Hyaluronan Fragments Synergize with Interferon-\(\gamma\) to Induce the C-X-C Chemokines Mig and Interferon-inducible Protein-10 in Mouse Macrophages*

Maureen R. Horton‡, Charlotte M. McKeet, Clare Bao, Fang Liao, Joshua M. Farber, Jennifer Hodge-DuFour, Ellen Puré, Bonnie L. Oliver,**‡‡, Timothy M. Wright,¶ and Paul W. Noble**‡‡§§

From the ‡Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, the ¶Laboratory of Clinical Investigation, NIAID, National Institutes of Health, Bethesda, Maryland 20892, the Wistar Institute, Philadelphia, Pennsylvania 19104, the **Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut 06520, and the ‡‡Department of Veterans Affairs Connecticut Healthcare System, West Haven, Connecticut 06516.

Hallmarks of chronic inflammation and tissue fibrosis are increased influx of activated inflammatory cells, mediator release, and increased turnover and production of the extracellular matrix (ECM). Recent evidence has suggested that fragments of the ECM component hyaluronan play a role in chronic inflammation by inducing macrophage expression of chemokines. Interferon-\(\gamma\) (IFN-\(\gamma\)), an important regulator of macrophage functions, has been shown to induce the C-X-C chemokines Mig and IP-10. These chemokines affect T-cell recruitment and inhibit angiogenesis. The purpose of this investigation was to determine the effect of hyaluronan (HA) on IFN-\(\gamma\)-induced Mig and IP-10 expression in mouse macrophages. We found a marked synergy between HA and IFN-\(\gamma\) on Mig and IP-10 mRNA and protein expression in mouse macrophages. This was most significant with Mig, which was not induced by HA alone. The synergy was specific for HA, was not dependent on new protein synthesis, was not mediated by tumor necrosis factor-\(\alpha\), was selective for Mig and IP-10, and occurred at the level of gene transcription. These data suggest that the ECM component HA may influence chronic inflammatory states by working in concert with IFN-\(\gamma\) to alter macrophage chemokine expression.

Activated macrophages play an essential role in inflammation through the release of a variety of mediators, including reactive oxygen species, reactive nitrogen species, proteases, chemokines, cytokines, and growth factors (1–5). Although the mechanisms controlling macrophage activation in inflammatory states are incompletely understood, recent studies suggest a role for extracellular matrix (ECM) components in the activation of inflammatory macrophages (6). In normal, healthy tissues, the ECM is composed of a complex array of proteins, proteoglycans, and glycosaminoglycans that play important roles in homeostasis (7) and maintenance of matrix structure. During an inflammatory response, there is increased production and degradation of the ECM, resulting in the accumulation of breakdown products of ECM components such as fibronectin, collagen, and glycosaminoglycans (8). Interestingly, these low molecular mass ECM components have been shown to have different biological activities compared with their larger, native precursors (9–11). In fact, fragments of the ECM components collagen and fibronectin have been recently shown to have proinflammatory properties (12). Likewise, recent work from our laboratory and others has shown that low molecular weight fragments of the ECM glycosaminoglycan hyaluronan (HA) may play a role in macrophage activation (13–16).

HA is a ubiquitously distributed component of the ECM. In its native form, it exists as a high molecular weight nonsulfated glycosaminoglycan polymer (17, 18) made up of repeating disaccharide units of \((\beta,1-4)-d-glucuronic acid-\((\beta,1-3)-N\)-acetyl-d glucosamine. High molecular mass HA is believed to have many functions in healthy tissue, such as water homeostasis, plasma protein distribution, and matrix structuring (17). However, at sites of inflammation and tissue injury, there is an accumulation of lower molecular mass HA species (19–21), which have different biological functions than their high molecular mass precursors (13–16). Recent studies have suggested that these lower molecular weight forms of HA may stimulate macrophages recruited to sites of inflammation to produce important mediators of tissue injury and repair (13–16). This effect is mediated, in part, by interaction with the HA receptor CD44 (13–16).

