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Biochemical and Biophysical Research Communications 327 (2005) 212–217
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# Synergistic induction of hepatocyte growth factor in human skin fibroblasts by the inflammatory cytokines interleukin-1 and interferon-γ

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Received 23 November 2004
Available online 10 December 2004

**Abstract**

Hepatocyte growth factor (HGF) is one of the vital factors for wound healing. HGF expression markedly increases in wounded skin and is mainly localized in dermal fibroblasts. HGF expression level in human dermal fibroblasts in vitro, however, is low and thus may be stimulated by some factors in the process of wound healing. Candidates of the factors are inflammatory cytokines released by polymorphonuclear and mononuclear cells infiltrating the wounded area, but HGF production in human dermal fibroblasts is only slightly induced by interleukin (IL)-1, tumor necrosis factor (TNF)-α or interferon (IFN)-γ. We here report that a combination of IL-1β and IFN-γ or a combination of TNF-α and IFN-γ very markedly induced HGF production. The synergistic effect of the former was more marked than that of the latter. Synergistic effects of IL-1β and IFN-γ were observed at more than 10 pg/ml and 10 IU/ml, respectively, and were detectable as early as 12 h after addition. Neither IFN-α nor IFN-β was able to replace IFN-γ. HGF mRNA expression was also synergistically upregulated by IL-1β and IFN-γ. IL-1β plus IFN-γ-induced synergistic production of HGF was potently inhibited by treatment of cells with the extracellular signal-regulated kinase (ERK) kinase inhibitor PD98059 and the p38 inhibitor SB203580 but not by the c-Jun N-terminal kinase (JNK) inhibitor SP600125. Taken together, our results indicate that a combination of IL-1β and IFN-γ synergistically induced HGF production in human dermal fibroblasts and suggest that activation of ERK and p38 but not of JNK is involved in the synergistic effect.


*Keywords:* Hepatocyte growth factor; Interleukin-1; Interferon-γ; Tumor necrosis factor-α; Induction; Dermal fibroblast

Wound healing is a complex process of inflammation, granulation tissue formation, angiogenesis, re-epithelialization, and remodeling [1]. The complexity of this process is compounded by the fact that skin is comprised of two distinct compartments, the ectodermally derived epithelial epidermis and the mesodermally derived mesenchymal dermis, which are separated by a basement membrane barrier. To regenerate this organ, numerous cellular, hormonal, matrix, and enzymatic activities in each compartment are required to act in a coordinated manner with those in the other compartment. If re-epithelialization occurs without sufficient underlying granulation tissue formation, which encompasses macrophage accumulation, fibroblast ingrowth, matrix deposition, and angiogenesis, then an atrophic scar results. If granulation tissue proceeds without the requisite re-epithelialization, then a nonhealed wound with hypergranulation tissue is the outcome. It has become increasingly apparent that epithelial cells and mesenchymal cells communicate with each other through cytokine networks to coordinate their migratory and proliferative responses to injury [2].

Hepatocyte growth factor (HGF), also known as scatter factor, was initially isolated as a mitogenic factor for adult rat hepatocytes in primary culture and is

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doi:10.1016/j.bbrc.2004.11.144

mainly produced by mesenchymal cells such as fibroblasts and smooth muscle cells [3–9]. It has been shown to stimulate proliferation of many kinds of epithelial cells and have multiple activities such as motogenic, morphogenic, and tumor-inhibiting activities besides mitogenic activity [10,11]. HGF is capable of stimulating migration and proliferation of keratinocytes, and thus has been suggested to be involved in cutaneous physiology and wound healing [12–14]. Recent studies have indicated that expression of HGF and its receptor, c-Met, increases in response to cutaneous wounding [15,16]. The expression level of HGF is high in fibroblasts at the wound edge, whereas expression of c-Met is upregulated in keratinocytes, vascular endothelial cells, and myofibroblasts in granulation tissue [16]. When neutralizing anti-HGF is locally and continuously delivered to subcutaneous lesions, retardation in the number of capillary vessels, expansion of granulation tissue, re-epithelialization, and rate of wound closure occur [16]. Since unstimulated dermal fibroblasts produced only a small amount of HGF [8,17], some factors may induce HGF production in fibroblasts during wound healing.

Possible sources of HGF-inducing factors are polymorphonuclear cells, activated macrophages, and T cells, which infiltrate the wound area and produce a series of inflammatory cytokines, including interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ. However, the magnitude of HGF induction by the inflammatory cytokines in human dermal fibroblasts is minimal [18,19]. Here we report that a combination of IL-1β and IFN-γ promptly and markedly induced HGF production in human dermal fibroblasts and that the synergistic induction of HGF was blocked by inhibitors of extracellular signal-regulated kinase (ERK) kinase and p38 mitogen-activated protein kinase (MAPK) but not by a c-Jun N-terminal kinase (JNK) inhibitor.

