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Short communication

Downregulation of microsomal prostaglandin E synthase-1 (mPGES-1) expression in chondrocytes is regulated by MAP kinase phosphatase-1 (MKP-1)

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ABSTRACT

Objectives: Microsomal prostaglandin E synthase-1 (mPGES-1) catalyses the formation of PGE_2 in inflammatory tissues. It is considered a potential drug target in inflammatory conditions to achieve clinical benefits comparable to NSAIDs with a better tolerability. Inhibitors of mPGES-1 are under development but the pharmacological regulation of mPGES-1 expression remains poorly known. MAP kinase phosphatase-1 (MKP-1) is an enzyme that limits the activity of pro-inflammatory MAP kinases p38 and JNK. In the present study, we discovered that dexamethasone down-regulates mPGES-1 expression in articular chondrocytes in an MKP-1 and p38 kinase dependent manner.

Methods: Primary human chondrocytes were isolated from cartilage samples obtained from osteoarthritis (OA) patients undergoing knee replacement surgery. Primary mouse chondrocytes were isolated from cartilage samples of MKP-1 deficient (knock-out, KO) and corresponding wild type (WT) mice. Expression of mPGES-1 and MKP-1 were measured by quantitative reverse transcription polymerase chain reaction (qRT-PCR) and Western blot, and MAP kinase phosphorylation by Western blot.

Results: Dexamethasone inhibited the expression of mPGES-1 in primary human chondrocytes and in chondrocytes from wild type but not from MKP-1 deficient mice. Dexamethasone enhanced MKP-1 expression in chondrocytes from wild type mice as well as in primary human OA chondrocytes. Dexamethasone induced the dephosphorylation of both p38 and JNK, whereas mPGES-1 expression was downregulated by selective inhibitors of p38 only.

Conclusions: The results show that MKP-1 is a crucial mediator of pharmacological control of inflammatory mPGES-1 expression by glucocorticoids, and underline MKP-1 as a potential anti-inflammatory drug target.

1. Introduction

Prostaglandin E_2 (PGE_2) belongs to prostanoids, which are produced from arachidonic acid in virtually all cell types. PGE_2 has various physiological functions but it also plays an essential role as a pro-inflammatory mediator. Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit prostanoid production through their effects on the cyclo-oxygenase enzymes (both the constitutive COX-1 and the inducible COX-2). Cyclo-oxygenases catalyse the production of prostaglandin endoperoxides, which are subsequently transformed to PGE_2 and other prostanoids by specific prostanoid synthases. The use of NSAIDs in the treatment of various inflammatory conditions is principally based on their ability to reduce excessive PGE_2 production. However, when COX enzymes are inhibited, the production of physiologically important prostanoids other than PGE_2 is also reduced. This is the proposed mechanism behind the known adverse effects of NSAIDs, for instance increased risk of myocardial infarction and renal insufficiency [1].

Transformation of prostaglandin endoperoxides to PGE_2 is catalyzed by three enzymes: microsomal prostaglandin E synthase-1 (mPGES-1), microsomal prostaglandin E synthase-2 (mPGES-2) and cytosolic prostaglandin E synthase (cPGES). mPGES-1 is an inducible enzyme and its expression is significantly enhanced in inflammation, whereas the two other enzymes are constitutively expressed and assumed responsible for the physiological PGE_2 production [2,3].

The expression of mPGES-1 is increased in cartilage/chondrocytes from osteoarthritis (OA) patients, as well as in synovia from patients

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with rheumatoid arthritis (RA) [4,5]. The incidence and histopathological severity of arthritis was found to be attenuated in mPGES-1 deficient (knock-out, KO) mice compared to wild type (WT) mice in experimentally induced inflammatory arthritis [6]. Therefore, mPGES-1 can be considered as a promising target to develop "NSAID-like" drugs with improved safety for the treatment of arthritis and related conditions. Inhibitors of mPGES-1 are under investigation but less is known about pharmacological control of mPGES-1 expression.