In the inflammatory milieu, there are numerous cytokines and chemokines that also influence macrophage expression of inflammatory genes. The cytokine IFN-\(\gamma\) is an important modulator of macrophage effector functions and regulator of the inflammatory response (22). In addition to its antiviral activity, IFN-\(\gamma\) also enhances certain macrophage functions, such as microbicidal and tumoricidal activity, through the production of reactive oxygen intermediates and reactive nitrogen intermediates (23, 24). Yet despite its many proinflammatory roles, IFN-\(\gamma\) also inhibits macrophage expression of certain LPS-induced chemokines, such as monokine chemotactic protein-1 and KC (24).

*This work was supported by grants from the National Institutes of Health (K11HL02886, R01HL65059, and 5F32HL09614-02) and the American Lung Association. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

§§ To whom correspondence should be addressed: Yale University School of Medicine, Department of Veterans Affairs Connecticut Healthcare System, Pulmonary Section/111A, 950 Campbell Ave., West Haven, CT 06516. Tel.: 203-937-4977; Fax: 203-937-3455; E-mail: paul.noble@yale.edu.

1 The abbreviations used are: ECM, extracellular matrix; HA, hyaluronan; Mig, monokine induced by interferon; IP-10, interferon-inducible protein-10; MIP, macrophage inflammatory protein; RANTES, regulated on activation normal T cell expressed and secreted; EPM, elicited peritoneal macrophages; CHX, cycloheximide; TNF, tumor necrosis factor; LPS, lipopolysaccharide; CAT, chloramphenicol acetyltransferase.
HA Fragments Synergize with IFN-γ to Induce Mig and IP-10

IFN-γ has recently been shown to induce macrophage expression of the novel chemokines monokine induced by interferon-γ (Mig) and interferon-inducible protein-10 (IP-10) (25, 26). Both Mig and IP-10 are members of the C-X-C chemokine family and may play roles in chronic inflammation (27, 28), as well as in viral and protozoan infections (25, 29, 30). In chronic infectious states, expression of Mig and IP-10 has been shown to correlate with IFN-γ expression (29). Mig and IP-10 have each been implicated in T-cell trafficking, chemotaxis, and activation (31–33). Mig and IP-10 have also been shown to have angiostatic properties (34–36) and thus may play an important role in regulating tissue granulation and remodeling by inhibiting angiogenesis. IP-10 is induced in macrophages by α, β, and IFN-γ, as well as by LPS (25, 37, 38). To date, Mig has only been shown to be induced in macrophages by IFN-γ (26, 39).

Recent investigations have described synergistic enhancement of IFN-γ-induced Mig and IP-10 expression by TNF-α in fibroblasts (40, 41).

In this report, we examined the effect of low molecular mass HA fragments on IFN-γ-induced expression of Mig and IP-10. We observed a striking synergy between HA and IFN-γ on the expression of Mig and IP-10 mRNA and protein levels in murine macrophages that occurs at the level of gene transcription. These results identify a previously uncharacterized mechanism by which the ECM, acting in conjunction with IFN-γ, may regulate the immune response by influencing the expression of specific chemokines.

EXPERIMENTAL PROCEDURES

Cells, Mice, and Cell Lines—The mouse alveolar macrophage cell line MH-S (42) was purchased from American Type Culture Collection (Manassas, VA). Cells were maintained in RPMI 1640 medium supplemented with 10% inactivated low LPS fetal bovine serum, 15% L-cell media, and 1% penicillin-streptomycin/1% glucose (Biofluids, Rockville, MD) at 37 °C under 5% CO2. Thioglycollate-elicited peritoneal macrophages were lavaged from Thioglycollate-elicited peritoneal macrophages were lavaged from Thioglycollate-elicited peritoneal macrophages were lavaged from Thioglycollate-elicited peritoneal macrophages were lavaged from Th...
the presence of IFN-γ. In order to assess the combined effect of HA and IFN-γ on Mig and IP-10 gene expression, macrophages were simultaneously stimulated with HA and IFN-γ for 6 h, mRNA was isolated, and Northern analysis was performed. As shown in Fig. 1A, HA alone had virtually no effect on Mig or IP-10 mRNA expression in inflammatory thioglycollate-elicited peritoneal macrophages from C3H/HeJ-LPS hyporesponsive mice, whereas IFN-γ induced moderate expression of Mig and IP-10 mRNA. However, we unexpectedly found that HA dramatically influences the effect of IFN-γ on Mig and IP-10 mRNA expression (Fig. 1A). Similar results were observed with MH-S cells, a murine alveolar macrophage cell line (Fig. 1B). In these alveolar macrophages, the synergy is most apparent for Mig where, in addition to no effect on Mig gene expression by HA alone, IFN-γ alone induced only a faint signal (Fig. 1B). However, the combination of HA and IFN-γ markedly induced Mig mRNA expression (Fig. 1B). In this alveolar macrophage cell line, HA minimally induced IP-10 mRNA, and IFN-γ had a moderate effect on IP-10 mRNA, but there was still marked enhancement of IP-10 mRNA when cells were stimulated both with HA and IFN-γ (Fig. 1B).

