IL-6 inhibits the proliferation of fibroblastic synovial cells from rheumatoid arthritis patients in the presence of soluble IL-6 receptor

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Keywords: IL-6, rheumatoid arthritis, soluble IL-6 receptor, synovial cell, tumor necrosis factor-α

Abstract

IL-6 and tumor necrosis factor (TNF-α) have been proven to play an important role in the development of rheumatoid arthritis (RA). It is well known that TNF-α induces IL-6 production from synovial cells as well as their proliferation. The effect of IL-6 on synovial cells, however, is not clear. An in vitro study was performed to determine the effect of IL-6 on the proliferation of synovial cells. Fibroblastic synovial cells isolated from the synovial tissues of eight RA patients were employed after the third to sixth passages. IL-6 in the presence of soluble IL-6 receptor (sIL-6R) inhibited the proliferation of synovial cells in a dose-dependent manner in seven cases without increasing the number of necrotic or apoptotic cells, while TNF-α increased synovial cell proliferation in all cases. The inhibitory effect of IL-6 was observed only in the presence of sIL-6R although small amounts of IL-6R were detected in these cells by RT-PCR analysis. However, anti-IL-6R or anti-gp130 mAb treatment increased spontaneous growth of synovial cells in all eight cases, suggesting that endogenous IL-6 and a small amount of IL-6R expressed in synovial cells suppressed their growth without exogenous IL-6 or sIL-6R. In addition, the IL-6–sIL-6R complex reduced the TNF-α-induced proliferation of synovial cells while TNF-α induced their IL-6 production. These data suggest that IL-6 may act as a negative feedback factor for TNF-α-induced synovial cell growth.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by persistent synovitis accompanied by synovial cell proliferation, progressive destruction of cartilage and bone, presence of rheumatoid factor, elevation of acute phase proteins, hyper-γ-globulinemia, and thrombocytosis. These clinical abnormalities may be explained by the uncontrolled hyperproduction of IL-6 found in both serum and synovial fluid of RA patients (1–4). This hypothesis is supported by the evidence that anti-IL-6 mAb treatment was therapeutically effective in RA patients (5). However, the direct effect of IL-6 on the proliferation of synovial cells which is a characteristic feature of RA has remained unclear.

IL-6 is a pleiotropic cytokine with a wide range of biological activities such as regulation of immune response and bone remodeling, generation of inflammatory responses, and support of hematopoiesis (6). IL-6 also acts as a growth factor for various cells such as epidermal keratinocytes (7), mesangial cells (8), renal carcinoma cells (9) and human multiple myeloma cells (10). On the other hand, IL-6 has a growth inhibitory effect on dermal fibroblasts (11), acute myeloid leukemia cells (12) and breast carcinoma cells (13,14). The receptor system of IL-6 consists of a ligand binding receptor (IL-6R) and its signal transducer, glycoprotein 130 (gp130), on the cell surface (15). The soluble form of IL-6R (sIL-6R) has been identified in vivo and the IL-6–sIL-6R complex can also induce homodimerization of gp130 and mediate the signal into cells which express not IL-6R but gp130 on their surface (16). Therefore, the increased


**Methods**

**Fibroblastic synovial cells**

Fibroblastic synovial cells were isolated from the synovial tissues of RA patients with their informed consent and in accordance with the guidelines of our institution’s ethical committee, and RA-6 synovial cells were kindly provided by Dr Mihara. The clinical features and medications of these patients are listed in Table 1. The synovial tissues were minced and treated with 0.2 mg/ml of DNase (Nacalai Tesque, Kyoto, Japan) and 2 mg/ml of collagenase (Sigma, St Louis, MO) for 1 h at 37°C as previously reported (17). Cell suspensions were passed through a mesh and synovial cells were isolated with the aid of Ficoll-Paque (Pharmacia Biotech, Uppsala, Sweden). The cells were then cultured in DMEM with 10% FCS, 2 mmol/l L-glutamine, 50 nmol/ml 2-mercaptoethanol, 100 U/ml penicillin and 100 µg/ml streptomycin in a culture flask, and the non-adherent cells were removed. Adherent fibroblastic cells were considered to be synovial cells and we used cells which had been passaged 3–6 times for this experiment. Flow cytometric analysis characterized the cell-surface markers of these cells as CD14−, CD3−, CD106 (vascular cell adhesion molecule-1)− and CD54 (intercellular adhesion molecule-1)−. This profile is consistent with that previously reported (18).

