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Differential Regulation of Monocyte Matrix Metalloproteinase and TIMP-1 Production by TNF-α, Granulocyte-Macrophage CSF, and IL-1β Through Prostaglandin-Dependent and -Independent Mechanisms

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Matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs (TIMPs) produced by monocytes are believed to be involved in the migration of these cells through the basement membrane and the ensuing destruction of connective tissue in chronic inflammatory lesions. Because monocytes encounter a variety of cytokines at these sites, we examined the effect of cytokines either alone or in combination on the production of monocyte MMPs and TIMP-1. TNF-α, granulocyte-macrophage-CSF (GM-CSF), or IL-1β when added individually enhanced the endogenous levels of 92-kDa gelatinase (MMP-9) and TIMP-1 but failed to induce interstitial collagenase (MMP-1). However, GM-CSF, when added with either TNF-α or IL-1β, induced MMP-1 and synergistically enhanced MMP-9 and TIMP-1. Th2 cytokines, such as IL-4, inhibited the induction of MMPs and TIMP-1 by TNF-α, GM-CSF, and IL-1. Cytokine stimulation of MMP-1 was due, at least in part, to an increase in the release of arachidonic acid and PG E2 (PGE2), because inhibition of MMP-1 by indomethacin could be reversed by exogenous PGE2. In contrast to MMP-1, cytokine stimulation of MMP-9 and TIMP-1 was unaffected by indomethacin. The PGE2-independent induction of monocyte MMP-9 and TIMP-1 by these cytokines differed from stimulation of MMP-9 and TIMP-1 by LPS, which is in large part PG-dependent. In addition, LPS stimulated higher levels of MMP-1 whereas cytokines induced higher levels of MMP-9 and TIMP-1. This is the first demonstration that monocyte MMP-1 can be induced by cytokines and that MMP-1, MMP-9, and TIMP-1 are differentially regulated by cytokines through PG-dependent and -independent mechanisms. The Journal of Immunology, 1998, 161: 3071–3076.
Although we have previously reported that Ag-activated spleen cells are capable of inducing MMP-1 production by macrophages (15), the potential cytokines involved in the induction of MMP-1 by monocytes or macrophages are unknown. Here we report that while TNF-α, GM-CSF, or IL-1β when added individually stimulated only MMP-9 and TIMP-1 but not MMP-1, the combination of GM-CSF with TNF-α or IL-1β or all three cytokines induced the synthesis of MMP-1 and caused a further enhancement of MMP-9 and TIMP-1. Moreover, the stimulation of MMP-1 occurs through a PG-dependent mechanism, whereas the induction of MMP-9 and TIMP-1 by these cytokines is PG-independent.

Materials and Methods

Purification of human monocytes

Human peripheral blood cells were obtained by leukapheresis of normal volunteers at the Department of Transfusion Medicine at the National Institutes of Health. These cells were diluted in endotoxin-free PBS without Ca2+ and Mg2+ (BioWhittaker, Walkersville, MD) and layered over 20 ml of endotoxin-free lymphocyte sedimentation medium (Organon Teknika, Durham, NC) in 50 ml tubes (Falcon, Becton Dickinson, Oxnard, CA). After density sedimentation at 400 × g for 30 min, the monocytes in the mononuclear cell layer were purified by counterflow centrifugal elutriation on a Beckman (Torrance, CA) elutriation system as previously described (16, 17), except that pyrogen-free PBS was used in the elutriation procedure. Monocytes were enriched to >90% as determined by morphology, nonspecific esterase staining, and flow cytometry. Moreover, the purification procedure did not activate the monocytes as shown by the fact that following overnight incubation at 37°C in suspension less than 4% of these cells were IL-2R positive, a sensitive marker of monocyte activation (18).

Culture conditions

Purified monocytes were cultured in DMEM (BioWhittaker) supplemented with 2 mM L-glutamine (Mediatech, Washington, DC) and 10 μg/ml gentamicin sulfate (BioWhittaker). TNF-α (1 × 10^7 U/mg) and GM-CSF (1 × 10^7 U/mg) were obtained from PeproTech (Rocky Hill, NJ), and IL-1β (1.9 × 10^7 U/mg) was obtained from DuPont (Wilmington, DE). LPS (Escherichia coli) (O55:B5; Difco, Detroit, MI), Bt2cAMP, PGE_2, and/or indomethacin (Sigma, St. Louis, MO) were also added to some of the cultures. Unless otherwise stated, following purification the monocytes were adhered for 30 min before the addition of reagents. Each experiment was repeated a minimum of three times with different donors.