HA and IFN-γ Synergize to Induce Mig and IP-10 mRNA Expression in Mouse Macrophages—To further delineate the effects of HA and IFN-γ on Mig and IP-10 mRNA expression, we stimulated MH-S cells simultaneously with HA and IFN-γ for varying time intervals and found that HA failed to independently induce Mig expression at any time point and only minimally induced IP-10 mRNA (data not shown). However, the synergistic effect of HA and IFN-γ on Mig and IP-10 mRNA expression was seen as early as 3 h after simultaneous stimulation of MH-S cells, peaked after 6–9 h, and decreased toward baseline after 24 h of stimulation (data not shown).

We then determined the dose-response relationships for HA and IFN-γ to induce Mig and IP-10 gene expression in MH-S cells. The effect of varying concentrations of HA with a constant concentration of IFN-γ on Mig and IP-10 mRNA expression by the alveolar macrophage cell line MH-S is shown in Fig. 2A. The synergy between HA and IFN-γ on Mig and IP-10 gene expression was observed with as little as 1 μg/ml HA and was maximal at 10 μg/ml HA in the presence of 300 units/ml IFN-γ. The converse is shown in Fig. 2B using a concentration of 100 μg/ml HA. The synergy between HA and IFN-γ occurs with as little as 1 unit/ml IFN-γ and is maximal at 10 units/ml IFN-γ.

IFN-γ Synergizes Specifically with HA Fragments to Induce Mig and IP-10 mRNA Expression in Mouse Macrophages—In order to determine whether the synergy between HA and IFN-γ was specific to low molecular mass HA fragments, we stimulated MH-S cells in the presence of IFN-γ and numerous other glycosaminoglycans. Fig. 3 shows that IFN-γ only synergizes with HA fragments and not high molecular mass HA, chondroitin sulfate A or B, or HA disaccharides to induce Mig or IP-10 mRNA expression. Thus, the synergy between HA and IFN-γ on Mig and IP-10 gene expression in MH-S cells appears to be specific to the low molecular mass HA fragments.

HA and IFN-γ Synergize to Induce Mig Protein Production in Mouse Macrophages—Having identified the synergistic effect between HA and IFN-γ on Mig and IP-10 mRNA levels, we investigated Mig and IP-10 production at the protein level. MH-S cells were simultaneously stimulated with HA in the presence of IFN-γ for 20 h. Mig protein secretion was determined in the supernatants by Western blot analysis. Fig. 4A shows that there was little Mig protein present in the conditioned media from unstimulated cells or cells stimulated with HA or IFN-γ alone. However, when the macrophages were stimulated with HA and IFN-γ together, there was marked induction of Mig protein production in the conditioned media. Fig. 4B shows similar synergistic induction of IP-10 protein production by MH-S cells stimulated with both HA and IFN-γ. However, unlike Mig, there was some IP-10 protein induced by HA and IFN-γ alone. Thus, the synergy between HA and IFN-γ is also demonstrated at the protein level.