**Cytokines and antibodies**

IL-6 was provided by Ajinomoto (Kawasaki, Japan), sIL-6R by Tosoh (Kanagawa, Japan), TNF-α by Hayashibara Biochemical Laboratory (Okayama, Japan), humanized anti-IL-6 mAb (rhPM-1) (19) by Chugai Pharmaceutical (Shizuoka, Japan) and mouse anti-gp130 mAb (gpx22) (20) by Tosoh. Anti-TNF-α mAb was purchased from R & D Systems (Minneapolis, MN), irrelevant polyclonal human IgG from Midorijuji (Osaka, Japan) and purified mouse IgG1 (MOPC21) from ICN (Costa Mesa, CA).

**Cell proliferation assay**

Cells were cultured hexacately (3×10³ cells/200 µl/well) with or without TNF-α (1–10 ng/ml), IL-6 (1–100 ng/ml) and/or sIL-6R (1–100 ng/ml) in 96-well flat-bottomed culture plates (Costar, Cambridge, MA) for 5 days. DNA synthesis was measured by liquid scintillation counting after the last 2 day label with 18.5 kBq/well of [³H]thymidine of a 5 day culture and the non-adherent cells were removed. Adherent fibroblastic cells were considered to be synovial cells and we used cells which had been passaged 3–6 times for this experiment. Flow cytometric analysis characterized the cell-surface markers of these cells as CD14−, CD3−, CD106 (vascular cell adhesion molecule-1)− and CD54 (intercellular adhesion molecule-1)−. This profile is consistent with that previously reported (18).

**IL-6–sIL-6R inhibit synovial cell proliferation**

**Table 1. Clinical features and medication of patients with RA**

<table>
<thead>
<tr>
<th>Sample</th>
<th>Age/sex</th>
<th>C-reactive protein (mg/dl)</th>
<th>Rheumatoid factor (IU)</th>
<th>BSG (mm/h)</th>
<th>Concomitant therapya</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA-1</td>
<td>61/M</td>
<td>3.8</td>
<td>78</td>
<td>53</td>
<td>SD</td>
</tr>
<tr>
<td>RA-2</td>
<td>53/F</td>
<td>2.9</td>
<td>84.5</td>
<td>66</td>
<td>PRD, SD</td>
</tr>
<tr>
<td>RA-3</td>
<td>67/F</td>
<td>1.5</td>
<td>27</td>
<td>104</td>
<td>SSP, DP, PRD, SD</td>
</tr>
<tr>
<td>RA-4</td>
<td>54/F</td>
<td>2.8</td>
<td>65.2</td>
<td>78</td>
<td>BUC, PRD, SD</td>
</tr>
<tr>
<td>RA-5</td>
<td>64/F</td>
<td>5.6</td>
<td>1550</td>
<td>20</td>
<td>BUC, GST, PRD, SD</td>
</tr>
<tr>
<td>RA-6</td>
<td>59/F</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>RA-7</td>
<td>70/F</td>
<td>4.7</td>
<td>78.3</td>
<td>88</td>
<td>BUC, PRD, SD</td>
</tr>
<tr>
<td>RA-8</td>
<td>70/F</td>
<td>0.8</td>
<td>161</td>
<td>63</td>
<td>MTX, PRD</td>
</tr>
</tbody>
</table>

*SD, sodium diclofenac; PRD, prednisolone; SSP, sulphasalazine; DP, d-penicillamine; BUC, bupivacaine; GST, gold sodium thiomalate; MTX, methotrexate.

![Diagram](image.png)
gels containing ethidium bromide, visualized by UV light and proliferation, we examined the relation between them. However, ACCACCTTCTTG-3/H11032 CT-3/H11032/ACCACCTTCTTG-3/H11032.

\[ \text{TTC-3} \]

(1319)

\[ \text{regimen of 30 s of denaturation at 94}^\circ \text{C and 30 s of extension/synthesis at 72}^\circ \text{C, for 25 cycles for IL-6R and for 18 cycles for GAPDH. The nucleotide sequence of ited it in a dose-dependent manner at a concentration of} \]

\[ \text{TTC-3} \]

