Evidence for two distinct pathways in TNFα-induced membrane and soluble forms of ICAM-1 in human osteoblast-like cells isolated from osteoarthritic patients

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Summary

Objective: The present study aimed to investigate the modulation of membrane-bound intercellular adhesion molecule-1 (mICAM-1) and soluble ICAM-1 (sICAM-1) expression by tumor necrosis factor-alpha (TNFα) in human osteoarthritic (OA) osteoblasts.

Methods: Cultured human primary osteoblasts were stimulated with increasing concentrations of human recombinant TNFα. Expression of mICAM-1 and sICAM-1 was evaluated by immunocytochemistry, enzyme-linked immunosorbent assay and semi-quantitative reverse transcriptase-polymerase chain reaction. In addition, we investigated the molecular mechanisms underlying ICAM-1 induction by TNFα, focusing on the activation of the mitogen-activated protein kinases (MAPKs) and nuclear factor-kappaB (NF-κB) pathways.

Results: Our data showed that TNFα dose-dependently increased mICAM-1 and sICAM-1 expression at the protein and mRNA levels in OA osteoblasts. The inhibitor of de novo mRNA synthesis, actinomycin D, suppressed TNFα-induced mICAM-1 and sICAM-1 expression. Upon examination of the signaling components, we found that TNFα was a potent activator of p38, p44/42, p54/46 MAPK, and IkappaBalpha (IκBα). The chemical inhibitors of p38, p44/42 MAPK, and NF-κB blocked TNFα-induced mICAM-1 expression but not that of sICAM-1. Transfection experiments revealed that p38 MAPK or IkappaB kinase alpha (IKKα) overexpression enhanced TNFα-induced mICAM-1 production. Furthermore, osteoblasts treatment with a chemical inhibitor of metalloproteinase-9 (MMP-9) activity, a proteolytic enzyme involved in ICAM-1 cleavage, evoked a significant 25% decrease of TNFα-induced sICAM-1 release.

Conclusion: Taken together, these findings illustrate the central role played by TNFα in the regulation of ICAM-1. We suggest that TNFα differentially regulates sICAM-1 and mICAM-1 expression and that sICAM-1 release involves, in part, the proteolytic cleavage of mICAM-1 by MMP-9. The capacity of the MMP-9 inhibitor to prevent sICAM-1 production may be useful for the development of novel therapeutic approaches relevant to OA.

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Key words: ICAM-1, Osteoarthritis, Bone, Cytokines, MMP-9.
epithelial cells. A soluble form of ICAM-1 (sICAM-1) is also detected in the serum of normal individuals, and elevated levels are found during various pathological conditions, including inflammatory, immune and malignant diseases. However, the role of sICAM-1 and its mode of production remain elusive. Controversy still surrounds the exact origin of sICAM-1. In some cell types, proteolytic cleavage from membrane-bound ICAM-1 (mICAM-1) has been proposed as a mechanism for the generation of sICAM-1, and its presence would therefore reflect membrane expression of the protein. On the other hand, some researchers have identified a specific mRNA coding for sICAM-1 in cells, suggesting that at least two modes of sICAM-1 production exist.

In bone metabolism, ICAM-1 exerts important osteotropic effects by mediating cell–cell adhesion of osteoblasts and osteoclast precursors, thereby facilitating osteoclast differentiation and bone resorption. Furthermore, it has been shown that osteoblasts adhere to opposing cells through ICAM-1, VCAM-1 and LFA-3, resulting in the activation of intracellular signals and leading to the production of bone-resorbing cytokines, such as TNFα, IL-1β and IL-6. Interestingly, ICAM-1 expression and sICAM-1 release from cells are increased by these cytokines, which are found to be major contributors to bone diseases. Abnormal sICAM-1 levels in bone diseases have been reported solely in rheumatoid arthritis so far, but no direct role has been attributed in the pathogenesis of this disease. Our group has demonstrated the induction of intracellular signaling in pre-osteoclast cells after incubation with sICAM-1 (study in progress), indicating a possible active role for sICAM-1 in osteoclast-dependent diseases. Although widely reported in other cell types, less attention has been paid to the regulation of mICAM-1 expression and sICAM-1 production in osteoblasts.