## Materials and methods

*Reagents*. Dulbecco's modified Eagle's medium (DMEM) was purchased from Nissui Pharmaceutical (Tokyo, Japan). Recombinant human IL-1α and IL-1β were obtained from Otsuka Pharmaceutical (Tokyo, Japan) and R&D Systems (Minneapolis, MN), respectively. Natural human TNF-α, IFN-α, and IFN-γ were purchased from Hayashibara Biochemical Laboratories (Okayama, Japan). Recombinant human IFN-β was obtained from PBL Biomedical Laboratories (Piscataway, NJ). PD98059 and SB203580 were purchased from Calbiochem (San Diego, CA). SP600125 was obtained from BIOMOL Research Laboratories (Plymouth Meeting, PA). Other reagents were obtained from previously reported sources [20].

*Cell culture*. Normal human dermal fibroblasts isolated from 200 individual neonatal donors were obtained from Cell Systems (Kirkland, WA) and used between 7th and 10th passages. Normal human dermal fibroblasts isolated from a 3-day-old baby were obtained from the Riken Cell Bank (Tsukuba, Japan) and used between 7th and 10th passages in some experiments. The cells were grown as monolayers in DMEM supplemented with 10% fetal bovine serum, 4 mM L-glutamine, 100 U/ml penicillin, and 100 μg/ml streptomycin at 37 °C in a humidified atmosphere of 5% $CO_2$ and 95% air as described previously [20].

*Determination of HGF levels in conditioned media*. Human dermal fibroblasts, trypsinized and suspended in the medium described in the previous section, were seeded in 96-well plates (Nunc) at a density of $1.8 \times 10^4$ cells/cm$^2$ (0.17 ml/well). After reaching confluence, the medium was replaced with the same fresh medium or that containing IL-1β, IFN-γ or IL-1β plus IFN-γ, and the cultures were incubated for 72 h, unless stated otherwise. The conditioned medium was then collected and was frozen at −30 °C for a human HGF ELISA. The sandwich ELISA for human HGF was performed at room temperature as described previously [21], with a slight modification [19].

*Northern blot analysis*. The medium of confluent human dermal fibroblasts grown in 9-cm dishes (Nunc) was replaced with the same fresh medium and incubated for 15 h. IL-1β, IFN-γ or IL-1β plus IFN-γ was then added, and the cultures were further incubated for 12 h. Total RNA was isolated from the cells using RNA-Bee (TEL-TEST). Northern blotting was performed as described previously [20].

## Results

### *Synergistic induction of HGF production by IL-1β and IFN-γ in human dermal fibroblasts*

IL-1β or TNF-α effectively induces HGF production in MRC-5 and IMR-90 human embryonic lung fibroblasts, but it is a weak inducer of HGF production in human dermal fibroblasts [18,19,22]. Induction of HGF production in human dermal fibroblasts by IFN-γ is also minimal, although IFN-γ markedly induces HGF production in human leukemia cell lines such as KG-1 and RPMI-8226 [18]. However, a combination of IL-1β and IFN-γ or a combination of TNF-α and IFN-γ synergistically induced HGF production in human dermal fibroblasts (Fig. 1). The synergistic effect of the former was more marked than that of the latter. IL-1β dose-dependently induced HGF production at doses of more than 10 pg/ml in the presence of IFN-γ (100 IU/ml) (data not shown). Similarly, IFN-γ dose-dependently induced HGF production at doses of more than 10 IU/ml in the presence of IL-1β (1 ng/ml) (data not shown). A combination of IL-1β and IFN-γ also synergistically induced HGF production in human dermal fibroblasts from a 3-day-old baby (data not shown). Cells treated with IL-1β plus IFN-γ produced more HGF than that produced by cells treated with EGF (3 ng/ml), which has been shown to induce HGF [23] (Fig. 1). The effect of IL-1α was also synergistic with IFN-γ (data not shown). In contrast, IL-1β plus TNF-α, IL-1β plus IFN-α or IL-1β plus IFN-β showed no synergistic induction of HGF production (data not shown). The synergistic effect of IL-1β plus IFN-γ was not further enhanced by TNF-α (Fig. 1). Time courses of the synergistic effects of IL-1β plus IFN-γ are shown in Fig. 2. Significant synergism occurred as early as 12 h after the start of incubation, when EGF-induced HGF production does not occur. Both constitutive and in-