Phospholipase activity assay

Purified monocytes (2 × 10^5/0.5 ml of DMEM) were plated in 24-well plates for 30 min at 37°C. Then autologous or AB serum (final concentration, 10%) and 1 μCi/well of [5,6,8,9,11,12,14,15]H-arachidonic acid were added. After 18 h of incubation the cultures were washed three times in EB, cold, 0.02% fatty-acid-free human serum albumin (Sigma) to remove the unincorporated arachidonic acid and cultured in the same medium for varying times after the addition of cytokines. Aliquots of culture medium were assayed for the release of [1H]arachidonic acid by liquid scintillation counting.

PGE_2 assay

PGE_2 levels in the media supernatants from monocyte cultures were determined by RIA as described (19) using a polyclonal anti-PGE_2 antibody (Novex, San Diego, CA) in SDS Laemmli loading buffer (25 mM Tris-HCl, pH 8.3/192 mM glycine/10% SDS). After electrophoresis, the proteins from membranes or conditioned supernatants were transferred onto 0.45-μm nitrocellulose in a buffer containing 25 mM Tris-HCl, pH 8.3/192 mM glycine/20% methanol and blocked with 50 mM Tris-HCl, pH 7.5/150 mM NaCl/0.3% Tween-20 (TBST) containing 5% nonfat dry milk for at least 1 h. The blots were washed three times with TBST and then incubated for 1 h overnight with primary Ab. For the detection of MMP-1 or TIMP-1, the blots were incubated with a peptide specific Ab or TIMP-1 Ab (generously provided by Dr. Henning Birkedal-Hansen, National Institute of Dental Research, National Institutes of Health) followed by protein A-horseradish peroxidase (Amersham, Arlington Heights, IL) 1:3000 dilution in TBST containing 5% nonfat dry milk and developed with the enhanced chemiluminescence (ECL) detection system (Amersham). The Ab against MMP-1 recognized the active (ACL) and pro-collagenase (PC) forms.

Detection of MMP-9 by zymography

MMP-9 was analyzed by zymography which involves the determination of the ability of culture supernatants to digest gelaatin in polyacrylamide gels. Culture supernatants (10 μl) were added to loading buffer (10 μl) as described above for Western blot analysis except that the samples were not heated or reduced. The samples were loaded on 10% polyacrylamide gels (Novex) containing 0.1% gelatin. Following electrophoresis the gels were incubated in 0.05 M Tris-HCl, pH 7.5, containing 0.2 M NaCl, 5 mM CaCl_2, and 2.5% Triton X-100 for 30 to 60 min and subsequently incubated for 2 to 4 h at room temperature in the same buffer without Triton X-100. The gels were then stained with Coomassie blue (0.25% Coomassie blue/45.4% methanol/2.2% glacial acetic acid) and destained (75% ethanol/25% glacial acetic acid).