(1319) below with a DNA thermal cycler, Gene Amp PCR system 2400 The effects of IL-6 and sIL-6R on the proliferation of synovial cells

polymerase (Toyobo, Osaka, Japan), 10 nmol of each dNTP, cDNA derived from 200 ng of total RNA, 1.25 U of rTaq DNA Growth inhibitory effect of IL-6 and sIL-6R were 100 ng/ml respectively.

dConcentration of anti-IL-6R mAb was 25 µg/ml.

\[ \text{Measurement of culture supernatant IL-6 and sIL-6R} \]

Cells were cultured (1.5×10⁴ cells/500 µl/well) in a 48-well flat-bottomed culture plate (Costar) for 1 or 3 days. Culture supernatants were collected and filtered by a 0.22 µm filter unit (Millipore, Bedford, MA), and IL-6 concentration was measured by means of a chemiluminencescence enzyme immunoassay system (Lumipulse 1200, sensitivity 0.2 pg/ml; Fujirebio, Tokyo, Japan). sIL-6R concentration was measured by ELISA (sensitivity 3.5 pg/ml; R & D Systems).

Statistical analysis

Statistical analysis was performed by Student’s t-test for the inhibitory effect of IL-6–sIL-6R complex on the proliferation of synovial cells which were stimulated with or without TNF-α and for the elimination of the inhibitory effect by anti-IL-6R antibody or anti-gp130 antibody.

Results

Growth inhibitory effect of IL-6–sIL-6R complex on fibroblastic synovial cells

The effects of IL-6 and sIL-6R on the proliferation of synovial cells were first examined. Representative data from RA-1 are shown in Fig. 1. Although IL-6 alone had no effect on the proliferation of synovial cells, a combination of IL-6 and sIL-6R inhibited it in a dose-dependent manner at a concentration of >1 ng/ml of IL-6 (Fig. 1A). This inhibitory effect was also dependent on the concentration of sIL-6R (1–100 ng/ml), and maximum effect (76% inhibition) was obtained with the combination of binding IL-6R or 5 µg/ml of IL-6 (Fig. 1B). Of the eight RA cases we examined, a combination of IL-6 and sIL-6R inhibited the synovial cell growth in seven (63 ± 24% inhibition, mean ± SD, n = 7) (Table 2). There is no difference in cell viability and apoptosis between groups with and without IL-6–sIL-6 inhibited by the Trypan blue exclusion and the TUNEL method (data not shown). Since medications, clinical characteristics and disease activities might have influenced the synovial cell proliferation, we examined the relation between them. However, there was no correlation between the inhibitory effect and med-

Table 2. Proliferation of synovial cells of patients with RA

<table>
<thead>
<tr>
<th>Sample</th>
<th>[³H]thymidine uptake [mean c.p.m. ± SD (SI)]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controla</td>
</tr>
<tr>
<td>RA-1</td>
<td>11489 ± 426</td>
</tr>
<tr>
<td>RA-2</td>
<td>5323 ± 347</td>
</tr>
<tr>
<td>RA-3</td>
<td>11241 ± 795</td>
</tr>
<tr>
<td>RA-4</td>
<td>1412 ± 81</td>
</tr>
<tr>
<td>RA-5</td>
<td>3576 ± 456</td>
</tr>
<tr>
<td>RA-6</td>
<td>1442 ± 249</td>
</tr>
<tr>
<td>RA-7</td>
<td>4597 ± 387</td>
</tr>
<tr>
<td>RA-8</td>
<td>1303 ± 287</td>
</tr>
</tbody>
</table>

aSI (stimulation index) = [³H]thymidine uptake with indicated reagent/control uptake.
bConcentration of anti-IL-6R mAb was 25 µg/ml.
cConcentration of IL-6 and sIL-6R were 100 ng/ml respectively.
dConcentration of TNF-α was 10 ng/ml.

γ1k respectively, in conjunction with phycoerythrin-labeled streptavidin as described before (22). Cells (2×10⁵) from single-cell suspensions were incubated with 500 ng of mAb for 20 min on ice, washed in PBS with 10% FCS and 0.1% NaN₃, and incubated with the appropriate second-stage reagents. Iso-type-matched γ1k mAb with irrelevant specificity was used as negative control. Flow cytometric analysis was performed on a FACScan (Becton Dickinson, Mountain View, CA) calibrated with fluorescent CaliBRITE beads using AutoCOMP software (Becton Dickinson). Data were obtained with CellQuest software (Becton Dickinson).