Mitogen-activated protein (MAP) kinase pathways, particularly p38 and JNK, play an evident role to activate inflammatory responses and accordingly, they have been investigated as drug targets in various types of arthritis [7]. MAP kinase phosphatase-1 (MKP-1) is an enzyme that dephosphorylates and thus inactivates p38 and JNK MAP kinases and subsequently limits inflammatory responses in various cells and tissues. Accordingly, the incidence and severity of experimentally induced arthritis are pronounced in mice lacking MKP-1 [8].

In the present study, we investigated the role of MKP-1 in the regulation of mPGES-1 expression in chondrocytes by using activated primary chondrocytes from MKP-1 KO and corresponding WT mice. To translate the results to human context, we studied the effects of dexamethasone on MKP-1 and mPGES-1 expression and MAP kinase phosphorylation in primary human OA chondrocytes, and investigated the effects of MAP kinase inhibitors on mPGES-1 expression.

2. Materials and methods

2.1. Mouse chondrocytes

WT and MKP-1 (−/−) C57BL/6 mice originally generated in the laboratory of R. Bravo at Bristol-Myers Squibb Pharmaceutical Research Institute (Princeton, NJ, USA) were used [9]. Animal experiments were carried out in accordance with the legislation for the protection of animals used for scientific purposes (Directive 2010/63/EU), and the study was approved by the National Animal Experiment Board.

After the mice were euthanized, full-thickness articular cartilage from the femoral heads was removed and chondrocytes were isolated by enzymatic digestion o/n without agitation at 37 °C in 5% CO_2 with Collagenase D enzyme (3 mg/ml, Collagenase D, Sigma-Aldrich, St. Louis, MO, USA), according to the protocol by Jonason et al. [10]. Isolated chondrocytes were plated on 24-well plates (2.0×10^5 cells/ml) in Dulbecco's Modified Eagle's Medium (DMEM, Sigma-Aldrich) supplemented with penicillin (100 U/ml), streptomycin (100 µg/ml) and amphotericin B (250 ng/ml, all from Gibco/Life Technologies, Carlsbad, CA, USA) containing 10% fetal bovine serum (Lonza, Verviers, Belgium), and cultured for seven days before conducting the experiments. During experiments, the cells were treated with IL-1β (R&D Systems Europe, Abingdon, UK) and/or dexamethasone (Orion Corp., Espoo, Finland), and the expression of mPGES-1 and MKP-1 were measured at indicated time points.

2.2. Human OA chondrocytes

The study was approved by the Ethics Committee of Tampere University Hospital, Finland and carried out in accordance with the declaration of Helsinki. Written informed consent was obtained from the patients. Leftover pieces of cartilage from knee replacement surgery from OA patients were processed and cells isolated as previously described [11]. Chondrocytes were plated on 24-well plates (2.0×10^5 cells/ml) in DMEM (Sigma-Aldrich) supplemented with penicillin (100 U/ml), streptomycin (100 µg/ml) and amphotericin B (250 ng/ml, all from Gibco/Life Technologies), containing 10% fetal bovine serum (Lonza), and cultured for 24 h before conducting the experiments. During the experiments, the cells were treated with IL-1β (R&D Systems Europe Ltd., Abingdon, UK) and dexamethasone (Orion Corp., Espoo, Finland), SB203580 (p38 inhibitor; Sigma-Aldrich), BIRB796 (p38 inhibitor; Axon MedChem, Groningen, The Netherlands), SP600125 (JNK inhibitor; Sigma-Aldrich) and/or JNK inhibitor VIII (Calbiochem, Darmstadt, Germany), and the expression of mPGES-1 and MKP-1 were measured at indicated time points.