Results

Differential regulation of monocyte MMP-9 and MMP-1 by cytokines

Previous studies have identified cytokines, IFN-γ, IL-4, and IL-10, which inhibit the production of MMPs by monocytes (11, 12, 20–22). Here we examined cytokines that may enhance or induce MMP production by monocytes with the potential implications this may have at an inflammatory site. Addition of TNF-α, GM-CSF, or IL-1β alone significantly enhanced MMP-9 production in a dose-dependent manner (Fig. 1, A–C). The individual cytokines, particularly TNF-α and GM-CSF, were very potent at inducing MMP-9, with many of the experiments demonstrating that a maximal stimulation was reached by 10 ng/ml. Thus, as shown in Figure 1B, as little as 1 ng/ml of TNF-α or GM-CSF enhanced MMP-9 production and a maximal stimulation occurred by 5 to 10 ng/ml of TNF-α or GM-CSF. Moreover, when GM-CSF was added with either TNF-α or IL-1β there was a synergistic increase in MMP-9 (Fig. 1, A and C). In contrast to MMP-9, MMP-1 was not induced by the individual cytokines. However of considerable interest was the ability of the combination of TNF-α and GM-CSF to induce significant levels of MMP-1 (Fig. 1A). Similar results were also obtained with TNF-β (data not shown). In addition, the combination of IL-1β with TNF-α or GM-CSF also induced MMP-1, but generally at lower levels than TNF-α plus GM-CSF (Fig. 1C). The degree of MMP-1 conversion from the PCL form to the ACL form varied between experiments, which may be dependent on the extent of activation and/or the length of incubation. An example of this is shown in Figure 1A in which only the ACL form was observed whereas both PCL and ACL were detected in the experiment shown in Figure 1C. The PCL forms had molecule weights of approximately 57 and 55 kDa and the ACL forms were 45 and 43 kDa.

Stimulation of monocyte arachidonic acid release by cytokine combinations

The signal transduction pathway leading to the induction of monocyte MMP-1 production by activators such as Con A has been shown to involve an increase in phospholipase activity with the subsequent release of arachidonic acid (20). To determine whether this early step in activation accounted for the differential regulation of MMPs by
cytokines, we examined the effect of TNF-α, GM-CSF, or IL-1β individually or in combination on the release of arachidonic acid by monocytes (Fig. 2). TNF-α, GM-CSF, or IL-1β when added individually at the indicated concentrations, or at higher concentrations (data not shown), did not significantly increase the release of arachidonic acid above control levels. However, the addition of these cytokines in combination induced a substantial increase in arachidonic acid release.

Stimulation of monocyte PGE2 production by cytokines

The arachidonic acid released following stimulation of the monocytes is metabolized into various metabolites including the eicosanoids. Of particular importance is PGE2, which has been shown to regulate the production of monocyte MMPs (6). Therefore, we also determined the levels of PGE2 in cytokine-treated monocyte cultures, because this more accurately reflects the effect on MMPs than does arachidonic acid release, which is metabolized into many products. The combination of cytokines caused a substantial increase in PGE2, with the combination of GM-CSF and TNF-α inducing the greatest increase, whereas cultures treated with a single cytokine had levels of PGE2 similar to that of control cultures (Fig. 3).

Effect of indomethacin, PGE2, and Bt2cAMP on the induction of monocyte MMPs by cytokines

The finding that the individual cytokines did not increase arachidonic acid or PGE2 whereas the combination of cytokines did suggested that this may account for the differential regulation of MMP-1 and MMP-9. To determine whether this was the case, indomethacin was added to some of the cultures. As shown in Figure 4A, the induction of MMP-1 by GM-CSF plus TNF-α or IL-1β or all three cytokines was significantly inhibited by indomethacin. The data used in Figure 4A were from a donor whose monocytes, unlike the monocytes from the majority of donors, were partially activated since very low levels of MMP-1 were stimulated by GM-CSF or IL-1β treatment alone, which were also inhibited by indomethacin. The lack of complete inhibition by indomethacin of MMP-1 induced by the combination of cytokines is also most likely related to prior partial activation in vivo. This differed from the majority of experiments, as represented by Figure 4B, in which indomethacin caused a complete inhibition of MMP-1. In contrast to MMP-1, the enhancement of MMP-9 by TNF-α, GM-CSF, or IL-1β alone or in combination was not inhibited by indomethacin. Thus the induction of MMP-1 by cytokines occurs through a PG-dependent mechanism whereas the enhancement of MMP-9 is PG-independent.

To further demonstrate the role of PGs and cAMP in the regulation of monocyte MMP-1 production by cytokines, PGE2, or

![Figure 2](http://www.jimmunol.org/)

**Figure 2.** The addition of TNF-α, GM-CSF, or IL-1β in combination, but not alone, induces significant levels of arachidonic acid release by monocytes. Purified monocytes (2 × 10^6/ml of DMEM) were adhered in 24-well plates for 30 min before the addition of 10% autologous serum and 1 μCi of [^3]H]arachidonic acid/well. Following incubation for 18 h, the cultures were washed three times with DMEM containing 0.02% fatty acid free serum albumin and cultured in this medium. GM-CSF (50 ng/ml), TNF-α (50 ng/ml), and IL-1β (100 ng/ml) alone or in combination were added to the monocyte cultures and the supernatants harvested 1 h later; radioactive counts were determined as an indicator of arachidonic acid release. The data are the mean ± SD of duplicate cultures and are representative of three experiments with different donors.