RT-PCR assay

RNA was prepared by using TRIzol (Life Technologies, Grand Island, NY) according to the manufacturer’s instructions. Briefly, 1 µg of total RNA was reverse transcribed with 200 U of MMLV reverse transcriptase (Promega, Madison, WI), 0.5 µg of oligo(dT) primer, 10 nmol of each dNTP and 20 U of RNase inhibitor in 20 µl at 37°C for 60 min and denatured at 90°C for 5 min. PCR was performed in 50 µl of reaction solution containing cDNA derived from 200 ng of total RNA, 1.25 U of Taq DNA polymerase (Toyobo, Osaka, Japan), 10 nmol of each dNTP, and 0.5 nmol of sense and antisense primers pairs shown below with a DNA thermal cycler, Gene Amp PCR system 2400 (Perkin-Elmer, Norwalk, CT). PCR cycles were operated on a regimen of 30 s of denaturation at 94°C, 30 s of primer annealing at 60°C and 30 s of extension/synthesis at 72°C, for 25 cycles for IL-6R and for 18 cycles for GAPDH. The nucleotide sequence of the sense primer for IL-6R was 5’-CATTGCCATTGTCTGAGGGTTC-3’ (1580–1601 nucleotides of the cDNA) for membrane binding IL-6R or 5’-CCAGGAGGAGGTCCGGGCAAGG-3’ (1319–1339 nucleotides of the cDNA) for sIL-6R, that of the antisense primer for IL-6R was 5’-AGTACTGGTATTGCTGATGTC-3’ (1809–1830 nucleotides of the cDNA), the sense primer for GAPDH was 5’-GTATTACTGCTGATTGCTGATGTC-3’ (1415–438 nucleotides of the cDNA) and that of the sense primer for sIL-6R was 5’-AGCGCTGTGCCTACCCACTTCTG-3’ (834–857 nucleotides of the cDNA). PCR products were separated by electrophoresis on 2.5% agarose gels containing ethidium bromide, visualized by UV light and photographed.

\[ \text{[3H]thymidine uptake with indicated reagent/control uptake.} \]

α(10 ng/ml) in a 48-well flat-bottomed culture plate (Costar) for 1 or 3 days. Culture supernatants were collected and filtered by a 0.22 µm filter unit (Millipore, Bedford, MA), and IL-6 concentration was measured by means of a chemiluminencescence enzyme immunoassay system (Lumipulse 1200, sensitivity 0.2 pg/ml; Fujirebio, Tokyo, Japan). sIL-6R concentration with anti-gp130 antibody.

\[ \text{anti-gp130 antibody.} \]

\[ \text{anti-foil} \]

\[ \text{anti-gp130 antibody.} \]

\[ \text{anti-gp130 antibody.} \]

\[ \text{anti-gp130 antibody.} \]

\[ \text{anti-gp130 antibody.} \]

\[ \text{anti-gp130 antibody.} \]
IL-6–sIL-6R inhibit synovial cell proliferation

Fig. 2. IL-6 and TNF-α compete in the growth stimulatory effect on RA synovial cells. (A) DNA synthesis in the cells cultured with or without TNF-α (1–10 ng/ml), IL-6 (1–100 ng/ml) and/or sIL-6R (100 ng/ml) was determined by measuring [3H]thymidine uptake. Representative data from RA-4 are shown in these figures. Comparison of mean values were performed using Student’s t-tests. NS, not significant; *P < 0.0001. Each bar indicates the value of [3H]thymidine uptake (c.p.m.) on day 5 averaged from six wells and error bars represent the SD. TNF-α-induced synovial cell growth was inhibited by the IL-6–sIL-6R complex at every TNF-α concentration. sIL-6R alone also showed some inhibitory effect on TNF-α-induced synovial cell growth. (B) Kinetic study for the DNA synthesis of RA synovial cells was performed on day 3, 5, 7 and 9 with (1) TNF-α (10 ng/ml), (2) TNF-α (10 ng/ml) and IL-6 (100 ng/ml), (3) TNF-α (10 ng/ml) and sIL-6R (100 ng/ml), (4) TNF-α (10 ng/ml), IL-6 (100 ng/ml) and sIL-6R (100 ng/ml), (5) TNF-α (10 ng/ml), IL-6 (100 ng/ml) and sIL-6R (100 ng/ml), (6) IL-6 (100 ng/ml), sIL-6R (100 ng/ml), and (7) without reagents. Each bar indicates the value of [3H]thymidine uptake (c.p.m.) averaged from six wells and error bars represent the SD. Comparisons of mean values were performed using Student’s t-tests. NS, not significant; *P < 0.0001.