2.3. RNA extraction and quantitative reverse transcription polymerase chain reaction (qRT-PCR)

At the indicated time-points, the culture medium was removed, and the cells were homogenized and the RNA was extracted using GenElute™ Mammalian Total RNA Miniprep Kit (Sigma Aldrich) according to the manufacturer's instruction. Reverse transcription of RNA to cDNA was performed by TaqMan Reverse Transcription Reagents (Applied Biosystems, Foster City, CA, USA). Primers and probes were purchased from Metabion (Martinsried, Germany). Their sequences and concentrations were optimized according to the manufacturer's guidelines in TaqMan Universal PCR Master Mix Protocol part number 4304449 revision C (Applied Biosystems). The primer and probe sequences for mouse genes were as follows: mPGES-1 CCTGGATACATT TCCTCGTTGTC (forward, 300 nM), GAAGGCGTGGGTTCAGCTT (reverse, 300 nM) and ACAGGCCGTGTGGTACACACCG (probe, 150 nM); mouse MKP-1 CTCCTGGTTCAACGAGGCTATT (forward, 300 nM), TGCCGGCCTGGCAAT (reverse, 300 nM) and TGCCGGCCTGGCAAT (probe, 150 nM); mouse GAPDH GCATGGCCTTCCGTGTTC (forward, 300 nM), GATGTCATCATACTTGGCAGGTTT (reverse, 300 nM) and TCGTGGATCTGACGTGCCGCC (probe, 150 nM). The primer and probe sequences for human genes were as follows: mPGES-1 CACGCTGCTG GTCATCAAGA (forward, 300 nM), CCGTGTCTCAGGGCATCCT (reverse, 300 nM) and AGCCTCACTTGGCCCGTGATG (probe, 150 nM); MKP-1 ACGAGGCCATTGACTTCATAGAC (forward, 300 nM), TCGATT AGTCCTCATAAGGTAAGCAA (reverse, 300 nM) and CCACTGCCAGGC AGGCATTTCC (probe, 150 nM); GAPDH AAGGTCGGAGTCAACGGA TTT (forward, 300 nM), GCAACAATATCCACTTTACCAGAGTTAA (reverse, 300 nM) and CGCCTGGTCACCAGGGCTGC (probe, 150 nM).

2.4. Western blot

Preparation of cell lysates and the Western blot analysis were carried out as described previously [12]. Following antibodies were used in the Western blot analysis: mPGES-1 antibody (AS-03031; Agrisera AB, Vännäs, Sweden); polyclonal goat anti-rabbit (sc-2004), actin (sc-1616) and JNK antibody (#9251; Santa Cruz Biotechnology, CA, USA), MKP-1 antibody (SAB2500331; Sigma-Aldrich), p38 MAPK antibody (ab27986; Abcam, Cambridge, UK), phospho-p38 MAPK (#9211) and phospho-JNK antibody (#9251; Cell Signaling Technology, Beverly, MA, USA).

2.5. Statistics

Results are expressed as mean + standard deviation (sd). Data were analyzed with GraphPad InStat version 3.10 for Windows. *t*-test and ANOVA with Bonferroni's post-test were used in the statistical analysis. Differences were considered significant at $P < 0.05$.

3. Results

The expression of mPGES-1 was strongly enhanced in chondrocytes from WT as well as MKP-1 deficient mice when IL-1β was introduced to the culture (Fig. 1A). In the cells from WT mice, dexamethasone distinctly inhibited mPGES-1 expression whereas in the cells from MKP-1 KO mice dexamethasone did not have any statistically significant effect, indicating that MKP-1 mediates the downregulation of mPGES-1 expression by dexamethasone in chondrocytes. Moreover, in unstimulated chondrocytes from MKP-1 deficient mice, mPGES-1 expression was higher than in chondrocytes from WT mice (Fig. 1B), which supports the concept that MKP-1 regulates mPGES-1 expression in chondrocytes.