Therefore, the aim of this study was to demonstrate the effect of the bone-resorbing cytokine TNFα on mICAM-1 and sICAM-1 expression in human osteoblasts isolated from OA patients. We also wanted to examine whether sICAM-1 is cleaved from the membrane of osteoblasts by a proteolytic cleavage mechanism. We believe that clarifying the modulation and production of mICAM-1 and sICAM-1 in the bone environment could lead to a better understanding of their respective roles in bone pathology.

Materials and methods

**IN VITRO OSTEOBLAST CULTURE**

Trabecular bone specimens were collected from patients suffering from advanced OA and undergoing primary total knee replacement (n = 36). The diagnosis was established according to American College of Rheumatology criteria. The experimental protocol was approved by the Research Ethics Board at Sacré-Cœur Hospital. Bone specimens were taken within 5 mm of the subchondral bone plate. Every specimen was harvested from the most damaged portion of the tibial plateau. Osteoblast cultures were prepared as already described.

Briefly, trabecular bone samples were cut into small pieces of 2 mm³ prior to their sequential digestion in the presence of 1 mg/ml collagenase type I (Sigma–Aldrich, Oakville, ON, Canada) in BGMb media (Invitrogen Life Technologies, Burlington, ON, Canada) without serum at 37°C for 30, 30, and 240 min. After being washed with the same media, the digested bone pieces were cultured in 25 cm² plastic cell culture flasks (Corning Incorporated - Life Sciences, Acton, MA, USA) with BGMb medium containing 20% fetal bovine serum (PBS) (Invitrogen Life Technologies). This medium was replaced every 2 days until cell outgrowth appeared around the explants. It was demonstrated that cells obtained under these culture conditions had an osteoblast-like cell phenotype. At confluence, the cells were split once and plated at 50,000 cells/cm² in culture plates (Falcon, Lincoln Park, NJ, USA) with Ham’s F12/Dulbecco’s modified Eagle medium (HAFM12/DMEM; Sigma–Aldrich) containing 10% FBS plus 50 µg/ml ascorbic acid, and grown to confluence again. Only first-passage cells were used in our experiments.

**ENZYME-ASSOCIATED IMMUNOSORBENT ASSAY (ELISA)**

First-passage trabecular osteoblasts were incubated in 0.5% FBS/HAFM12/DMEM for 48 h with increasing concentrations of TNFα (0–10 ng/ml). After incubation, the culture medium was collected, and sICAM-1 level was quantified with a specific commercial kit from R&D Systems (Minneapolis, MN, USA), according to the manufacturer’s instructions. The sensitivity of the assays was 3 pg/ml. Each ELISA was performed in duplicate according to the manufacturer’s specifications. Protein level in the cell lysates was measured by the bicinchoninic acid method.

**IMMUNOCYTOCHEMICAL STAINING**

Cellular surface ICAM-1 expression was analyzed by immunocytochemical staining. Osteoblasts (5 × 10⁴) were transferred to eight-well culture chamber slides (Lab-Tek, Nalge Nunc International, Naperville, IL, USA), and incubated for 16 h without or with 1 ng/ml TNFα (R&D Systems). Afterwards, the cells were washed twice with phosphate buffered saline (PBS) and fixed for 15 min at room temperature with PBS containing 10% formaldehyde (Tissuefix, Labokone Laboratories, Acton, MA, USA). In our experiments, we have used different dilutions of the anti-mICAM antibody 1:100, 1:500, 1:1000, and 1:2000 with or without 1 ng/ml TNFα (R&D Systems). The cells were washed three times with PBS, the cells were incubated for 30 min in a DAKO antibody diluent buffer containing mouse monoclonal anti-ICAM-1 antibody (DAKO, Carpinteria, CA, USA). In our experiments, we have used different dilution of the anti-mICAM antibody 1:100, 1:500, 1:1000, and 1:10,000. The optimal dilution of the antibody obtained in our experiments was 1:1000. Each ELISA was performed in duplicate according to the manufacturer’s specifications. Protein level in the cell lysates was measured by the bicinchoninic acid method.

