Inhibition by Interleukin-10 of Inducible Cyclooxygenase Expression in Lipopolysaccharide-Stimulated Monocytes: Its Underlying Mechanism in Comparison With Interleukin-4

By Hironori Niimi, Takeshi Otsuka, Tadashi Tanabe, Shuntaro Hara, Yoshiaki Nemoto, Youseke Tanaka, Hitoshi Nakashima, Shigetaka Kitajima, Masayoshi Abe, and Yoshiyuki Niho

Both interleukin-10 (IL-10) and IL-4 inhibited the prostanooid synthesis of lipopolysaccharide (LPS)-stimulated human monocytes and their inhibition was shown to be based on a common mechanism to suppress the gene expression of inducible cyclooxygenase (COX). COX has been shown to exist in at least two distinct isoforms, designated COX-1 and COX-2, and their gene expressions exhibit different profiles. At both the protein and mRNA levels, the expression of COX-1 was constitutive and was not modulated by treatments with LPS, IL-10, or IL-4. In contrast, the expression of COX-2 was observed only after stimulation with LPS. IL-10 and IL-4 significantly inhibited LPS-induced COX-2 expression. Kinetic studies showed that they inhibited COX-2 mRNA expression within 1 hour after stimulation and that maximal inhibition was consistently observed at 5 hours. Moreover, the addition of cycloheximide (CHX) to LPS-stimulated monocytes resulted in a superinduction of COX-2 mRNA, whereas CHX almost abrogated the abilities of IL-10 and IL-4 to inhibit this gene expression. Experiments with actinomycin D showed that both cytokines accelerated the degradation of COX-2 mRNA. Furthermore, nuclear run-on experiments showed that both cytokines modestly inhibited LPS-induced COX-2 gene transcription. Thus, both cytokines seemed to regulate the COX-related pathway in a similar manner, although their receptor systems did not show any structural similarities. Considering recent findings showing that the drugs that exhibit a selective effect on COX-2 may be more preferable in inflammatory conditions, such biologic activities of IL-10 and IL-4 described above may offer useful tools in controlling inflammatory disorders in the future.

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isoforms described above, we have focused this study on the regulation by IL-10 of the expression of these isoforms in human monocytes and further compared its effect with that of IL-4.

MATERIALS AND METHODS

Reagents. Fetal bovine serum (FBS) and RPMI-1640 were purchased from Gibco (Grand Island, NY) and Nissui Chemical Co (Tokyo, Japan), respectively. RPMI-1640 supplemented with supplements (10%), glutamine (1mmol/L), penicillin (100 U/mL), and Kanamycin (80 μg/mL) was used for the experiments except for instances noted. LPS from Escherichia coli 011:B4, purified by the Westphal method, was from Difco (Detroit, MI). Actinomycin D (Act D), cycloheximide (CHX), and AA were obtained from Sigma (St Louis, MO). [³H]AA was obtained from New England Nuclear (Boston, MA). Human rIL-4 was kindly provided by Dr K.W. Moore (DNAX, Palo Alto, CA). Human rIL-10 was generously provided by Schering-Plough Research (Bloomfield, NJ). Human rIL-4 was kindly provided by Dr K.W. Moore (DNAX, Palo Alto, CA). The anti–COX-1 antibody was a polyclonal rabbit antihep antibody (Oxford Biomedical Research, Inc, Oxford, MI) that reacts with human COX-1 but does not cross-react with human COX-2. The anti–COX-2 antibody was a polyclonal rabbit antihuman antibody (Cayman Chemical Co, Ann Arbor, MI) that was found to be highly specific. The antibody did not cross-react with human COX-1 and it had no apparent cross-reactivity against other human cell proteins.

Isolation and culture of human monocytes. Human peripheral blood monocytes were isolated from freshly drawn blood from healthy donors with anti-PEC-C. First, mononuclear cells were separated over Ficoll-Hypaque. Subsequently, these mononuclear cells were allowed to adhere to culture dishes for 2 hours and were then washed twice vigorously with warmed phosphate-buffered saline (PBS) to remove nonadherent cells. The remaining adherent cells were greater than 90% nonspecific esterase positive and greater than 99% viable as determined by trypan blue exclusion. These cells were cultured in RPMI-1640 media with 1mmol/L glutamine and 10% FBS at 37°C in a humidified atmosphere with 5% CO₂.