Next, we investigated the effect of dexamethasone on MKP-1

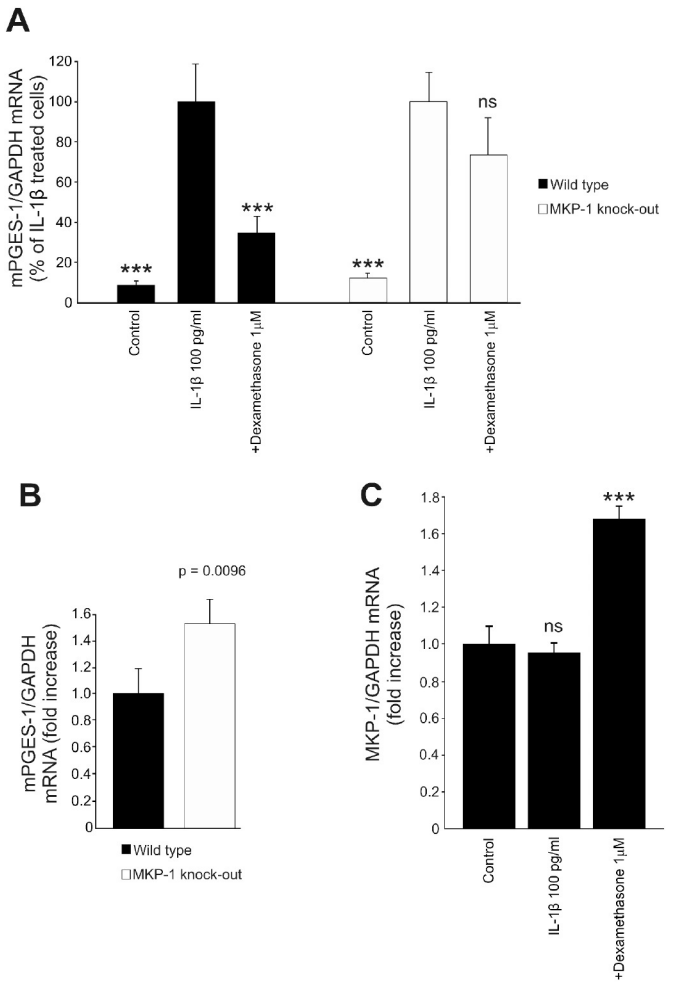

Fig. 1. A) Effect of dexamethasone on mPGES-1 expression in IL-1β-stimulated primary chondrocytes from wild-type and MKP-1 deficient (knock-out) mice. Chondrocytes from wild-type and MKP-1 knock-out mice were stimulated with IL-1β and incubated in the presence or absence of dexamethasone for 24 h. mPGES-1 mRNA levels were measured by quantitative RT-PCR and normalized against GAPDH levels. Mean expression level of mPGES-1 in IL-1β-stimulated cells was set as 100% and the other values were related to that. The results are expressed as mean + sd, n = 9–13. One-way ANOVA with Bonferroni's post-test was performed and statistical significance is indicated as $***P < 0.001$ and ns = not significant as compared to the in IL-1β-stimulated cells.
B) Baseline expression of mPGES-1 in unstimulated primary chondrocytes from wild-type and MKP-1 deficient (knock-out) mice. The expression of mPGES-1 mRNA was measured by quantitative RT-PCR and normalized against GAPDH mRNA. The mean expression of mPGES-1 in cells from wild-type mice was set as 1.0 and the mPGES-1 expression in MKP-1 knock-out mice was compared to that. The results are expressed as mean + sd, n = 7–9. Data were analyzed by using unpaired *t*-test and the actual *p* value between the groups is given in the Figure.
C) Effect of dexamethasone on MKP-1 expression in IL-1β-stimulated primary chondrocytes from wild-type mice. Chondrocytes from wild-type mice were stimulated with IL-1β and incubated with dexamethasone for 90 min. MKP-1 mRNA levels were measured by quantitative RT-PCR and normalized against GAPDH mRNA levels. Mean MKP-1 expression level in the unstimulated cells was set as 1.0 and the other values were related to that. The results are expressed as mean + sd, n = 5. One-way ANOVA with Bonferroni's post-test was performed and statistical significance is indicated as $***P < 0.001$ and ns = not significant as compared to the unstimulated control cells.