**SEMI-QUANTITATIVE REVERSE TRANSCRIPTASE-POLYMERASE CHAIN REACTION (RT-PCR)**

Total RNA was extracted from the treated or untreated osteoblasts using TRIzol reagent (Invitrogen Life Technologies), according to the manufacturer’s instructions. RT-PCR was performed in a Thermocycler (Waterman, Biometra Gmbh, Göttingen, Germany) with 1 µg of total RNA. These assays were undertaken with enzymes and reagents of the SuperScript one-step RT-PCR kit manufactured by Invitrogen Life Technologies. Each RT-PCR consisted of cDNA synthesis for 30 min at 42°C and denaturation for 5 min at
95°C, followed by an amplification cycle consisting of a denaturation step of 45 s at 95°C and an annealing/elongation step of 60 s at 55°C. For the last cycle, the elongation step was prolonged to 10 min at 72°C. Primers for the detection of mICAM-1 and sICAM-1 were based on those described previously by Wakatsuki et al.\textsuperscript{23} The sequences of the forward primer used to detect mICAM-1 and sICAM-1 were: 5'-CAA GGG GAG GTC ACC CGC GAG GTG-3' and 5'-CAA GGG AGG TCA CCC GCG AGC C-3'. Both primers were combined with a common reverse primer having the following sequence: 5'-TGC AGT GCC CAT TAT GAC TG-3'. The sequences for GAPDH, which served as a positive control, were 5'-CACCCATGGCAAATCCATGGCA-3' (forward) and 5'-TCTAGACGGCAGTCAQGGTCCAQCC-3' (reverse) (BioCorp Inc., Montreal, QC, Canada).

RT-PCR products were separated on 2% agarose gel and stained with ethidium bromide solution (10 ng/ml). Semi-quantitative measurements were made by taking densitometric readings of each band in a digital imaging system (G-image 2000, Canberra Packard Canada, Mississauga, ON, Canada). cDNA relative units for ICAM-1 were normalized to that of glyceraldehyde-6-phosphate dehydrogenase (GAPDH). The data were expressed as percentages of the non-treated control value\textsuperscript{25}.

WESTERN BLOTTING

Briefly, 20 μg of cellular protein extract were subjected to 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis under reducing conditions and transferred onto nitrocellulose membrane (Bio-Rad, Hercules, CA, USA). The membranes were immersed for 3 h in a blocking solution consisting of TTBS (Tris 20 mM, pH 7.4, NaCl 137 mM, 0.1% Tween 20) and 5% skim milk, and washed twice with TTBS for 15 min. They were then incubated overnight in TTBS containing 0.25% skim milk, polyclonal rabbit anti-phospho-p38, anti-phospho-p44/42, anti-phospho-p54/52 (Cell Signaling Technology), then washed again. Immunoreactive proteins were visualized with LumiGLO (1:1000, Cell Signaling Technology), then washed again. The membranes were prepared for autoradiography and exposed to Kodak X-Omat film (Eastman Kodak Ltd., Rochester, NY, USA).

PROTEIN KINASES, NUCLEAR FACTOR-KAPPAB (NF-κB), AND MMP-9 INHIBITION

Osteoblasts were pre-incubated for 60 min with actinomycin D (ActD) (RNA polymerase II inhibitor), MAPK inhibitors (PD98059 and SB202190), NF-κB inhibitor (PDTC), or MMP-9 inhibitor I (Calbiochem, San Diego, CA, USA). The membranes were washed three times with TTBS, and incubated for 1 h at 22°C with the second antibody anti-rabbit IgG-HRP (1:1000, Cell Signaling Technology), then washed again. Immunoreactive proteins were visualized with Lumiglo Chemiluminescent substrate (Cell Signaling Technology). The membranes were prepared for autoradiography and exposed to Kodak X-Omat film (Eastman Kodak Ltd., Rochester, NY, USA).

STATISTICAL ANALYSIS

The results are expressed as means ± S.E.M. All assays were performed in duplicate. Statistical significance was assessed by Student’s t test, and P < 0.05 was considered significant.

RESULTS

We first examined the presence of TNFα levels in osteoblast cultures to be certain that endogenous production would not influence ICAM-1 expression. TNFα could not be detected in the cell culture supernatant, even with a high-sensitivity ELISA kit (data not shown). However, the addition of increasing concentrations of TNFα to osteoblasts significantly enhanced mICAM-1 and sICAM-1 production [Fig. 1(A and B)]. These results were confirmed at the mRNA level in OA osteoblasts where, again, dose-dependent increases of mICAM-1 and sICAM-1 were observed after TNFα stimulation, correlating with the protein expression pattern [Fig. 1(C)].