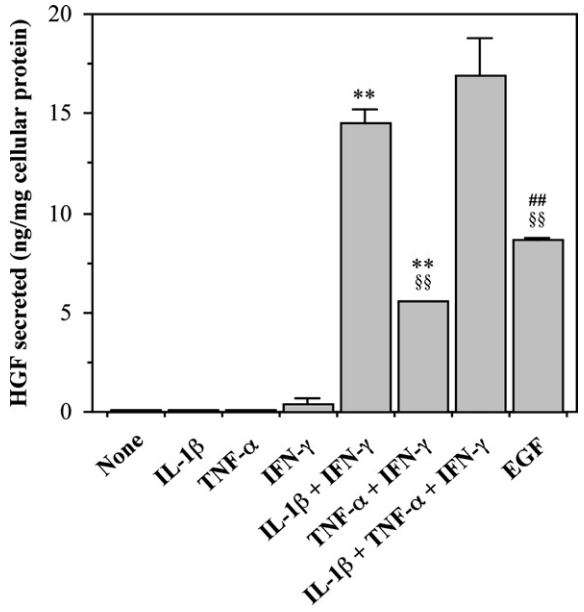


Fig. 1. Synergistic induction of HGF production in human dermal fibroblasts by a combination of IL-1β and IFN-γ, and of TNF-α and IFN-γ. Confluent human dermal fibroblasts were incubated for 72 h with or without IL-1β (1 ng/ml), TNF-α (30 JRU/ml), IFN-γ (1000 IU/ml), their combinations indicated, or EGF (3 ng/ml). The data are means of three independent experiments. Bars indicate SEM. Synergistic induction of HGF production is indicated by $^{**}P < 0.01$ (2-way ANOVA). $^{\#\#}P < 0.01$ (Dunnett's $t$ test), as compared with the values of the medium alone. $^{\S\S}P < 0.01$ (Dunnett's $t$ test), as compared with the values of IL-1β plus IFN-γ.

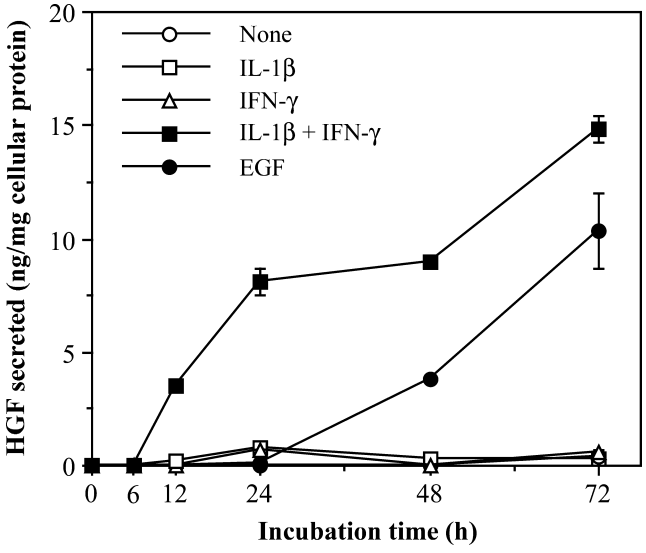


Fig. 2. Time courses of synergic induction of HGF production in human dermal fibroblasts by IL-1β and IFN-γ. Confluent human dermal fibroblasts were incubated for the indicated periods with or without IL-1β (1 ng/ml), IFN-γ (100 IU/ml), their combination, or EGF (3 ng/ml). The data are representative of two independent experiments and are expressed as means ± SEM of triplicate cultures.

duced HGF production in various kinds of cells are inhibited by TGF-β and dexamethasone [17,24–26]. The synergistic production of HGF induced by IL-1β plus IFN-γ was also potently inhibited by TGF-β1 and dexamethasone (data not shown).

### *Synergistic upregulation by IL-1β and IFN-γ of HGF mRNA expression*

The effects of IL-1β, IFN-γ, and IL-1β plus IFN-γ on HGF gene expression in human dermal fibroblasts determined 12 h after addition are shown in Fig. 3. IL-1β or IFN-γ significantly upregulated HGF mRNA