Cycloheximide Has a Minimal Effect on the Synergy between HA and IFN-γ on Mig or IP-10 Gene Expression in Mouse Macrophages—In order to further dissect the mechanism for the observed synergy, we examined the role of new protein synthesis on the synergy between HA and IFN-γ on Mig and IP-10 mRNA expression in MH-S cells. We pretreated MH-S cells with cycloheximide (CHX) for 30 min before the addition of HA and IFN-γ for 6 h. As shown in Fig. 5, CHX minimally inhibited the synergistic expression of Mig and IP-10 mRNA by HA and IFN-γ. Similarly, CHX had no effect on Mig or IP-10 gene expression from unstimulated cells or cells stimulated with HA alone, and it had little effect on cells stimulated with IFN-γ alone (Fig. 5). Thus, the synergistic induction of Mig and IP-10 gene expression by HA and IFN-γ does not appear to require new protein synthesis.

The Synergistic Induction of Mig and IP-10 Gene Expression by HA and IFN-γ Is Not Dependent on TNF-α—Recently, Ohmori et al. (40, 41) have provided data that TNF-α and IFN-γ synergize to induce Mig and IP-10 mRNA in fibroblasts. We have previously shown that HA induces TNF-α expression by mouse macrophages (16). Therefore, we investigated the possible role of TNF-α in the synergistic induction of Mig and IP-10 gene expression by HA and IFN-γ. First, using anti-
TNF-α neutralizing antibodies, we found that TNF-α was not necessary for the induction of Mig or IP-10 mRNA by HA and IFN-γ in MH-S cells (data not shown). In addition, we isolated thioglycollate-elicited peritoneal macrophages from mice that have had the TNF-α gene deleted (43). As shown in Fig. 6, HA and IFN-γ synergize to induce Mig and IP-10 mRNA expression despite the complete absence of TNF-α. Similar results were also found in thioglycollate-elicited peritoneal macrophages from wild type littermate controls (Fig. 6). Thus, the synergy between HA and IFN-γ on Mig and IP-10 gene expression occurs independently of TNF-α expression.

**HA and IFN-γ Synergize to Induce Mig and IP-10 Gene Expression in MH-S Cells at the Level of Gene Transcription**—We examined the direct effect of HA and IFN-γ on the induction of Mig and IP-10 gene transcription by performing nuclear run-on assays. The mRNA transcribed in nuclei isolated from MH-S cells stimulated with HA, IFN-γ, and HA + IFN-γ for 3 h was radiolabeled. As shown in Fig. 7, there was little transcription of Mig mRNA in unstimulated cells or cells stimulated with HA or IFN-γ alone. However, there was marked enhancement of Mig transcription in cells stimulated with the combination of HA and IFN-γ. Similar results were found with IP-10, although

**FIG. 2.** Dose response of HA and IFN-γ for Mig and IP-10 gene expression in MH-S cells. A, Northern analysis of mRNA derived from MH-S cells stimulated with varying doses of HA ± IFN-γ (300 units/ml) for 6 h. B, Northern analysis of mRNA derived from MH-S cells stimulated with varying doses of IFN-γ ± HA (100 μg/ml) for 6 h. These data are representative of four experiments.

**FIG. 3.** Specificity of HA in synergy with IFN-γ to induce Mig and IP-10 gene expression in MH-S cells. Northern analysis of mRNA derived from MH-S stimulated with HA (100 μg/ml) or alternative ECM components in the presence of IFN-γ (300 units/ml) for 6 h. These data are representative of four identical experiments.

**FIG. 4.** HA and IFN-γ synergize to induce Mig and IP-10 protein secretion in MH-S cells. Western analysis was performed on supernatants from MH-S cells stimulated with HA (100 μg/ml) and IFN-γ (300 units/ml) for 24 h. Recombinant Mig and IP-10 protein were included as controls. A, Mig; B, IP-10. These data are representative of three identical experiments.
the baseline levels of IP-10 mRNA transcription were higher (Fig. 7). At earlier time points, after 1 h stimulation, there was modest enhancement of Mig and IP-10 mRNA transcription in cells treated with IFN-γ alone, but the synergistic enhancement with HA was not present (data not shown). Thus, HA and IFN-γ synergize to induce Mig and IP-10 gene expression at the level of transcription.