Analysis of AA metabolites from human monocytes labeled with [³H]AA using high-performance liquid chromatography (HPLC). For analysis of AA metabolites, monocytes (2 x 10⁶ cells) labeled with [³H]AA (5 μCi/mL) for 12 hours were incubated with or without IL-10 (500 μU/mL) in the presence of LPS (10 μg/mL) for the final 18 hours. At the end of the incubation, the reaction was terminated by addition of ethanol. The supernatant was diluted with 15% to 30% of methanol and with 10 μL of solubilization buffer at 25°C (1% Tween 20, 10 mmol/L phenylmethylsulfonyl fluoride, and 50 mmol/L Tris·HCl, pH 8.0). Cell lysates were then sonicated for 15 seconds and centrifuged at 15,000 g for 15 minutes. Supernatants were subsequently mixed with 1:1 with sodium dodecyl sulfate (SDS) sample buffer. Equal amounts of protein (25 μg) were then separated on a 9% SDS-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred onto a nitrocellulose membrane. The membrane was then blocked with PBS buffer containing 5% skim milk and 0.1% Tween 20 and then incubated with polyclonal rabbit anti–COX-1 antibody (1:200 dilution) or anti–COX-2 antibody (1:1,000 dilution) in the blocking buffer at 25°C for 2 hours. The membrane was subsequently incubated with alkaline phosphatase-conjugated goat antirabbit IgG (1:10,000 dilution) and analyzed using the Western-Light Chemiluminescent Detection System (Boehringer Mannheim Biochemicals, Indianapolis, IN). Fuji X-omat AR film with cassette closure times of 5 to 10 minutes resulted in adequate exposure to visualize the bands (Fuji Photo Film Co, Tokyo, Japan).

Northern blot analysis. Monocytes (2 x 10⁶ cells) were incubated as described in the text, and total cellular RNA was isolated by the acid guanidium thiocyanate/phenol/chloroform extraction method as described by Chomczynski and Sacchi. Five micrograms of total RNA was fractionated on 1.5% agarose gel containing 2.2 mol/L formaldehyde and were subsequently transferred to a zeta-probe blotting membrane (BioRad, Richmond, CA). Hybridization was performed (overnight at 42°C) in 5X SSPE containing 30% formamide, 5X Denhardt’s solution, 1% SDS, and 0.2 mg/mL of denatured salmon sperm DNA. The filter was washed in 2X SSC, 0.1% SDS at 50°C (twice for 25 minutes each time) followed by 0.5X SSC, 0.1% SDS at 50°C (twice for 15 minutes each time). The CDNA probes used were the 1.5-kb fragment of human COX-2 and the 1.7-kb fragment of human COX-1. Probes were labeled using a random primer labeling kit (Takara Shuzo, Kyoto, Japan) with [³²P]dCTP. All the membranes were reprobed with human β-actin cDNA (Wako, Osaka, Japan). To estimate the relative levels of each mRNA, the filters were exposed to a Fujifilm imaging plate (BAS-III; Fuji Photo Film Co) for 12 hours. The hybridized bands were visualized with the BAS-2000 Bio-image analyzer (Fuji Photo Film Co). Specific COX mRNA was quantified using a densitometric analysis of the signal’s intensities in reference to β-actin mRNA.

Nuclear run-on assay. Monocytes (2 x 10⁶ cells) were incubated for 3 hours with medium, LPS, LPS plus IL-4, or LPS plus IL-10. Cells were collected, treated in 1 mL of NP-40 lysis buffer (10 mmol/L Tris·HCl, pH 7.4, 10 mmol/L NaCl, 3 mmol/L MgCl₂, and 0.5% NP-40) at 4°C for 10 minutes, and their nuclei were pelleted at 500g for 55 minutes. The lysis procedure was repeated twice and the nuclei were resuspended in 100 μL of storage buffer (40% glycerol, 50 mmol/L Tris·HCl, pH 8.3, 5 mmol/L MgCl₂, and 0.1 mmol/L EDTA) and frozen in liquid N₂. Elongation of nascent RNA chains
was initiated by mixing the above nuclear suspension with 100 μL of reaction buffer (50 mmol/L Tris-HCl, pH 8.0, 5 mmol/L MgCl2, 300 mmol/L KCl, and 0.5 mmol/L each of ATP, CTP, and GTP) plus 100 μCi of [α-32P]UTP (Amersham Corp; 3,000 Ci/mmol) and incubated at 37°C for 30 minutes. RNA synthesis was terminated by incubation with 5 μg/mL RNase-free DNase I (Boehringer Mannheim Biochemicals) at 30°C for 10 minutes. The mixture was then digested with proteinase K (200 pg/mL) in 10 mmol/L Tris-HCl, pH 7.4, 5 mmol/L EDTA, and 1% SDS at 50°C for 1 hour and extracted twice with phenol-chloroform after adding SO as a carrier. Radiolabeled RNA was purified by two ethanol precipitations and dissolved in 100 μL of 50% formamide, pH 7.4, 5 mmol/L EDTA, and 1% SDS at 30°C for 3 days. The membranes were washed in reference to those of p-actin.