Immunostaining of osteoblasts with ICAM-1 antibody revealed that this protein was expressed at basal levels in unstimulated cells with a mean ± S.E.M. of 29 ± 6% (n = 3 experiments) [Fig. 2(A)]. In the presence of 1 ng/ml TNFα (16 h of incubation), the percentage of positively-stained osteoblasts increased significantly with a mean ± S.E.M. of 87 ± 9% (n = 3 experiments) [Fig. 2(B)]. Staining specificity was confirmed by substitution of the primary mICAM-1 antibody with an autologous preimmune serum [Fig. 2(C)]. Incubation of osteoblasts with 1 ng/ml TNFα for different incubation periods revealed that the effect on mICAM-1 surface expression was time-dependent as heightened surface expression was apparent as early as 4 h after exposure to TNFα, with a maximal effect at 16 h (results not shown).

Next, we demonstrated that TNFα increased mICAM-1 and sICAM-1 mRNA levels required de novo mRNA synthesis, by pre-incubating osteoblasts with ActD before adding 10 ng/ml TNFα (Fig. 3). The expression of both mICAM-1
Osteoarthritis and Cartilage Vol. 15, No. 3

![Graph A](image.png)

**Fig. 1.** (A) Effects of TNFα on mICAM-1 expression. OA osteoblasts were incubated for 18 h in the absence or presence of the indicated concentrations of TNFα (n = 6). Then, mICAM-1 expression was evaluated by immunocytochemical staining using a specific anti-mICAM-1 antibody. Data are expressed as the percentage of positive osteoblasts and are means ± S.E.M.. (B) Effects of TNFα on sICAM-1 release. OA osteoblasts (n = 3) were incubated for 48 h in the absence or presence of the indicated concentrations of TNFα. Then, sICAM-1 production was evaluated by ELISA. The data were expressed as pg/mg protein and are means ± S.E.M.. (C) Representative semi-quantitative RT-PCR gel for ICAM-1 mRNA analysis. The cells were incubated for 1 h in the absence or presence of the indicated concentrations of TNFα. The experiment was completed with 1 μg RNA for each test and 35 cycles of PCR for ICAM-1 and 25 cycles of PCR for the internal positive control, GAPDH. The gel is representative of three independent experiments. mRNA levels (arbitrary units) were then quantified by densitometry. mICAM-1 and sICAM-1 levels were normalized against those of GAPDH mRNA and expressed as a percentage of untreated cells. Statistical analysis was performed by Student’s t-test. P values are compared to the corresponding value for cells incubated in the absence of TNFα. *P < 0.05, **P < 0.01, ***P < 0.001.

**Discussion**

ICAM-1 has previously been reported to be involved in osteoclast differentiation and bone resorption. In a co-culture system of mouse spleen cells and osteoblasts or stromal cells, cellular interaction through ICAM-1 could be blocked by anti-CD54 monoclonal antibodies, which resulted in decreased osteoclast formation in vitro. Further, a previous study by our group showed that ICAM-1 levels were normalized against those of GAPDH mRNA and expressed as a percentage of untreated cells. Statistical analysis was performed by Student’s t-test. P values are compared to the corresponding value for cells incubated in the absence of TNFα. *P < 0.05, **P < 0.01, ***P < 0.001.
expression on human osteoblasts obtained from OA or osteoporotic patients was higher when compared to normal human osteoblasts. Also, IL-6 and PGE_2 levels in supernatant were found to be elevated with high ICAM-1 expression. Several studies have demonstrated increased bone remodeling and osteoclast activity in OA. Biphosphonates, drugs known to inhibit osteoclasts, and licofelone, a COX inhibitor capable of lowering IL-6 and PGE_2 levels, have been seen to reduce osteoclast activity in the setting of OA. Because of the role of ICAM-1 in osteoclast recruitment, its differential expression in diseases such as OA, and the increased osteoclast activity observed in OA, the understanding of the modulation of ICAM-1 expression and the mechanisms regulating it in OA bone could offer new potential therapeutic targets in OA.

So far, no study has looked at the expression and intracellular signaling of mICAM-1 and sICAM-1 in human osteoblasts. As demonstrated in our investigation, stimulation of osteoblasts with TNF_α increased mICAM-1 and sICAM-1 expression at the protein and mRNA levels. It is noteworthy that sICAM-1 mRNA expression in response to TNF_α occurs at a higher concentration (100-fold) than that of mICAM-1. However, it is possible to detect, in the extracellular milieu, a significant elevation of sICAM-1 after treatment with TNF_α.

