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# Endogenous IL-11 is pro-inflammatory in acute methylated bovine serum albumin/interleukin-1-induced (mBSA/IL-1)arthritis☆

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**Abstract**

**Objective**: To evaluate the role of interleukin-11 (IL-11) in acute mBSA/IL-1-induced inflammatory arthritis.

**Methods**: IL-11 was administered via intra-articular (IA) injection into knee joints of C57BL/6 mice and joint histology was assessed. The mitogenic response to IL-11 was measured in wild-type (WT) synovial fibroblasts. IL-1 was used as a comparator in both the studies. The severity of acute methylated bovine serum albumin (mBSA)/IL-1 arthritis was determined in WT and IL-11 receptor null (IL-11Ra1−/−) mice. In parallel experiments, a neutralising antibody to IL-11 was administered to WT mice throughout this model.

**Results**: IA injections of IL-11 resulted in mild-to-moderate joint inflammation which was less than that due to IA IL-1. IL-11 had a dose-dependent mitogenic effect on WT synovial fibroblasts ($P < 0.01$). mBSA/IL-1 acute arthritis was reduced in IL-11Ra1−/− versus WT mice (histological arthritis score: $10.1 \pm 0.5$ versus $12.8 \pm 0.7$, respectively; $P = 0.01$). Administration of an IL-11 neutralising antibody to WT mice reduced mBSA/IL-1 acute arthritis scores compared to control antibody ($10.6 \pm 0.7$ versus $13.3 \pm 0.6$, respectively; $P = 0.02$).

**Conclusions**: These data demonstrate that endogenous IL-11 exerts relatively mild but consistent pro-inflammatory effects in acute inflammatory arthritis.

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*Keywords:* Interleukin-11; Arthritis; Inflammation

## 1. Introduction

There is increasing evidence that the interleukin-6 (IL-6) family of cytokines, comprising IL-6, interleukin-11 (IL-11), leukemia inhibitory factor (LIF) and oncostatin M (OSM), is important in the pathogenesis of inflammatory arthritis [1]. In contrast to other IL-6 family members, there is relatively little information regarding the role of IL-11 in inflammatory arthritis.

IL-11 mRNA levels were greater in synoviocytes from patients with rheumatoid arthritis (RA) compared to those with osteoarthritis (OA) [2]. RA synovial fibroblast cell lines produced IL-11 when stimulated with tumor necrosis factor (TNF) and interleukin-1 (IL-1). Neutralisation of IL-11 activity increased TNF production by RA synoviocytes and administration of exogenous IL-11 inhibited metalloproteinase expression

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(MMP-1 and -3), while up-regulating tissue inhibitor of metalloproteinase-1 (TIMP-1) [3]. IL-11 down-regulated lipopolysaccharide-induced TNF production in mouse peritoneal and lung macrophages [4]. Systemic administration of IL-11 reduced the severity of collagen-induced arthritis (CIA) [5]. In one clinical trial of systemic administration of IL-11 in RA, a mild beneficial effect on tender joint count was noted at the highest dose [6]. These data suggest that IL-11 may function as an anti-inflammatory cytokine. However, IL-11 stimulated immunoglobulin production from B-cells [7] and over-expression of IL-11 in airways resulted in bronchial inflammation [8].

Osteoblasts constitutively expressed mRNA for both IL-11R and gp130, the common transmembrane receptor for IL-6 family ligands, while multiple stimuli, including IL-1, TNF, and parathyroid hormone, induced production of IL-11 by osteoblasts [9]. IL-11 also promoted in vitro osteoclastogenesis [10], which may be of relevance in RA as the disease is characterised by excessive subchondral osteoclastic bone resorption [11]. Rheumatoid synovial cell production of IL-11 is inhibited by IL-4 [12], a cytokine clearly shown to down-regulate joint inflammation [13–15]. These data indicate that IL-11 may have both pro-and anti-inflammatory actions.

This study aimed to clarify the role of endogenous IL-11 in inflammatory arthritis by comparing the severity of experimental arthritis in mice deficient in IL-11 receptor to that in WT controls. The effect on acute arthritis in WT mice of systemic administration of a neutralising antibody to IL-11 was determined. We also report the effect of intra-articular (IA) injection of IL-11 in WT mice and the mitogenic effect of IL-11 on murine synovial fibroblasts.

## 2. Materials and methods

### 2.1. Mice

Interleukin-11 receptor null (IL-11Ra1−/−) mice [16] were backcrossed onto a C57BL/6 (B6) background for more than 10 generations (Mouse Genome Informatics nomenclature Il11ra1$^{tm1Wehi}$). Congenic inbred B6 mice were obtained from WEHI Animal Supplies. All mice were more than 8 weeks of age at the time of experimentation and fed standard rodent chow and water ad libitum. All animal procedures were approved by the institutional ethics committee.

### 2.2. Intra-articular (IA) injection of cytokines

IA knee injections of recombinant human IL-11 (5 μg/day in 10 μl of normal saline, a generous gift from Genetics Institute Inc., Cambridge, MA) were performed in WT B6 mice on 3 consecutive days. The contralateral knee joint was injected with an equivalent volume of normal saline. Age- and sex-matched mice received IA recombinant human IL-1β (25 ng/day for 3 days; National Cancer Institute, Bethesda, MD) as a positive control [17]. Knee joints were harvested on day 3. Joints were processed and scored by a blinded observer as described below for histological features of arthritis.

### 2.3. Synovial fibroblast proliferation assays

Primary cultures of synovial fibroblasts (SF) were established from patellae harvested from WT mice and cultured in RPMI with 10% fetal calf serum (FCS). Over 2–4 weeks, fibroblasts grew out from the patellae and then the confluent cells were passaged and cultured further in RPMI. Cells from the third to the sixth passage were seeded into 96-well plates at a density of $1 \times 10^4$/well, left to adhere overnight and serum starved (0.5% FCS) for 24 h to coordinate the cell cycle. Quadruplicate cultures were stimulated for 24 h with the indicated concentration of recombinant human IL-11 or recombinant human 1β in RPMI + 1% FCS and pulsed for the last 6 h with 0.5 μCi per well of methyl-[$^3$H]-thymidine before harvesting and measuring incorporated radioactivity.

### 2.4. Induction of acute inflammatory arthritis with mBSA and IL-1 (mBSA/IL-1-induced arthritis)

Induction of acute arthritis was performed as previously described [18]. The advantages of this model are the high incidence of arthritis in injected knee joints and the rapid, reproducible disease kinetics. Arthritis severity is scored by detailed histological assessment as clinically observable synovitis is not a feature of this model [18–20]. IL-1 is a major mediator of RA and converts the transient CD4+ T-cell-dependent inflammatory reaction to methylated bovine serum albumin (mBSA) into a florid monoarthritis.

Briefly, adult mice were anesthetized and injected IA with 10 μl of a 20 mg/ml solution of mBSA (Sigma–Aldrich, St. Louis, MO) into knee joints. Mice were then injected with 20 μl of 12.5 μg/ml recombinant human IL-1β subcutaneously in the footpad. The IL-1 injection was repeated for the next 2 days. At least 4 mice were included in each experimental group and results shown are pooled from two separate experiments. As the IL-11Ra1−/− mice were backcrossed onto a B6 background for more than 10 generations, age- and sex-matched WT B6 mice were used as controls.

### 2.5. Histologic assessment of mBSA/IL-1-induced arthritis

Mice were euthanized on day 7 following IA mBSA injection, the knee joints were removed, fixed in 10%

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