Denhardt's solution, and 0.1% SDS. Approximately 5 μg of COX-2 and β-actin cDNA probes were immobilized on a zeta-probe blotting membranes were baked at 80°C for 2 hours, prehybridized for at least 3 hours, and hybridized with the hybridized bands were visualized with the BAS-2000 Bio-image analyzer (Fuji Photo Film Co) by using an RIA (Fig 2). As observed in HPLC, IL-10 (10 U/mL) significantly inhibited TXB2 production, whereas it did not affect LTxB2 production. Moreover, Fig 2 also shows that IL-4 (10 U/mL) exerts an effect similar to that of IL-10 on the production of these metabolites. Together with our previous data, these results indicate that IL-10 as well as IL-4 could act at the COX level, thereby inhibiting the synthesis of products of COX pathway, such as TXB2 and PGE2, in monocytes.

Effects of IL-10 and IL-4 on COX activity of human monocytes. To examine whether both IL-10 and IL-4 would affect COX activity of monocytes, the cells were cultured for 18 hours with either IL-10 (10 U/mL) or IL-4 (10 U/mL) in the presence or absence of LPS (100 ng/mL), and COX activity was analyzed. The results are depicted in Fig 3. In the absence of extracellular stimuli such as LPS, monocytes constitutively exhibited a weak but significant COX activity. Neither IL-10 nor IL-4 affected this activity. After activation by LPS, a significant increase in COX activity was observed.

Effects of IL-10 and IL-4 on the protein expression of two COX isoforms in human monocytes. As recently shown, IL-10 and IL-4 significantly decreased the release of products of COX pathway (6-keto-PGF_1α, TXB2, and PGE2), whereas the lipoxygenase products (LTB4 and HETEs) and AA were less affected by IL-10. We further determined the effect of IL-10 on the production of TXB2 and LTxB2 in LPS-stimulated monocytes by using an RIA (Fig 2). As observed in HPLC, IL-10 (10 U/mL) significantly inhibited TXB2 production, whereas it did not affect LTxB2 production. Moreover, Fig 2 also shows that IL-4 (10 U/mL) exerts an effect similar to that of IL-10 on the production of these metabolites. Together with our previous data, these results indicate that IL-10 as well as IL-4 could act at the COX level, thereby inhibiting the synthesis of products of COX pathway, such as TXB2 and PGE2, in monocytes.
monocytes constitutively possessed COX-1 enzyme that consisted of a single major band at approximately 70 kD. Then, the amount of this isoform was unaffected by any treatment with LPS, IL-10, or IL-4. However, in contrast to COX-1, the expression of COX-2 enzyme was not observed constitutively but was drastically induced after activation of monocytes by LPS. This enzyme consisted of a single major band at approximately 74 kD. Then, both IL-10 and IL-4 effectively inhibited the expression of this isoform.

Effects of IL-10 and IL-4 on the gene expression of two COX isoforms in human monocytes. Because the protein expression of two COX isoforms is regulated at the RNA level, we further examined the effects of IL-10 and IL-4 on the accumulation of these mRNAs in human monocytes. Monocytes were cultured with either IL-10 (10 U/mL) or IL-4 (10 U/mL) in the presence or absence of LPS (100 ng/mL), and total RNA was isolated from the cells at 5 hours. The gene expression of both isoforms was then examined by Northern blot analysis. As a result, consistent with the data of Fig 4, the expression of COX-1 mRNA was constitutive and was not modulated by any treatment with either IL-10 or IL-4 in the presence or absence of LPS (data not shown). In contrast to COX-1, there was no constitutive expression of COX-2 mRNA. However, COX-2 mRNA was dramatically induced after stimulation by LPS, and both IL-10 and IL-4 at the concentrations of 10 U/mL significantly inhibited the gene expression of this isoform (Fig 5).