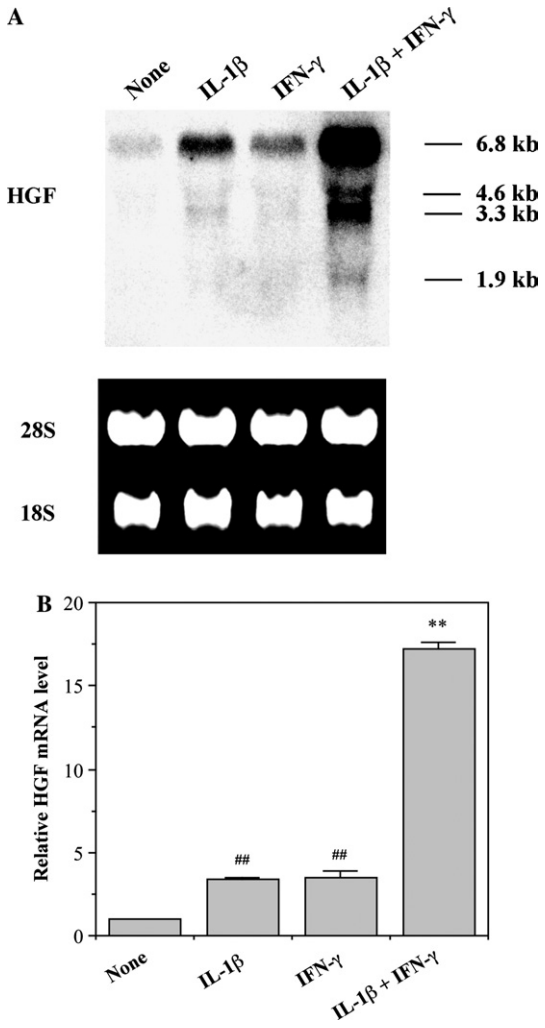


Fig. 3. Synergistic upregulation of HGF gene expression in human dermal fibroblasts by IL-1β and IFN-γ. Confluent human dermal fibroblasts were incubated for 12 h with or without IL-1β (1 ng/ml), IFN-γ (100 IU/ml) or their combination. Autoradiographs and fluorescence photographs (A) are representative of three independent experiments. The signal intensity of the 6.8-kb HGF mRNA band was normalized to the fluorescence intensity of the 28S rRNA band and expressed as fold-change relative to the control cultures, which were incubated in the medium alone. The data (B) are means of three independent experiments. Bars indicate SEM. Synergistic upregulation of HGF mRNA expression is indicated by $^{**}P < 0.01$ (2-way ANOVA). $^{\#\#}P < 0.01$ (Dunnett's $t$ test), as compared with the values of the medium alone.

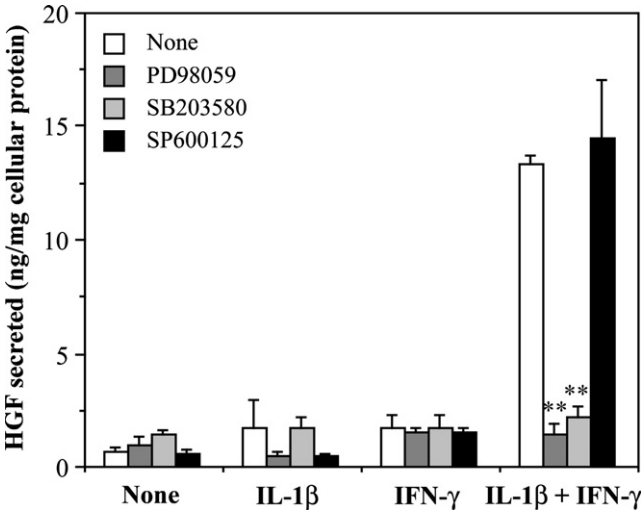


Fig. 4. Synegistic induction of HGF production by a combination of IL-1β and IFN-γ is blocked by the inhibitors of ERK kinase and p38 MAPK but not by the inhibitor of JNK. Confluent human dermal fibroblasts were pre-incubated for 2 h with or without 25 μM PD98059, 5 μM SB203580 or 10 μM SP600125 and incubated for 72 h with or without IL-1β (1 ng/ml), IFN-γ (100 IU/ml) or their combination. The data are means of three independent experiments. Bars indicate SEM. $^{**}P < 0.01$ (Dunnett's $t$ test), as compared with the values of the inducer alone.

expression, and IL-1β plus IFN-γ synergistically increased the level of HGF mRNA.

*Involvement of ERK and p38 MAPK in the synergistic induction of HGF production by IL-1β and IFN-γ*

After binding to its cell-surface receptor, IL-1β triggers a cascade of signaling events, including activation of ERK, p38 MAPK, and JNK, which upregulate the expression of many inflammation-related genes in the nucleus. We examined the roles of these pathways in mediating the synergistic effect of IL-1β plus IFN-γ on HGF induction by use of their selective pharmacological inhibitors. The inhibitors we used are the MEK inhibitor PD98059, the p38 MAPK inhibitor SB203580, and the JNK inhibitor SP600125. IL-1β plus IFN-γ-caused induction of HGF was potently inhibited either by PD98059 or SB203580 but not by SP600125 (Fig. 4).