To further elucidate the mechanism responsible for the synergy between HA and IFN-γ on Mig promoter activity, we transiently transfected MH-S cells with a 5′ promoter construct spanning base pairs −1117 to +43 upstream from a firefly luciferase reporter gene. As shown in Fig. 8A, IFN-γ alone induced firefly luciferase activity by 12-fold, whereas stimulation of transfected cells with HA and IFN-γ together showed over a 32-fold induction of luciferase activity over unstimulated cells. We also transiently transfected MH-S cells with a promoter construct containing four copies of the interferon-γ-responsive site, −299 to +7 upstream of a CAT reporter gene (B). Transfected cells were stimulated with HA (100 µg/ml) ± IFN-γ (300 units/ml) for 18 h. Promoter activity was assessed by luciferase or CAT activity. Shown are the results of six identical experiments.

The purpose of this study was to examine the effects of the ECM glycosaminoglycan HA on the expression of the inflammatory chemokines Mig and IP-10 in the presence of IFN-γ.
Previous work in our laboratory has shown that low molecular mass HA fragments can stimulate mouse macrophages to express numerous chemokines (13–15). Mig is unique in that no stimulus other than IFN-γ has been shown to induce its expression in macrophages. IP-10, on the other hand, has been shown to be induced by IFN-α, -β, and -γ, as well as LPS. The results presented herein identify a new role for the ECM in enhancing IFN-γ-induced Mig and IP-10 gene expression. Interestingly, the effect of HA on IFN-γ-inducible Mig and IP-10 expression appeared to be unique among the chemokines we examined. We have recently shown that IFN-γ inhibits HA-induced expression of MIP-1α, MIP-1b, and KC, while having no significant effect on RANTES and monokine chemotactic protein-1 (51).

HA alone did not induce Mig and only minimally induced IP-10 mRNA and protein production in a variety of murine macrophages. However, HA enhanced the IFN-γ-induced steady state mRNA levels of Mig and IP-10 in both primary mouse macrophages (elicited peritoneal macrophages) and in MH-S cells, an alveolar macrophage cell line. The increased Mig and IP-10 mRNA levels were found to correlate with Mig and IP-10 protein production in cells stimulated with both HA and IFN-γ.

To further characterize the mechanisms by which HA and IFN-γ synergize to induce Mig and IP-10 gene expression in macrophages, we performed time course and dose-response experiments. The peak synergy between HA and IFN-γ occurs after 6–9 h of stimulation and with as little as 1 μg/ml of HA and 1 unit/ml of IFN-γ. Furthermore, the effect of HA on IFN-γ-induced Mig and IP-10 expression is specific to HA and not a general characteristic of glycosaminoglycans. Low molecular mass HA fragments alone, not high molecular mass native HA, chondroitin sulfate A or B, or HA disaccharides, influenced the effect of IFN-γ on Mig or IP-10 expression. These results suggest that the synergistic effect of HA on IFN-γ-induced Mig and IP-10 mRNA expression is immediate, specific to HA fragments, and quite sensitive as it occurs with low concentrations of these mediators.

In an attempt to delineate whether new protein synthesis was necessary for synergy, we performed a series of experiments in the presence of the protein synthesis inhibitor cycloheximide. Evaluation of these experiments revealed that HA- and IFN-γ-induced Mig and IP-10 expression was minimally blocked by CHX, suggesting that the synergy does not require synthesis of a secondary mediator.

Recent investigations have determined that TNF-α and IFN-γ synergize to induce Mig and IP-10 mRNA expression in fibroblasts (40, 41); therefore, we examined the role of TNF-α in mediating the effect of HA on IFN-γ-inducible Mig and IP-10 expression. Although HA independently induces TNF-α expression in macrophages, sufficient concentrations of TNF-α blocking antibodies to inhibit all HA-induced TNF-α activity failed to inhibit the induction of Mig or IP-10 by HA and IFN-γ in MH-S cells (data not shown). Furthermore, thionoglycollate-elicited peritoneal macrophages from TNF-α-deficient mice exhibited the same synergy between HA and IFN-γ on Mig and IP-10 expression as did littermate mice expressing TNF-α. Thus, unlike with fibroblasts, the synergistic effect of HA and IFN-γ on Mig expression is independent of TNF-α.