expression in the chondrocytes. Incubation with dexamethasone showed a significant increase in MKP-1 expression in chondrocytes from WT mice (Fig. 1C), which effect has been shown earlier in other cell types [12,13]. In order to translate this finding to human cells, we investigated the effect of dexamethasone in primary chondrocytes from patients with OA. As shown in Fig. 2, the expression of MKP-1 mRNA (Fig. 2A) and protein (Fig. 2B) was increased by dexamethasone in the presence and absence of IL-1β. Subsequently, dexamethasone inhibited mPGES-1 mRNA and protein expression in IL-1β-stimulated human OA chondrocytes in a dose-dependent manner (Fig. 2C).

MKP-1 has been shown to limit the phosphorylation of MAP kinases p38 and JNK in many cell types [8]. To confirm the situation in OA chondrocytes, we determined the effects of dexamethasone on the phosphorylation of these MAP kinases in primary human OA chondrocytes. Dexamethasone did not affect the phosphorylation of p38 or JNK in unstimulated cells, in which the phosphorylation level of MAP kinases was generally low. By contrast, IL-1β induced a strong phosphorylation of both p38 and JNK kinases and that was attenuated by dexamethasone treatment (Fig. 2D) supporting the functional significance of the observed increase in MKP-1 expression. To gain evidence on the role of MAP kinase activation in mPGES-1 expression, we tested if the selective inhibitors of p38 or JNK pathways could inhibit the expression of mPGES-1 in IL-1β-stimulated human OA chondrocytes. In these studies, two different p38 inhibitors (SB203580 and BIRB796) inhibited mPGES-1 expression whereas the inhibitors of JNK pathway (SP600125 and JNK inhibitor VIII) were ineffective (Fig. 2E).

4. Discussion

PGE_2 plays a notable role in the pathophysiology of rheumatic diseases, as it induces the production of degradative enzymes and cytokines in the cartilage in addition to its sensitizing effects in sensory nerves to augment pain and its proinflammatory functions in synovium [14,15]. mPGES-1, as a terminal PGE_2 producing enzyme, has been indicated as an essential drug target in animal models of inflammatory arthritis, where selective inhibitors of mPGES-1 have been effective in attenuating the signs and symptoms of inflammation, along with their inhibitory effect on PGE_2 production [16]. In addition to the decreased PGE_2 production, genetic deletion of mPGES-1 has been shown to alter the distribution of other prostanoids and non-prostanoid lipid mediators in a tissue-dependent manner, which is believed to provide another potential anti-inflammatory mechanism for pharmacological inhibition or down-regulation of mPGES-1 [17].

In the present study, we found that dexamethasone decreases mPGES-1 expression in human articular chondrocytes, most likely through enhanced expression of MKP-1 and subsequent dephosphorylation and inactivation of p38 kinase. Increased phosphorylation of p38 is especially linked to the pathophysiology of arthritis [18]. Previous studies have shown that p38 mediates the production of degradative MMP enzymes and inflammatory factors in human chondrocytes [11,19] and it has been proposed as a target of disease modifying drugs in RA and OA [20]. The present study shows that p38 inhibitors suppress mPGES-1 expression in human OA chondrocytes, and that glucocorticoids induce MKP-1 expression and p38 dephosphorylation introducing that as a mechanism to regulate mPGES-1 expression in chondrocytes in inflammatory conditions.

Signaling pathways and transcription factors involved in mPGES-1 upregulation are not known in detail [3]. Involvement of MAP kinase pathways in the regulation of mPGES-1 expression has been studied previously, and disruption of p38 pathway was suggested to inhibit mPGES-1 expression in IL-1β-stimulated human chondrocytes [4], which is in agreement with our current results. However, other MAP kinase pathways have also been suggested to participate in the regulation of mPGES-1 expression in other cell types [12,21], which indicates a cell-type dependent specificity of MAP kinase phosphorylation as a regulator of mPGES-1 expression. It is as well likely that there are other, still elusive, signaling pathways mediating mPGES-1 expression in chondrocytes.