Time-dependent regulation by IL-10 and IL-4 of COX-2 mRNA expression. To determine the kinetics for COX-2 mRNA expression, monocytes were incubated with LPS...
Effects of IL-10 and IL-4 on COX-2 mRNA expression.

(100 ng/mL), LPS plus IL-10 (10 U/mL), or LPS plus IL-4 (10 U/mL) for 1, 3, or 5 hours (Fig 6). As reported previously, the accumulation of COX-2 mRNA was continuously increased for 5 hours after LPS stimulation. The inhibition by IL-10 and IL-4 of COX-2 mRNA expression appeared after 1 hour, and maximal inhibition was consistently observed at 5 hours.

Effects of timing of IL-10 and IL-4 addition on COX-2 mRNA expression. Because simultaneous addition of LPS and 10 U/mL of IL-10 and IL-4 resulted in significant inhibition of COX-2 mRNA expression, we thus examined the effects of IL-10 and IL-4 pretreatment on this gene expression. For this purpose, monocytes were preincubated with 10 U/mL of IL-10 or IL-4 for 6 or 3 hours, washed free of these cytokines, and stimulated with LPS (100 ng/mL) for 5 hours to observe COX-2 mRNA expression. As shown in Fig 7, these treatments inhibited COX-2 mRNA expression by about 50%. We next assessed the abilities of IL-10 and IL-4 to alter COX-2 mRNA expression when added after LPS stimulation. Monocytes were stimulated with LPS (100 ng/mL) for 5 hours, and both cytokines (10 U/mL) were added 1 or 3 hours after LPS stimulation. As shown in Fig 7, later addition of these cytokines to the cultures, after LPS challenge, resulted in less inhibition of COX-2 mRNA expression. Thus, these results indicated that both IL-10 and IL-4 are most potent inhibitors of monocyte COX-2 mRNA expression when added simultaneously with LPS.

Effect of CHX on COX-2 mRNA expression. To investigate whether both IL-10 and IL-4 inhibited monocyte COX-2 mRNA expression through de novo protein synthesis, we assessed the effect of CHX on this gene expression. Monocytes were preincubated with CHX (5 μg/mL) for 1 hour and stimulated for 5 hours with LPS (100 ng/mL), LPS plus IL-10 (10 U/mL), or LPS plus IL-4 (10 U/mL). These data are depicted in Fig 8. The addition of CHX to LPS-stimulated monocytes resulted in a superinduction of COX-2 mRNA, whereas CHX almost abrogated the abilities of IL-10 and IL-4 to inhibit this gene expression. Thus, these results suggest that COX-2 mRNA expression in LPS-stimulated monocytes is susceptible to superinduction by de novo protein inhibitor (CHX) and that both IL-10 and IL-4 may inhibit COX-2 mRNA expression through newly synthesized repressor proteins.

Effects of IL-10 and IL-4 on the stability of COX-2 mRNA. The gene expression is regulated at the transcriptional and/or posttranscriptional levels. The rate of mRNA degradation is an important regulatory mechanism that may control the level of gene expression at the posttranscriptional level. To address the mechanism of inhibitory effects of IL-10 and IL-4 on COX-2 mRNA expression, we examined the effects of both cytokines on the stability of COX-2 mRNA. Monocytes were stimulated with LPS (100 ng/mL), LPS plus IL-10 (10 U/mL), or LPS plus IL-4 (10 U/mL) for 1 hour. Act D (10 μg/mL) was then added, and the decay of COX-2 mRNA was examined by Northern blot analysis. These data are depicted in Fig 9. In comparison with LPS treatment alone, both IL-10 and IL-4 accelerated the degradation of COX-2 mRNA by approximately 50%. Thus, these data indicated that the regulation by IL-10 and IL-4 of monocyte COX-2 mRNA expression occurs, at least in part, at the posttranscriptional level.

Effects of IL-10 and IL-4 on COX-2 gene transcription. To further determine whether both IL-10 and IL-4 inhibit COX-2 mRNA expression by inhibiting COX-2 gene transcription, nuclear run-on experiments were performed. Monocytes were incubated for 3 hours with medium, LPS (100 ng/mL), LPS plus IL-4 (10 U/mL), or LPS plus IL-10 (10 U/mL). The nuclei were then harvested and the RNA transcripts initiated in vivo were allowed to elongate in vitro in the presence of 32P-UTP. As shown in Fig 10, the radiolabeled RNA was subsequently hybridized to slot-blotted cDNA encoding COX-2 or β-actin. The transcriptional activity of COX-2 gene was enhanced by about threefold after activation by LPS. IL-10 and IL-4 inhibited LPS-induced COX-2 gene transcription by approximately 29% and 26%, respectively. Thus, these results indicated that both cytokines can also affect at the transcriptional level of COX-2 gene expression.