The synergistic induction of Mig and IP-10 by HA and IFN-γ is due to the up-regulation of Mig and IP-10 gene transcription. Nuclear run-on studies in the MH-S cells show that HA does not induce Mig mRNA transcription and only minimally induces IP-10. IFN-γ alone has minimal effect on Mig and IP-10 transcription compared with unstimulated cells. However, cells stimulated with both HA and IFN-γ have a marked enhancement of Mig and IP-10 gene transcription. Similarly, when MH-S cells were transfected with a Mig promoter construct containing the 5′ regulatory region previously shown to convey the IFN-γ responsiveness, there was over a 32-fold induction in Mig promoter activity compared with only a 12-fold induction in promoter activity by IFN-γ alone. Similarly, when MH-S cells were transfected with a IP-10 promoter construct containing the 5′ regulatory region previously shown to convey the IFN-γ responsiveness, there was over a 28-fold induction in IP-10 promoter activity compared with only an 8-fold induction in promoter activity by IFN-γ alone. Furthermore, in the case of Mig, the γRE, although enough to convey responsiveness to IFN-γ, failed to account for the HA- and IFN-γ-induced synergistic enhancement of Mig gene expression. Thus, the γRE is not sufficient to allow for the synergistic effects of HA and IFN-γ. Together, these results suggest that HA profoundly enhances IFN-γ-induced Mig and IP-10 steady-state mRNA expression and does so at the level of Mig and IP-10 gene transcription.

Recent studies have suggested that IFN-γ induction of Mig is mediated by the transcription factor γRF-1(50). γRF-1, the unique IFN-γ-responsive cis element in the Mig promoter, is an imperfect palindromic consisting of the following sequence: 5′-TTTATxxCTAAAAACxxGTTTATxxXXXXA-3′(50). γRF-1 has recently been shown to consist of a complex containing STAT-1α and STAT-1β (49). The electrophoretic and binding properties of γRF-1 are distinct, however, from the previously described dimeric form of STAT-1 also known as γ-interferon-activated factor (GAF) (reviewed in Ref. 52). In contrast to the ability of GAF to bind to a monomeric STAT-1 binding site, purified γRF-1 does not bind to the STAT-1 site (49) but rather is specific for the imperfect palindrome resembling a STAT binding site. These studies are further supported by the report by Ohmori et al. (41), which has shown that in STAT 1-deficient mice, IFN-γ fails to induce Mig gene expression in fibroblasts (41). One possible mechanism for synergy between HA and IFN-γ could be enhanced phosphorylation of STAT-1 in the presence of HA. We investigated this possibility and found no effect of HA on IFN-γ-induced phosphorylation of STAT-1 (data not shown).

Similarly, investigators have defined the IFN-γ-responsive element in the IP-10 promoter in macrophages (40). The IP-10 promoter contains an interferon stimulus response element, as well as two κB sites located at −228 to −102 in the 5′ proximal promoter (40). Although the interferon stimulus response element is necessary and sufficient for IFN-γ-induced IP-10 gene expression, optimal response to IFN-γ required both the interferon stimulus response element and one of two κB sites.

Low molecular mass HA fragments have been shown to activate the NF-κB/κB-α transcriptional regulatory system (53). Interestingly, analysis of the Mig promoter reveals that there are three NF-κB binding sites on the 5′ promoter downstream from the γRE and, as noted, two NF-κB sites downstream from the interferon stimulus response element on the 5′ IP-10 promoter. Thus, HA may be synergizing with IFN-γ to induce chemokine gene expression through interactions between a STAT-1α like protein and/or NF-κB for Mig and IP-10 gene expression. Studies to address this possibility are ongoing.

Interactions between ECM and cytokines in regulating inflammatory gene expression may have an important role in determining the resolution of an inflammatory response. Recent studies have shown that HA and IFN-γ promote the expression of macrophage-derived IL-12 and reactive nitrogen intermediates (14, 15) while abrogating the ability of HA to induce MIP-1α, MIP-1β, and KC (51). These new data add Mig and IP-10 to the subgroup of chemokines produced in the presence of low molecular mass HA and IFN-γ. It is interesting to
speculate that introducing IFN-γ at the appropriate time in the inflammatory response will promote resolution through the direct effects on macrophage chemokine production. Thus, understanding the molecular mechanisms regulating the interaction between ECM- and IFN-γ-inducible genes may lead to new approaches to ameliorate chronic inflammation.