Expression of IL-6R on synovial cells

In order to identify the IL-6R and gp130 expression by the synovial cells, we first performed flow cytometric analysis using mAb specific to these receptor components. Cell-surface IL-6R was not detectable in any cases, while gp130 was always detected on the synovial cells, although both IL-6R and gp130 were strongly detected on the human myeloma cell line, U266, as a positive control (Fig. 4). Similar FACS profiles of IL-6R and gp130 expression were obtained from all eight cases. Next, we used ELISA to examine whether sIL-6R was secreted in the culture supernatant of synovial cells, but no significant amount of sIL-6R was detected. Thirdly, RT-PCR analysis, however, revealed that most of the synovial cells expressed only a small amount of IL-6R including the transmembrane region which was ~100th of that expressed by U266 (Fig. 5), which contain a large quantity of IL-6R (11,000 sites per cell) (27) and show an autocrine growth mechanism mediated by IL-6 (28). At the same time, a very small quantity of truncated transcript, which had lost a membrane portion as a result of alternative splicing and was to be translated to sIL-6R, was observed when we used an appropriate combination of primer pairs (data not shown). These findings indicate that synovial cells express gp130, but not much IL-6R or sIL-6R so that they require exogenous sIL-6R to transduce the IL-6 signal. In RA-2, whose synovial cell growth was not inhibited by exogenous IL-6 and sIL-6R but increased by anti-IL-6R antibody treatment, a relatively larger amount of IL-6R was detected by RT-PCR, while no
IL-6 production by synovial cells

To determine the possible contribution of endogenous IL-6 to growth inhibition, production of IL-6 in culture supernatant was examined. Synovial cells produced considerable amounts of IL-6 (2.02 ± 1.31 ng/ml on day 3, n = 8) without any stimulation. Furthermore, TNF-α (10 ng/ml) augmented IL-6 secretion (34.4 ± 29.8 ng/ml on day 3, n = 8) from synovial cells as was previously reported (29,30). The enhanced production of endogenous IL-6 by TNF-α can explain the observation that additional sIL-6R alone showed some inhibitory effect on synovial cell growth in the presence of TNF-α (Fig. 2). Therefore, endogenous IL-6 can also contribute to the growth inhibition of synovial cells.

Discussion

It was demonstrated in our study that IL-6 in the presence of sIL-6R inhibited the proliferation of synovial cells without any increase in cell death in seven out of eight RA patients. Furthermore, endogenous IL-6 produced by the synovial cells seemed to inhibit their own growth because anti-IL-6R mAb treatment increased their DNA synthesis in all cases. Our observation contradicts the one previously reported by Mihara et al. (21), i.e. that IL-6 induced synovial cell growth. It is not clear why there was such a different response. Since the stimulatory activity of IL-6 reported was observed in only one of three cases they examined (C. Mihara, pers. commun.), it might have been an exception. Furthermore, when we re-examined the same synovial cell sample provided by Mihara, IL-6 with sIL-6R acti-

Table 3. IL-6 secretion by synovial cells of patients with RA

<table>
<thead>
<tr>
<th>Sample</th>
<th>IL-6 concentration (pg/ml) in the culture supernatant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
</tr>
<tr>
<td></td>
<td>TNF-α (-)</td>
</tr>
<tr>
<td>RA-1</td>
<td>1317 ± 126</td>
</tr>
<tr>
<td>RA-2</td>
<td>1780 ± 151</td>
</tr>
<tr>
<td>RA-3</td>
<td>1119 ± 89</td>
</tr>
<tr>
<td>RA-4</td>
<td>1781 ± 146</td>
</tr>
<tr>
<td>RA-5</td>
<td>443 ± 26</td>
</tr>
<tr>
<td>RA-6</td>
<td>787 ± 38</td>
</tr>
<tr>
<td>RA-7</td>
<td>1807 ± 126</td>
</tr>
<tr>
<td>RA-8</td>
<td>1015 ± 100</td>
</tr>
</tbody>
</table>

\(^a\)TNF-α (+) = synovial cells were cultured in the presence of 10 ng/ml of TNF-α.