![Figure 3](http://www.jimmunol.org/)

**Figure 3.** Effect of TNF-α, GM-CSF, or IL-1β alone or in combination on PGE2 production by monocytes. Purified monocytes (2 × 10^6/ml of DMEM) were plated in 24-well plates. GM-CSF (50 ng/ml), TNF-α (50 ng/ml), and IL-1β (50 ng/ml) alone or in combination were added to the monocyte cultures, and the 24-h supernatants were assayed for PGE2. The data are the mean ± SD of duplicate cultures and are representative of three experiments with different donors.
PGE2 (10 ng/ml) either individually or in combination in the presence or absence of human monocytes (20 × 10\(^6\)/ml) or Bt$_2$cAMP. Purified human monocytes (20 × 10\(^6\)/ml of DMEM) were adhered in 60-mm Petri dishes for 30 min. A. Indomethacin was added to some of the cultures 30 min before TNF-α (50 ng/ml), GM-CSF (50 ng/ml), and IL-1β (200 ng/ml) either alone or in combination, and the 36-h supernatants were assayed for MMP-1 and MMP-9. B. Monocyte cultures that had been pre-treated with indomethacin for 30 min were exposed to TNF-α and GM-CSF either individually or in combination in the presence or absence of PGE$_2$ (10\(^{-6}\) M) or Bt$_2$cAMP (5 × 10\(^{-5}\) M), and the 48-h supernatants were assayed for MMP-1. C. To determine the effect of exogenous PGE$_2$ or Bt$_2$cAMP on cytokine-induced MMP-1, TNF-α (50 ng/ml) plus GM-CSF (50 ng/ml) were added in the presence or absence of PGE$_2$ or Bt$_2$cAMP. The cultures were harvested at 36 h and the media assayed for MMP-1.

Bt$_2$cAMP was added to the cultures in the presence of indomethacin. As shown in Figure 4B, PGE$_2$ or Bt$_2$cAMP reversed the inhibition by indomethacin of cytokine induced MMP-1 production. Moreover, the addition of PGE$_2$ or Bt$_2$cAMP with TNF-α and GM-CSF, in the absence of indomethacin, resulted in a significant enhancement of MMP-1 over that induced by the cytokines (Fig. 4C). Thus, exogenous PGE$_2$ or Bt$_2$cAMP can increase MMP-1 production beyond the maximum stimulation by the combination of cytokines, indicating that the exogenous levels of PGE$_2$ at an inflammatory site may potentiate the induction of MMP-1 by cytokines. This was in contrast to cytokine induction of MMP-9, which was not enhanced by PGE$_2$ or Bt$_2$cAMP (data not shown).

Effect of TNF-α and GM-CSF on TIMP-1

In addition to the contribution of MMPs, the degree of connective tissue destruction is also influenced by TIMPs. Of the family of TIMPs, TIMP-1 and TIMP-2 have been reported to be produced by monocytes/macrophages (5). Because TIMP-1 is inducible as compared with TIMP-2 which is constitutively expressed, we focused on the effect of cytokines on TIMP-1. As shown in Figure 5, TIMP-1, like MMP-9, was enhanced by TNF-α or GM-CSF with a further increase when these cytokines were added together. Also similar to MMP-9, TIMP-1 induction by these cytokines was not inhibited by indomethacin. These findings were in contrast to the stimulation of TIMP-1 by LPS, which could be decreased by indomethacin (Fig. 5). In addition, the stimulation of TIMP-1 production by cytokines was unaffected by the addition of PGE$_2$ or Bt$_2$cAMP (data not shown).