REFERENCES

1. Carre, P., Mortensen, R., King, T., Noble, P., Sable, C., and Riches, D. (1991) J. Clin. Invest. 88, 1802–1810
2. Gauldie, J., Jordana, M., and Cox, G. (1993) Thorax 48, 931–935
3. Martinet, Y., Rom, W. N., Grotendorst, G. R., Martin, G. R., and Crystal, R. G. (1987) N. Engl. J. Med. 317, 202–209
4. Nathan, C. (1987) J. Clin. Invest. 76, 319–322
5. Rom, W. N., Basset, P., Fells, G. A., Nukiwa, T., Trapnell, B. C., and Crystal, R. G. (1988) J. Clin. Invest. 82, 1685–1693
6. Juliano, R. L., and Haskill, S. (1993) J. Cell Biol. 120, 577–585
7. Hidenori, K., Raines, E. W., Bornfeldt, K. E., Roberts, J. M., and Ross, R. (1996) Cell 87, 1069–1078
8. Hance, A. J., and Crystal, R. G. (1975) Am. Rev. Respir. Dis. 112, 657–668
9. Laskin, D., Wilkner, N., Doherty, D., and Norris, D. (1988) J. Biol. Chem. 263, 12115–12123
10. West, D., Hampson, I., Arnold, F., and Kumar, S. (1985) Science 228, 1324–1326
11. Launder, S. I., Hunninghake, P. B., Bitterman, P. R., and Crystal, R. G. (1981) Proc. Natl. Acad. Sci. U. S. A. 78, 7147–51
12. McKee, C., Penno, M., Cowman, M., Burdick, M., Strieter, R., Bao, C., and Noble, P. (1996) J. Clin. Invest. 98, 2403–2413
13. McKee, C., Lowenstein, C., Jackson, M., Lu, C., Bao, C., and Noble, P. (1997) J. Biol. Chem. 272, 8013–8018
14. Hodge-Dufour, J., Noble, P., Horton, M. R., Bao, C., Wysoka, M., Burdick, M. D., Strieter, R. M., Trinchieri, G., and Pure, E. (1997) J. Immunol. 158, 2492–2500
15. Noble, P., Lake, P., Henson, P., and Riches, D. (1993) J. Clin. Invest. 91, 2368–2375
16. Laurent, T., and Fraser, J. (1992) FASEB J, 6, 2397–2404
17. Lazaar, A., Alveda, S., Pilewski, J., Brenner, B., Pure, E., and Panetti, R. (1994) J. Exp. Med. 180, 807–816
18. Balazs, E. A., Watson, D., Duff, I. F., and Roseman, S. (1967) Arthritis Rheum. 10, 357–370
19. Bjerner, L., Lundgren, R., and Hallgren, R. (1989) Thorax 44, 126–131
20. Hallgren, R., Ekholm, A., Engstrom-Laurent, B., and Schnekel, B. (1985) Br. Med. J. 290, 1778–1787
21. Gazzinielli, R. T., Oswald, I. P., James, S. L., and Shen, A. (1992) J. Immunol. 148, 4753–4769
22. Fleisch, I., Hess, J. H., Oswald, I. P., and Kaufmann, S. H. E. (1994) Int. Immunol. 6, 693–702
23. Ohmori, Y., and Hamilton, T. A. (1994) J. Immunol. 153, 2204–2212
24. Ohmori, Y., and Hamilton, T. A. (1994) J. Biol. Chem. 269, 15049–15056
25. Farber, J. M. (1990) Proc. Natl. Acad. Sci. U. S. A. 87, 5238–5242
26. Nakamura, S., Tominaga, Y., Tamura, M., Shimai, S., Okamura, H., Nishioji, K., Itoh, Y., and Okanoue, T. (1997) J. Immunol. 158, 5536–5544
27. Luster, A. D., Unkeless, J. C., and Ravetch, J. V. (1985) Nature 317, 672–676
28. Amici, D., Gazzinelli, R., Karupiah, G., Moench, T., and Farber, J. M. (1990) J. Immunol. 157, 4511–4520
29. Asensio, V., and Campbell, I. (1997) J. Virol. 71, 7832–7840
30. Liano, F., Rhain, R. L., Yannelli, J. R., Koniaris, L. G., Vanguri, P., and Farber, J. M. (1995) J. Exp. Med. 182, 1301–1314
