-12-treated or medium control cultures (Fig. 6B). Similar data were obtained when responses in adherent spleen cells from arthritic and naïve mice were compared, although baseline TNF-α secretion was higher in the former (data not shown). IL-18 did not induce detectable IL-10 production, indicating that its effects on macrophages are selective and probably proinflammatory. These data clearly demonstrate that IL-18, but not IL-12, can directly promote TNF-α production, independent of IFN-γ production and provide a rationale for the enhanced TNF-α levels detected in IL-18-treated mice.

Anti-collagen Ab production in vivo

Finally, we sought evidence for anti-collagen Ab production. As expected, collagen-specific IgG2a Abs, which are typically produced during a Th1 response, were detected in the sera of IL-12-, IL-18-, and IL-12/IL-18-treated mice on day 42 (Fig. 7B). However, titers of collagen-specific IgG1 were also elevated in IL-18 and IL-12/IL-18 recipients compared with PBS recipient controls (Fig. 7A). In contrast, IgG1 Abs were not elevated in IL-12-treated mice. Thus, IL-18 may promote Ab responses through pathways that are not strictly Th1 cell regulated in vivo.

Discussion

Although a critical role in infectious diseases has been identified, the precise contribution of IL-18 to the development of autoimmune diseases is as yet poorly understood. We recently detected IL-18 in RA synovial membrane and demonstrated that such expression might promote the production of proinflammatory cytokines and nitric oxide. Injection of IL-18 together with type II collagen induced clinically detectable inflammatory arthritis in DBA/1 mice (1). The present report now compares this activity of IL-18 with that of IL-12, and documents mechanisms by which IL-18 can promote such inflammatory arthritis. The inflammation induced was at least comparable to that induced by IL-12, in combination with which it exerted additive effects to promote severe erosive arthritis. Importantly, the mechanisms by which IL-12 and IL-18 promoted inflammation appeared distinct, indicating that the
actions of these cytokines in vivo are not identical. A corollary remains, however, that such divergent immune mechanisms contributed to broadly similar inflammatory changes assessed at the clinical level.

IL-18 has been identified as a critical regulatory factor in the evolution of Th1 immune responses, usually acting in synergy with IL-12 (15). However, the mechanisms by which IL-18 promoted articular inflammation in the present study were unlikely to be fully explained by synergy with endogenous expression of IL-12. Key differences emerged on comparing IL-12- and IL-18-treated mice. The kinetics of IFN-γ induction by collagen were delayed in IL-18 recipient mice, since only by day 42 did IL-18-treated mice exhibit an IFN-γ response comparable with that of IL-12 recipients. TNF-α levels were consistently higher in serum of IL-18-treated mice than in that of IL-12-treated mice. This may reflect a direct effect of IL-18 on TNF-α production. Of interest, IL-18, but not IL-12, directly induced high levels of TNF-α production by macrophages in vitro, with no apparent effect on IL-10 production. However, indirect effects mediated through promotion of T cell/dendritic cell interactions (9) are also possible and may explain the sustained effects of IL-18 on cytokine expression and disease onset (usually after day 29) despite the cessation of cytokine administration after day 24. Finally, the isotype of the anti-collagen Ab response in IL-12 recipient mice was not restricted to IgG2a, suggesting effects beyond Th1-mediated B cell help. Together, these data suggest effects for IL-18 in vivo in the development of inflammatory arthritis that extend beyond T cell differentiation.

IL-12 administration has previously been shown to promote the development of CIA (27, 30, 35). We have now demonstrated that addition of IL-18 to IL-12 significantly enhanced the severity of erosive disease progression. Our data suggest that enhanced Th1 responses to collagen were present early in combination cytokine-treated mice, associated with high levels of TNF-α production. The mechanism of such synergy between IL-12 and IL-18 in vivo is unknown at present, but may include enhanced IL-18R expression by IL-12 (36, 37), enhanced TNF-α production through direct effects of IL-18, and accelerated Ig production by IL-18 in both IgG1 and IgG2a subclasses. The role of Th1 responses in CIA, and in particular the contribution of IL-12, continue to be debated. Type 1 cytokines predominate during disease development (25), and administration of type 2 cytokines, including IL-4 and IL-10, is generally beneficial, indicating that Th1 responses are important (32, 38). However, IL-12 exhibits biphasic effects during CIA (27, 30), perhaps through differential IL-10 induction, and in IFNγR-deficient mice it is proinflammatory through IFN-γ-independent pathways (39). Similarly, on collagen challenge, a proportion of IL-12-deficient mice develop arthritis, clearly suggesting that IL-12-independent pathways exist (26).

TNF-α production is of paramount importance in RA (40–42). Several studies have now demonstrated the efficacy of TNF-α blockade in murine arthritis models and in RA, confirming the pivotal importance of this cytokine (29, 43–45). Those factors that, in turn, drive TNF-α production in RA are less clear. IL-18 can induce significant TNF-α expression in synovial membrane cultures in synergy with IL-12 and IL-15 (1). Such TNF-α is induced both through direct effects on macrophages and through T cell activation. Others have demonstrated similar enhancement of monokine expression by IL-18 through CD14-negative cells in human peripheral blood (19). Together with the results of the present study, this suggests that cytokines such as IL-18 may promote TNF-α production with consequent articular inflammation and destruction. In comparison with the relatively restricted expression of IL-12 and its receptor, the broad distribution of IL-18 in macrophages, dendritic cells, chondrocytes, and synovial fibroblasts together with the presence of IL-18R on macrophages, Th1 cells, and NK cells suggest that IL-18 mediates an important general role in early immune regulation. Our data suggest that such effects may be of relevance in chronic autoimmune disorders beyond RA to include inflammatory bowel disease, in which IL-18 has also been detected (2, 3).

IL-18 retarded the effect of Th2 to Th1 transition in NOD mice (24). CIA differs from this model, in that IL-18 administration can be precisely timed with Ag priming and challenge. However, because mature Th1 cells continue to express IL-18R, whereas Th2 cells do not (37), the net effect of IL-18 in chronic lesions in which activated memory T cells predominate is likely to be proinflammatory. The present study clearly demonstrates that such proinflammatory potential can promote tissue destruction. IL-18 should therefore be regarded as a potential therapeutic target in RA synovitis and in other chronic autoimmune diseases in which similar pathophysioologic pathways are implicated.

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References