Effect of IL-4 on TNF-α and GM-CSF-induced MMPs and TIMP-1

We have shown previously that theTh2 derived cytokine IL-4 inhibits Con A or LPS induced MMP production by monocytes, suggesting that the ratio of cell types, particularly that of T cell subsets, may determine the outcome of an inflammatory lesion. Therefore, we examined the effect of IL-4 on the induction of monocyte MMP-1, MMP-9, and TIMP-1 by the combination of TNF-α and GM-CSF. IL-4 caused a significant inhibition of TNF-α and GM-CSF induced MMP-1 and MMP-9 production when added 60 to 30 min before these cytokines or even at the same time as the cytokines (Fig. 6). The inhibitory effect of IL-4 on MMP-1 or MMP-9 was still observed when IL-4 was added 30 to 60 min after TNF-α and GM-CSF, indicating IL-4 inhibits cytokine-mediated MMP production at a relatively late stage in the induction or processing of these enzymes. Similar results were observed with TIMP-1 (data not shown).

Comparison of cytokines with LPS in the induction of monocyte MMPs

LPS is a known potent activator of monocytes/macrophages and therefore we compared the degree of induction of monocyte MMPs by LPS with that of cytokines. As demonstrated in Figure 7, LPS induced substantially higher levels of MMP-1 than a combination of TNF-α and GM-CSF. The degree to which LPS increased MMP-1 above that stimulated with the cytokines varied between experiments, with the data in Figure 7 demonstrating an example of the maximal differential observed. In contrast to MMP-1, but similar to TIMP-1 induction (Fig. 5), the combination of TNF-α and GM-CSF inhibited MMP-9 production by monocytes (20 × 10\(^6\)/ml of DMEM) in 60-mm dishes for 30 min. Figure 6 shows the inhibition of MMP-9 production by IL-4 at various times with respect to the addition of GM-CSF plus TNF-α (50 ng/ml). The 48-h culture media were assayed for MMP-1 by Western blot analysis, and MMP-9 was assayed by zymography.
of TNF-α and GM-CSF stimulated monocytes to produce significantly higher levels of MMP-9 than LPS. These findings demonstrate that there is a differential expression of MMPs and TIMP-1 by monocytes depending on whether the monocytes are exposed to LPS or cytokines.

**Discussion**

Cytokines are prominent biologic mediators at sites of inflammatory lesions where monocytes/macrophages are a major cell type. The specific cytokines present and their interaction with monocytes/macrophages may well determine the degree of connective tissue loss at these sites. Production of MMPs by monocytes/macrophages are thought to play an important role in the immunopathology associated with these lesions. Cytokines are also important regulators of monocyte MMPs, as demonstrated by the ability of IFN-γ, IL-4, and IL-10 to inhibit the production of these enzymes (11–13, 20–22). Recently, monocyte/macrophage MMPs have been shown to be selectively up-regulated by cytokines with the demonstration that MMP-9 but not MMP-1 or TIMP-1 can be enhanced by IL-1 or TNF-α (14). Our findings confirm the ability of IL-1 or TNF-α to enhance MMP-9 but not MMP-1 and, in addition, show for the first time that monocyte MMP-1 production can be induced by cytokines when the combination of TNF-α and GM-CSF or GM-CSF and IL-1 are added simultaneously. In contrast to the findings of Saren et al. (14), TIMP-1 was increased by these cytokines. The different culture times before exposure of the monocytes/macrophages to cytokines may account for this discrepancy. In general, the combination of TNF-α and GM-CSF was significantly more effective in the induction of MMP-1 and in the enhancement of MMP-9 and TIMP-1 than if IL-1 was combined with GM-CSF.

Previous studies have demonstrated that monocytes stimulated with Con A, LPS, zymosan, type I and type III collagen, laminin peptides, and SPARC produce MMPs through a PG-dependent pathway (6–10). The findings in the present study demonstrate that the induction of MMP-1 by the combination of cytokines is also PG-dependent. Evidence for this was shown by the ability of indomethacin to inhibit the production of MMP-1 which could be restored by PGE_2 or Bt_2cAMP. Further support for this was the stimulation of the release of arachidonic acid and PGE_2 by the combination of cytokines, which was not the case for the individual cytokines. Other CSFs, such as IL-3 or macrophage-CSF, in combination with TNF-α also induced MMP-1 production, but not when added alone (data not shown). Although macrophage-CSF has been reported to increase the release of low levels of arachidonic acid and PGE_2 from monocytes (23), these amounts may be below that needed for the induction of MMP-1 and/or an additional signal event is required. This latter possibility is suggested by the failure to induce MMP-1 when Bt_2cAMP or PGE_2 was added to monocytes treated with either TNF-α or GM-CSF, but did enhance MMP-1 production when added to the combination of cytokines. As we have previously shown (6), the addition of cAMP elevating agents to monocytes in the absence of a primary stimulus fails to increase MMP-1 production by monocytes. An appropriate primary stimulus is likely required to cause alterations in the cytoskeletal framework and/or activation of additional transcription factors necessary for the PGE_2-mediated induction of MMP-1.