DISCUSSION

We have recently shown that IL-10 as well as IL-4 efficiently inhibits PGE2 production by LPS-stimulated human monocytes. The main purpose of this present study is to determine the underlying mechanism of the regulation of monocyte prostanooid synthesis by IL-10 and IL-4. HPLC and RIA studies suggested that the main regulatory portion of both cytokines is at the COX level. Further studies on COX activity have shown that both cytokines did not affect the constitutive COX activity but significantly inhibited LPS-induced COX activity.

Prostanoids are important modulators of inflammation whose synthesis is initiated by the release of AA from membrane phospholipids. The free AA is then converted to PGH2 by COX. The recent discovery of a second isoform of COX, namely COX-2, has raised new questions about the
regulation of prostanoid synthesis. Several studies have indicated that the expression of COX-2 is modulated by many extracellular stimuli, including mitogens, cytokines, and LPS, whereas COX-1 expression is constitutive and not affected by such stimuli. It was thus of interest to investigate the effects of IL-10 and IL-4 on the expression of these two isoforms in human monocytes. As a result, both IL-10 and IL-4 regulated the expression of COX-2, thereby modulating prostanoid synthesis in LPS-stimulated monocytes.

In preparing this manuscript, similar data on IL-10 have been reported by Mertz et al showing that IL-10 selectively suppresses the expression of COX-2 at both the RNA and protein levels, thereby inhibiting the synthesis of various COX products such as PGI2, TXB2, and PGE2 in concanavalin A (Con A)-stimulated monocytes. However, there seems to be some differences between our and their results. First, the optimal concentration of IL-10 to exert maximal suppression of COX-2 expression and PGE2 production is 20 ng/mL (approximately 200 U/mL), which is 20-fold higher than that (10 U/mL) observed in our study. Second, throughout their study they pretreated monocytes with IL-10 for 1 hour to exert maximal suppression. However, we observed that simultaneous addition of optimal concentration of IL-10 and LPS results in maximal suppression of both COX-2 expression and PGE2 production. Such data are consistent with the previous report by Bogdan et al on the inhibitory effect of IL-10 on TNF- production by LPS-stimulated mouse peritoneal macrophages. Therefore, further studies will be required for addressing such differences. It may be due to the nature of stimulation of monocytes (Con A v LPS).

The amount of COX-2 mRNA at 5 hours after LPS stimulation increased twofold as much as that after 1 hour of stimulation, whereas its amount in LPS-stimulated monocytes treated with IL-10 or IL-4 was almost unchanged. Such kinetic data on IL-10 and IL-4 may be partly explained by our recent findings. PGE2 is a representative agent that can elevate the intracellular cAMP level. The cAMP response
element (CRE) was found in the 5'-flanking region of human COX-2 gene and it was shown to play a crucial role in the expression of this gene. COX-2 mRNA seemed to be regulated through a PGE2-cAMP amplification pathway. Because further amplification of COX-2 mRNA would derive from simultaneous elevation of PGE2 induced by COX-2, both cytokines would have efficiently inhibited this amplification. Indeed, Mertz et al clearly showed that the suppression of COX-2 mRNA and protein by IL-10 was almost completely abrogated by the simultaneous treatment of monocytes with PGE2 or dibutyryl (B2c)AMP.

In this study, we also showed the time-dependent inhibition of COX-2 mRNA expression by IL-10 and IL-4. The inhibitory effects of both cytokines were most effective when both added simultaneously with LPS. Such data on IL-10 are in accordance with the previous report by Bogdan et al. Thus, these data indicate that IL-10 may regulate the early stage of monocyte/macrophage activation by LPS. Recent data from in vivo studies on endotoxin-shock model in mice are also in agreement with this idea.