In conclusion, our results show that the downregulating effect of dexamethasone on mPGES-1 expression in chondrocytes is mediated by

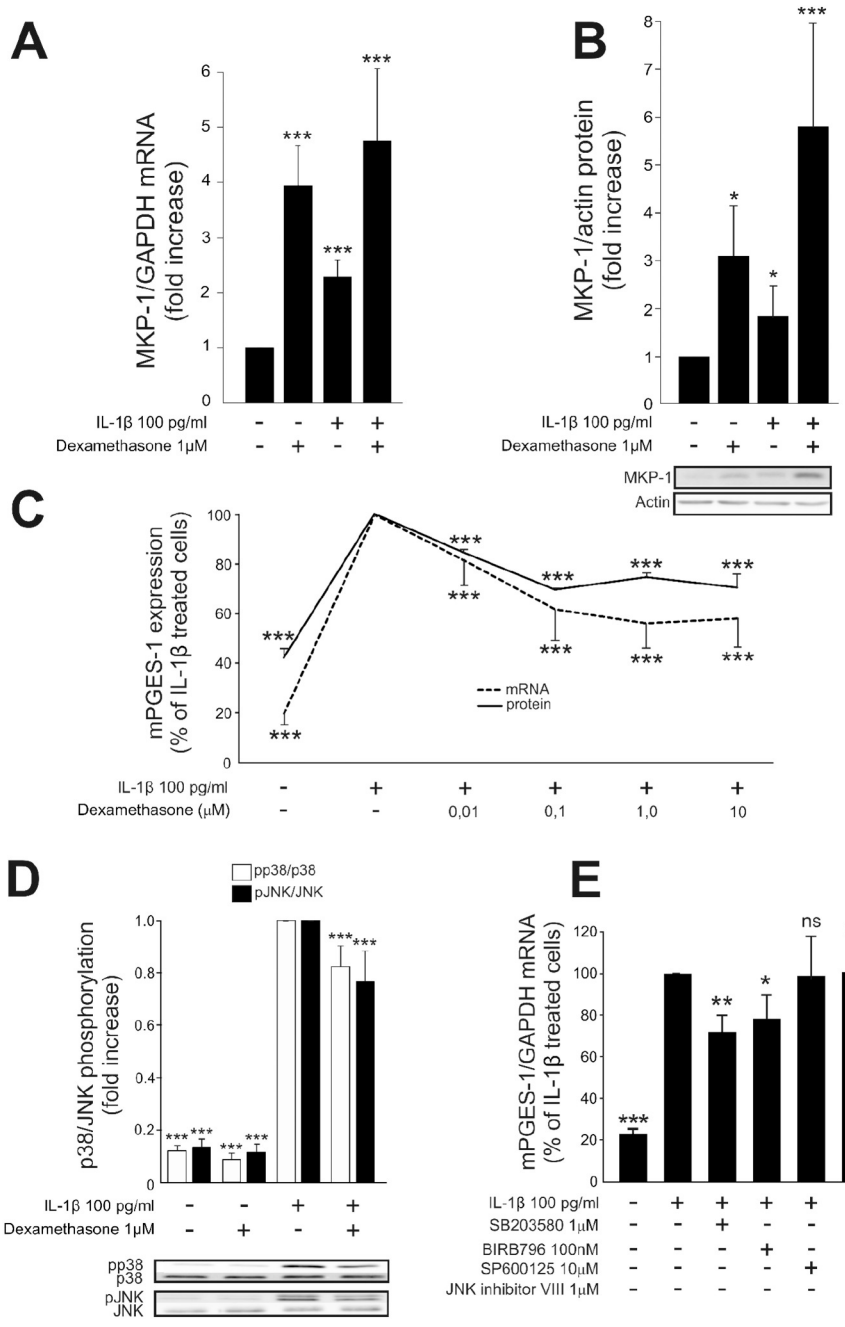

Fig. 2. A) Effect of dexamethasone on MKP-1 mRNA expression in primary human OA chondrocytes. Unstimulated and IL-1β-stimulated chondrocytes were incubated with or without dexamethasone for 90 min. MKP-1 mRNA levels were measured by quantitative RT-PCR and normalized against GAPDH levels. Mean MKP-1 expression in the unstimulated cells was set as 1 and the other values were related to that. The results from five (n = 5) patients were combined and the experiments were carried out in duplicate. The results are expressed as mean + sd. Repeated measures ANOVA with Bonferroni's post-test was performed and statistical significance is indicated as $***P < 0.001$ as compared to the unstimulated control samples.

B) Effect of dexamethasone on MKP-1 protein expression in primary human OA chondrocytes. Unstimulated and IL-1β-stimulated chondrocytes were incubated with or without dexamethasone for 90 min. MKP-1 protein expression was measured by Western blot and normalized against actin levels. Mean MKP-1 expression in the unstimulated cells was set as 1 and the other values were related to that. The results from six (n = 6) patients were combined and the experiments were carried out in duplicate. The results are expressed as mean + sd. Repeated measures ANOVA with Bonferroni's post-test was performed and statistical significance is indicated as $***P < 0.001$ and $*P < 0.05$ as compared to the unstimulated control samples.

C) Dose-dependent effect of dexamethasone on mPGES-1 mRNA and protein expression in primary human OA chondrocytes. The primary chondrocytes were stimulated with IL-1 β and treated with increasing concentrations of dexamethasone for 24 h (mRNA) or 48 h (protein). Mean expression of mPGES-1 in IL-1β-stimulated cells was set as 100% and the other values were related to that. The results are expressed as mean + sd. The results from six (mRNA, n = 6) and seven (protein, n = 7) patients were combined and the experiments were carried out in duplicate. Repeated measures ANOVA with Bonferroni's post-test was performed and statistical significance is indicated as $***P < 0.001$ as compared to the IL-1β-stimulated cells.