Fig. 2. Representative immunocytochemical staining of mICAM-1 expression. Osteoblasts were incubated for 16 h in the absence (A) or presence of TNF_α at 1 ng/ml (B). Then, cell surface ICAM-1 expression was evaluated by immunocytochemical staining with antibodies specific for this protein, or substitution of primary antibody mICAM-1 with autologous preimmune serum as a control of staining specificity (C). mICAM-1-positive cells were detected with diaminobenzidine, and nuclei were counterstained with Hematoxylin (see Materials and methods, original magnification 400×). Immunocytochemistry data represent three independent experiments.

Fig. 3. TNF_α-induced ICAM-1 required de novo mRNA synthesis. Human OA osteoblasts were pre-incubated for 1 h with 10 μg/ml ActD, followed by another incubation for 4 h with 10 ng/ml TNF_α. One microgram of total RNA was processed for RT-PCR analysis to determine the mRNA levels of mICAM-1 (A), sICAM-1 (C), and GAPDH, as described in Materials and methods. Protein levels of mICAM-1 (B) and sICAM-1 (D) were determined by immunocytochemical staining and ELISA. The data are expressed as in the Fig. 1 legend (n = 3). Statistical analysis was performed by Student’s t test. *P values are compared to the corresponding value for cells incubated in the absence of TNF_α. **P < 0.001.
with TNFα at a much lower concentration. This could simply reflect increased cleavage of already present mICAM-1 that is initiated at low TNFα concentration. However, if this were true, sICAM-1 levels would remain high with combined incubation of TNFα and ActD. Furthermore, in contrast to mICAM-1, sICAM-1 levels are not influenced by protein kinase inhibitors. Taken together, these results suggest that there are two separate pathways for the generation and regulation of mICAM-1 expression and sICAM-1 production in human OA osteoblasts.

Our data seem to be in accordance with those of Wakatsuki et al. who reported a specific mRNA coding for sICAM-1. We observed the presence of sICAM-1 mRNA splice in human osteoblasts using the specific primers of Wakatsuki et al. The meaning of this finding in bone remains to be defined. However, in various inflammatory and malignant pathological conditions, increased expression of sICAM-1 indicates a possible reciprocal relationship between sICAM-1 and inflammation. However, the relationship between circulating and membrane-bound ICAM-1 is controversial. Some studies report a similar physiological role for these two molecules, whereas others describe opposite actions. We can only postulate whether sICAM-1 inhibits cellular adhesion or promotes the effect of mICAM-1 in bone metabolism. An anti-osteoclastogenic role for sICAM-1 would place it in the same category as osteoprotegerin (OPG), while a pro-osteoclastogenic role would potentially act in the same manner as soluble receptor activator of nuclear factor-kappaB ligand (sRANKL). Although the exact role of sICAM-1 remains elusive, we believe that increased mICAM-1 expression in response to TNFα stimulation could facilitate the interaction of osteoblasts with osteoclast precursors.

TNFα, a pleiotropic cytokine primarily produced by activated macrophages and T-lymphocytes, has a wide range of biological effects, including inflammation, mitogenesis, differentiation, immune modulation and anti-tumor immunity. TNFα is also considered to be one of most important cytokines implicated in osteoporosis, arthritis and wear debris-induced osteolysis. It supports the differentiation and survival of osteoclasts, but not resorption activity. The ability of osteoblasts to express adhesion molecules, such as

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**Fig. 4.** Time course of the effect of TNFα on cell signaling pathways. Human OA osteoblasts were treated with 10 ng/ml TNFα for the indicated times. Total cell lysates (approximately 20 μg) were prepared and subjected to Western blot analysis with the phosphospecific antibodies anti-phospho-p38 MAPK (n = 3), anti-phospho-p44/42 MAPK (n = 3), anti-phospho-p54/46 MAPK (n = 3), or anti-phospho-IκBα (n = 3).