31. Tobias, G., Gerber, B., Leotscher, P., Jones, S. A., Piali, L., Clark-Lewis, I., Baggioni, M., and Moorer, B. (1996) J. Exp. Med. 184, 963–969
32. Tao, D., Lloyd, L., Conlon, K., Wang, J., Ontalbo, J., Harada, A., Matsushima, K., Kelvin, D., and Oppenheim, J. (1993) J. Exp. Med. 177, 1809–1814
33. Strieter, R. M., Polverini, P. J., Kunkel, S. L., Arenberg, D. A., Burdick, M. D., Kasper, J., Dzuba, J., Van Damme, J., Waltz, A., Marriotti, D., Chan, S., Rosenak, S., and Shanafelt, A. B. (1995) J. Biol. Chem. 270, 27348–27357
34. Strieter, R. M., Polverini, P. J., Arenberg, D. A., and Kunkel, S. L. (1995) Shock 4, 155–160
35. Angioli, A. L., Spadari, C., Taub, D. D., Liao, F., Farber, J. M., Maheshwari, S., Kleinman, H. K., Reaman, G. H., and Tosato, G. (1995) J. Exp. Med. 182, 155–162
36. Mabuikwe, I., and Herscowitz, H. (1989) J. Leukocyte Biol. 45, 112–117
37. Balazs, E. A., Watson, A. F., Duff, I. F., and Roseman, S. (1967) Ann. N. Y. Acad. Sci. 179, 107–117
38. Ohmori, Y., and Hamilton, T. (1993) J. Biol. Chem. 268, 6677–6688
39. Lee, T. H., Lee, G. W., Ziff, E. B., and Vilcek, J. (1990) Mol. Cell. Biol. 10, 1982–1988
40. Lokuta, M., Mahner, J., Nee, K., Pitha, P., Shin, M., and Shin, H. (1996) J. Biol. Chem. 271, 13731–13738
41. Bredt, D. S., Hwang, P. M., and Snyder, S. H. (1990) Nature 347, 768–770
42. Greenberg, M. E., and Bendler, T. P. (1995) in Current Protocols in Molecular Biology (Ausubel, F. M., Brent, R., Kingston, R. E., Moore, D. D., Seidman, J. G., Smith, J. A., and Struhl, K., eds) Vol. 1, pp. 4.10.1–4.10.11, John Wiley & Sons, Inc., New York
43. Wright, T. M., and Farber, J. M. (1991) J. Exp. Med. 173, 417–422
44. Guyer, N. B., Severns, C. W., Wong, P., Feghali, C. A., and Wright, T. M. (1995) J. Immunol. 155, 3472–3480
45. Wright, T. M., and Farber, J. M. (1994) Mol. Cell. Biol. 14, 914–922
46. Horton, M., Burdick, M., Strieter, R., Bao, C., and Noble, P. (1998) J. Immunol. 160, 3025–3030
47. Darnell, J. E. (1997) Science 277, 1630–1635
48. Noble, P., McKee, C., Cowman, M., and Shin, H. (1996) J. Exp. Med. 183, 2373–2378
Hyaluronan Fragments Synergize with Interferon-γ to Induce the C-X-C Chemokines Mig and Interferon-inducible Protein-10 in Mouse Macrophages

Maureen R. Horton, Charlotte M. McKee, Clare Bao, Fang Liao, Joshua M. Farber, Jennifer Hodge-DuFour, Ellen Puré, Bonnie L. Oliver, Timothy M. Wright and Paul W. Noble

J. Biol. Chem. 1998, 273:35088-35094.
doi: 10.1074/jbc.273.52.35088

Access the most updated version of this article at http://www.jbc.org/content/273/52/35088

Alerts:
- When this article is cited
- When a correction for this article is posted

Click here to choose from all of JBC's e-mail alerts

This article cites 53 references, 30 of which can be accessed free at http://www.jbc.org/content/273/52/35088.full.html#ref-list-1