## Discussion

Since expression of HGF in wounded skin of mice increases as early as 2 days post-wounding and reaches a peak on day 4 [16], levels of the factor(s) that induces HGF production in skin fibroblasts may increase prior to these events. A strong infiltration of polymorphonuclear cells has been detected in the wounded area between 6 and 12 h post-wounding [27]. Within 48–72 h, most of the polymorphonuclear cells are replaced by mononuclear cells such as macrophages: the number of activated macrophages markedly increases at 1 day post-wounding and the elevated levels are maintained for several days [28]. In accordance with the increase in the number of polymorphonuclear cells and activated macrophages, expression of IL-1β mRNA has been shown to increase markedly as early as 6 h post-wounding and peak at 48–72 h [27]. Induced IFN-γ mRNA and protein expression by infiltrating macrophages and T cells have also been detected as early as 1 day and have been highest 3 days post-wounding in the wounded area [29]. Although the HGF-inducing activity of each inflammatory cytokine is weak, IL-1β or TNF-α showed a marked induction of HGF production in human skin fibroblasts when combined with IFN-γ. Thus, it is possible that inflammatory cytokines that are released by cells infiltrating the wound site during the inflammation phase cooperatively induce HGF production. Increased HGF may act as a component of cytokine networks, through which epithelial cells and mesenchymal cells communicate with each other to coordinate their migratory and proliferative responses to injury, and play an important role in the formation of capillary vessels and granulation tissues, re-epithelialization, and wound closure [16].

Several other instances of synergism between IL-1β and IFN-γ are known: both cytokines synergistically upregulated mRNA or protein expression of interferon-inducible protein-10 and monocyte chemotactic protein-1 and -2, and production of nitric oxide [30–32], although the molecular mechanisms responsible for these synergistic effects have not been elucidated. IL-1β triggers a cascade of signaling events, including activation of three members of the MAPK family, ERK, JNK, and p38 MAP kinases [33–35]. Results of our experiments using specific pharmacological inhibitors suggested that activation of ERK and p38 but not that of JNK is involved in the synergistic induction of HGF production by IL-1β and IFN-γ. Since members of the MAPK family that participate in upregulation of IL-1 responsive genes differ among the genes, it seems likely that transcription factors involved in the transcriptional regulation of an IL-1 responsive gene determine which members of the MAPK family are required.

We previously reported that IL-1β, which alone exhibits a slight induction of HGF production, inhibited HGF production induced by the protein kinase A-activating agents cholera toxin and 8-bromo-cAMP in human dermal fibroblasts, and that the inhibitory effect of IL-1β was completely overcome by IFN-γ but not by either IFN-α or IFN-β [19]. Since inhibition by IL-1β of cholera toxin-induced phosphorylation of cAMP-responsive element-binding protein (CREB) was not attenuated in cells treated with IFN-γ [19], we speculated that IFN-γ may overcome the inhibitory effect of IL-1β on HGF induction not through a direct

antagonistic action but through a more complex mechanism(s). The results obtained in this study showing that IL-1β and IFN-γ synergistically induced HGF production may at least partly explain the mechanisms responsible for prevention by IFN-γ of IL-1β-caused inhibition of HGF induction.

Following partial hepatectomy, regeneration is usually accomplished by replication of remaining mature hepatocytes, but impairment of the regenerative capacity of hepatocytes may result in proliferation and migration of oval cells originating from ductular cells, which appear to form a reservoir capable of forming both mature hepatocytes and bile duct cells [36]. The gene network connected to IFN-γ, including IFN-γ receptor-α and -β, gp91phox, urokinase-type plasminogen activator, and IL-1β, has been shown to be modulated in this process [37]. It has also been shown that IL-1β is capable of inducing IFN-γ production in rat hepatocytes [38]. Moreover, HGF has been shown to stimulate proliferation and differentiation of oval cells [39,40]. Thus, marked induction of HGF production by a combination of IFN-γ and IL-1β is worthy of further study in the context of not only wound healing but also liver regeneration from oval cells.

In conclusion, the results of this study demonstrated that a combination of IL-1β and IFN-γ synergistically induced HGF production in human dermal fibroblasts and suggest that activation of ERK and p38 but not that of JNK is involved in the synergistic effect.

## Acknowledgment

This work was supported in part by Grant-in-Aid for Scientific Research (13672285) from the Japan Society for the Promotion of Science (JSPS).

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