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**Fig. 5.** Effect of protein kinase inhibitors and NF-κB inhibitor on TNFα-induced ICAM-1. The cells were pre-incubated for 30 min with different chemical inhibitors: (A) SB202190 (a p38 MAPK inhibitor), (B) PD98059 (a p44/42 MAPK inhibitor), and (C) PDTC (a NF-κB inhibitor), followed by another incubation for 24 h in the presence or absence of 10 ng/ml TNFα. Values are expressed as % of TNFα-treated osteoblasts (n = 4). Statistical analysis was performed by Student’s t test. P values are compared to the corresponding value for cells incubated in the absence of TNFα. *P < 0.05, **P < 0.01.
ICAM-1, in addition to their ability to produce and respond to different cytokines, such as TNF-α, IL-1β, IFN-γ, transforming growth factor-beta (TGFβ), and IL-6, suggests that osteoblasts can function as modulators and/or effectors of inflammatory processes and osteoclastogenesis. We believe that the osteoclastogenic action of these cytokines is, at least in part, modulated through ICAM-1.

Our results disclosed that the induction of ICAM-1 expression could be prevented by co-incubation with ActD (an inhibitor of RNA transcription). This means that the induction of ICAM-1 expression requires de novo mRNA synthesis, indicating its regulation at the transcriptional level. Investigations into the signal transduction pathways of TNF-α showed rapid and significant phosphorylation of p38, p44/42, p54/46 MAPK as well as IκBα. Next, we tested the effects of MAPK- and NF-κB-specific inhibitors on TNF-α-induced mICAM-1. Our data revealed that all chemical inhibitors, SB202190, PD98059 and PTDC, abrogated TNF-α-induced mICAM-1 protein expression. Interestingly, these chemical products failed to inhibit sICAM-1 upregulation by TNF-α. Furthermore, the overexpression of WT p38 MAPK and IKKα enhanced TNF-α-induced mICAM-1. These results were supported by other recent studies indicating that TNF-α is a potent inducer of ICAM-1 in various cell types. It has been reported that the activation of p38 MAPK and NF-κB appears necessary for the regulation of ICAM-1 expression. In the ICAM-1 promoter, numerous cis-elements have been identified to exert transcriptional control of ICAM-1. Among these elements, NF-κB and activator protein 1 (AP-1) were shown to act as the most critical of these regulatory elements for ICAM-1 transcription. Mutation in the AP-1 and NF-κB sequence attenuates pro-inflammatory cytokine-stimulated ICAM-1 promoter activity. While increased sICAM-1 levels can be attributed to its transcriptional regulation, another mechanism has been considered crucial in sICAM-1. This mechanism includes the proteolytic cleavage of mICAM-1 by MMPs. To investigate it, osteoblasts were co-treated with 10 nM of an inhibitor of MMP-9 and 10 ng/ml TNF-α. We observed that the addition of MMP-9 inhibitor I significantly reduced TNF-α-enhanced sICAM-1 expression, which was consistent with other reports. Other inhibitors of MMP-9, such as Batimastat, have been shown to inhibit TNF-α-induced mICAM-1 cleavage in primary glial cells. Further experiments using a specific antibody for splice variant-derived sICAM-1 (relative to conventional cell surface ICAM-1) will be performed to investigate the relationship between ICAM-1 and MMP-9.

**Conclusion**

This study reports an increase in ICAM-1 expression after the exposure of human osteoblasts to TNF-α. This heightened expression appears to be mediated through activation of MAPK and IKKα cascades. Further, the regulation of sICAM-1 includes two mechanisms: (1) shedding/cleavage of conventional cell surface ICAM-1 protein by MMP-9, and (2) de novo synthesis from a specific coding mRNA. It is well-known that ICAM-1 has a close relationship with inflammation, and TNF-α has many effects in producing inflammatory responses. Therapeutic approaches have been taken to induce anti-inflammatory effects by blocking the ICAM-1 or TNF-α-dependent pathway with a neutralizing antibody. In bone disease, blockage of the interaction between TNF-α and ICAM-1 may inhibit not only inflammation in the joint but also bone resorption by suppressing the
osteoblast-mediated formation of osteoclasts. These findings could have clinical implications in the future treatment of bone loss diseases, such as osteoporosis, arthritis and aseptic loosening.

Acknowledgments

We thank Drs M. Karin and R.J. Davis, respectively, for their generous gifts of IKKα and p38 MAPK expression plasmids. This study was supported by Fonds de la recherche en santé du Que´bec and Stryker-Howmedica Osteonics. Dr Fernandes is a research scholar of the FRSQ.

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