The gene expression is considered to be regulated at the transcriptional and/or posttranscriptional level. Previous reports showed that IL-10 as well as IL-4 induces the instability of mRNAs of many cytokine genes in LPS-stimulated monocytes/macrophages. In this study, we have shown that both IL-10 and IL-4 accelerated the degradation of COX-2 mRNA, thus indicating that the regulation by IL-10 and IL-4 of monocyte COX-2 mRNA expression occurs, at least in part, at the posttranscriptional level. Indeed, as often observed in many immediate early genes, the human COX-2 gene possesses at least 17 copies of the Shaw-Kamen’s sequence (ATTTA) that has been shown to confer enhanced mRNA degradation. Together with our finding that CHX abrogated the abilities of IL-10 and IL-4 to inhibit COX-2 mRNA expression in LPS-stimulated monocytes, it is thus speculated that newly synthesized repressor proteins induced by IL-10 and IL-4 may play significant roles in enhancing the degradation of COX-2 mRNA. In this study, we have also showed that both IL-10 and IL-4 inhibited LPS-induced COX-2 gene transcription. Such data on IL-10 are consistent
with a recent report showing that IL-10 inhibited the COX-2 gene transcription in Con A-stimulated monocytes. In addition, it was recently shown that both IL-10 and IL-4 inhibit LPS-induced cytokine gene transcription in human peripheral blood mononuclear cells (PBMCs) and porcine macrophages. However, in our present study, the degree of inhibition by both cytokines of COX-2 gene transcription was, at most, 30%. Thus, their marked inhibitory effects on COX-2 mRNA expression are not simply attributable to their inhibition of COX-2 gene transcription. It seems highly likely, therefore, that these cytokines can act at both transcriptional and posttranscriptional levels, thereby inhibiting synergistically the COX-2 mRNA expression in LPS-stimulated monocytes.

IL-10 and IL-4 exhibit many similar biologic activities on monocytes/macrophages. For example, these cytokines inhibited the production of inflammatory cytokines, reactive oxygen intermediates, and reactive nitrogen intermediates as shown in Figure 8.

![Fig 8. Effect of CHX on IL-10- and IL-4-induced inhibition of monocyte COX-2 mRNA expression. (I) Human monocytes (2 × 10^6 cells) were preincubated with or without CHX (5 μg/mL) for 1 hour and then cultured with either IL-10 (10 U/mL) or IL-4 (10 U/mL) in the presence of LPS (100 ng/mL) for 5 hours. Total RNA was isolated and analyzed by Northern blot with either COX-2 or β-actin probe. β-Actin probe was used as an internal control to ensure equal loading of RNA. COX-2 mRNA levels were normalized to β-actin mRNA levels for each experimental condition. Similar results were obtained in three replicate experiments.](image1)

![Fig 9. Effects of IL-10 and IL-4 on the stability of monocyte COX-2 mRNA. (I) Human monocytes (2 × 10^6 cells) were cultured with either IL-10 (10 U/mL) or IL-4 (10 U/mL) in the presence of LPS (100 ng/mL) for 1 hour before Act D (10 μg/mL) was added to stop RNA synthesis. At indicated times after Act D addition, total RNA was isolated and analyzed by Northern blot with either COX-2 or β-actin probe. Quantitation of COX-2 transcripts was assessed by image analysis. COX-2 mRNA levels were normalized to β-actin mRNA levels for each experimental condition. Similar results were obtained in three separate experiments.](image2)
The levels of COX-2 gene transcription were normalized to those of actin gene transcription in the same experimental sample and expressed as fold induction compared with the control (medium). Similar results were obtained in three separate run-on assays.

COX-2 may be more preferable. Very recently, a new anti-inflammatory agent, NS-398, has been reported to exhibit selective inhibition for COX-2 activity, thereby resulting in the less gastrointestinal toxicity. Therefore, both IL-10 and IL-4, which selectively inhibit COX-2 expression, may exhibit novel therapeutic effects in inflammatory diseases. In addition, both cytokines are able to not only inhibit the production of proinflammatory cytokines but also enhance IL-1ra production. Both efficiently inhibit the production of collagenase that is believed to be responsible for the extensive destruction of connective tissues observed in chronic inflammatory diseases. Considering these biologic activities of IL-10 and IL-4, both cytokines may offer useful tools in controlling inflammatory disorders in the future.

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Inhibition by interleukin-10 of inducible cyclooxygenase expression in lipopolysaccharide-stimulated monocytes: its underlying mechanism in comparison with interleukin-4

H Niiro, T Otsuka, T Tanabe, S Hara, S Kuga, Y Nemoto, Y Tanaka, H Nakashima, S Kitajima and M Abe