D) Effect of dexamethasone on the phosphorylation of MAP kinases p38 and JNK in IL-1β-stimulated primary human OA chondrocytes. The cells were preincubated with dexamethasone for 60 min and stimulated with IL-1β for 30 min. The protein levels of phosphorylated p38 (pp38) and phosphorylated JNK (pJNK) were measured by Western blot and normalized against the levels of total p38 (p38) and total JNK (JNK), respectively. Results are expressed in arbitrary units where the ratio between phosphorylated and total MAP kinase levels in IL-1β-stimulated cells was set as 1.0 and the other values were related to that. The results from eight (p38, n = 8) or seven (JNK, n = 7) patients were combined and the experiments were carried out in duplicate. The results are expressed as mean + sd. Repeated measures ANOVA with Bonferroni's post-test was performed and statistical significance is indicated as $***P < 0.001$ as compared to the IL-1β-stimulated cells.

E) Effects of selective MAP kinase inhibitors on mPGES-1 expression in IL-1β-stimulated primary human OA chondrocytes. The cells were stimulated with IL-1 β and treated with selective inhibitors of p38 (SB203580 and BIRB796) or JNK (SP600125 and JNK inhibitor VIII)) for 24 h. Mean expression of mPGES-1 in IL-1β-stimulated cells was set as 100% and the other values were related to that. The results are expressed as mean + sd. The results from five patients (n = 5) were combined and the experiments were carried out in duplicate. Repeated measures ANOVA with Bonferroni's post-test was performed and statistical significance is indicated as $***P < 0.001$, $**P < 0.01$, $*P < 0.05$ and ns = not significant as compared to the IL-1β-stimulated cells.

enhanced MKP-1 expression and subsequent dephosphorylation of MAP kinase p38. MKP-1 also appears to mediate the baseline expression of mPGES-1 in chondrocytes. These findings increase our knowledge about the mechanisms regulating mPGES-1 expression and underline the role of MKP-1 as an anti-inflammatory drug target.

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Conflict of interest

None.

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