Data represent the mean value observed in three individual cell cultures of each group (± SD).
in synovial cells. Therefore, exogenous sIL-6R was required to analysis could demonstrate a small amount of IL-6R transcript fl α fi

An intracellular signal of IL-6 may cause cell cycle arrest. Quite IL-6R IL-6 receptor whether the growth inhibition was caused by IL-6-induced programmmed cell death. However, no loss of cell viability or increase in apoptosis was found after IL-6–sIL-6R treatment. An intracellular signal of IL-6 may cause cell cycle arrest. Quite recently, Taniguchi et al. have demonstrated the expression of p16INK4a, which induced the cell cycle arrest in RA synovial fibroblast (31). IL-6 may induce p16INK4a expression. The intracellular mechanism of IL-6–sIL-6R to inhibit the synovial cell proliferation should be elucidated in future experiments.

Next, we wish to address the relation between IL-6 and TNF-α in the pathophysiology of RA. It was demonstrated that murine anti-IL-6 mAb treatment reduced the activity of RA (5). TNF-α induced IL-6 secretion from synovial cells in vitro (29,30) and chimeric anti-TNF-α antibody (cA2) was also found to be therapeutically effective for RA, resulting in the normalization of serum IL-6 levels during treatment with cA2 (32,33). Therefore, Feldmann et al. hypothesized a cytokine cascade in which TNF-α was placed upstream from IL-6 in RA pathogenesis and caused abnormalities through IL-6 (34). However, we demonstrated that IL-6 and TNF-α had an opposite effect at least on the proliferation of fibroblastic synovial cells. In addition, Alonzi et al. reported DBA/1J, IL-6−/− mice were completely protected from collagen-induced arthritis by inactivation of the IL-6 gene, while arthritis in TNF-α transgenic mice was not affected (35). This demonstrates that IL-6 does not always act as a mediator of TNF-α in the cytokine cascade of RA development. Since TNF-α induces the secretion of IL-6 from synovial cells and IL-6 in turn negatively controls the TNF-α function which augments the proliferation of synovial cells, IL-6 may act as a negative feedback factor in TNF-α-induced synovial cell growth. This feedback mechanism can partly explain the in vivo phenomenon that synovial tissue grows slowly in RA affected joints. Then, the question of how blockade of the IL-6 signal could demonstrate a therapeutic effect needs to be addressed. Recently, we reported the histological improvement by the administration of the humanized anti-IL-6R mAb in a RA animal model established by an engraft of RA synovial tissue into severe combined immunodeficiency mice (36). Anti-IL-6R mAb treatment markedly reduced the number of inflammatory cells especially in the pannus portion. These findings, together with the data presented here, suggest that the therapeutic effect of the blockade of the IL-6 signal is achieved through modulating the function of inflammatory cells rather than through direct regulation of synovial cell growth. Elimination of inflammatory cells may then cause a reduction of TNF-α production in the synovium and may consequently decrease synovial cell proliferation. Immunological responses in RA are regulated by a complex network of many factors such as cytokines, the soluble form of cytokine receptors, chemokines, proteases and prostaglandins. Further study is required to understand the interactions of these factors which result in failure to appropriately regulate immunological responses in RA.

**Acknowledgements**

We thank Mrs Chieko Aoki, Mrs Kaori Nakahara, Mr Noriyuki Danno and Mrs Ritsuko Ōkamoto for their excellent technical assistance, and Ms Takako Nakao for her outstanding secretarial assistance.

**Abbreviations**

<table>
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<tr>
<th>gp130</th>
<th>glycoprotein 130</th>
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<tr>
<td>IL-6R</td>
<td>IL-6 receptor</td>
</tr>
<tr>
<td>OA</td>
<td>osteoarthritis</td>
</tr>
<tr>
<td>RA</td>
<td>rheumatoid arthritis</td>
</tr>
<tr>
<td>rhPM-1</td>
<td>recombinant humanized anti-IL-6R mAb</td>
</tr>
<tr>
<td>sIL-6R</td>
<td>soluble form of IL-6 receptor</td>
</tr>
<tr>
<td>TNF</td>
<td>tumor necrosis factor</td>
</tr>
<tr>
<td>TUNEL</td>
<td>TdT-mediated dUTP-biotin nick end-labeling</td>
</tr>
</tbody>
</table>
References


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