In contrast to MMP-1, regulation of MMP-9 and TIMP-1 by cytokines differed in several aspects. First, unlike MMP-1, MMP-9 and TIMP-1 were enhanced by the individual addition of TNF-α, GM-CSF or IL-1. Second, the cytokine-induced increase in MMP-9 and TIMP-1 was not inhibited by indomethacin. This differs from previous findings with stimulants such as Con A, LPS, zymosan, denatured collagen, and SPARC, in which the enhancement of the basal levels of 92-kDa gelatinase could be substantially inhibited by indomethacin (9–11). Similarly, the stimulation of TIMP-1 by LPS, zymosan, or denatured collagen has also been shown to be inhibited by indomethacin (9). Thus, the signal transduction pathway(s) utilized by the cytokines individually or in combination for the enhancement of MMP-9 and TIMP-1 are PG-independent. It is unclear at this time as to how cytokines differ in their regulation of monocyte MMP-9 from other agonists; however, TNF-α, GM-CSF, and IL-1 are known to influence or act through several signal transduction pathways (24–27). Depending on the signal transduction pathways invoked by the individual or combined cytokines, differing sets or levels of transactivating factors may be affected. The cytokine-mediated signal transduction pathways and promoter elements leading to MMP production by monocytes appear to differ, at least in part, from other cell types. For example, in contrast to monocytes, TNF-α or IL-1 alone have been shown to directly induce MMP-1 in cells such as fibroblasts and synovial adherent cells (1). In addition, studies with U937 cells, a human monocytic cell line, have demonstrated that the upstream promoter elements such as the polyoma enhancer A-binding protein-3 site (PEA-3) and TTCA sequence involved in the induction of MMP-1 in fibroblasts do not play a major role, if any, in the activation of the collagenase gene in monocytic cells (28). The critical sequences in the collagenase promoter for MMP-1 production by LPS stimulated U937 cells were from −72 to the transcription start site which included AP-1. The sequence of events initiated by the combination of cytokines leading to the production of MMP-1 by primary monocytes may involve upstream events in multiple pathways that converge on a specific combination of transactivating factors.

From this and previous studies it is clear that the types and amounts of cytokines present at an inflammatory site may determine the extent of connective tissue degradation. For example, the Th2 cytokines, IL-10 and IL-4, have been shown to suppress monocyte MMPs (11, 12, 21, 22). As shown here, Th2 cytokines, as represented by IL-4, can also effectively suppress the induction of MMP-1 and the enhancement of MMP-9 and TIMP-1 by TNF-α and GM-CSF. Thus, the balance between cytokines such as TNF-α, GM-CSF, and IL-1 and the Th2 cytokines may be important in the outcome of an inflammatory response. This is further indicated by the paucity of Th2-derived cytokines in many inflammatory lesions (29, 30), which may allow unabated production of MMPs.

The findings presented here demonstrate that the cytokines present at the tissue site may have a dramatic impact on the degree and specificity of the MMPs produced by monocytes/macrophages. The initial exposure of monocytes to low levels of a single or a combination of cytokines emating from the vascular wall at an inflammation site may induce MMP-9, which would facilitate...
their migration through the basement membrane. Once at the site of inflammation the higher levels of a combination of cytokines would induce MMP-1 and initiate the destruction of fibrillar collagen. The stimulation of monocyte MMPs by cytokines through PG-independent (MMP-9) and PG-dependent (MMP-1) mechanisms provide insight into the therapeutic considerations aimed at regulating these MMPs.

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