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Brief Communication

Anti-inflammatory Effects of Neuregulin-1 via the Downregulation of IL-6, IL-8, and MCP-1 Secretion

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The trophic factor Neuregulin-1 (NRG-1) plays a critical role in the development of the peripheral nervous system and the repair of nerve injuries. The regulation of neutrophil apoptosis by cytokine secretion from structural cells is an important process in inflammatory diseases, including asthma. This study aimed to investigate the relationship between NRG-1 and the alteration of neutrophil apoptosis by the regulation of cytokine release in the human lung epithelial BEAS-2B cells. Tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ) induce the increase in the release of interleukin (IL)-6, IL-8, and monocyte chemoattractant protein-1 (MCP-1). NRG-1 alone had no effect on the secretion of IL-6, IL-8, and MCP-1. However, co-treatment of TNF-α and IFN-γ with NRG-1 inhibited the secretion of IL-6, IL-8, and MCP-1 that had been increased by TNF-α and IFN-γ. Treatment with NRG-1 did not have a direct effect on neutrophil apoptosis. Co-treatment of TNF-α and IFN-γ with NRG-1 was not effective on suppression of neutrophil apoptosis due to TNF-α and IFN-γ. The supernatant of BEAS-2B cells after co-treatment of TNF-α and IFN-γ with NRG-1 suppressed the inhibition of neutrophil apoptosis that had been caused due to the supernatant treated with TNF-α and IFN-γ. Taken together, NRG-1 has an anti-inflammatory effect in an inflammatory milieu by the regulation of cytokine secretion and neutrophil apoptosis.

Key Words: Inflammation, Neuregulin-1, Neutrophil apoptosis, Cytokine

Neuregulin-1 (NRG-1) exerts biological functions by interacting with ErbB receptors. Action and dysregulation of NRG-1 are closely related to neurodegenerative disorders, including Alzheimer's disease and cardiovascular diseases (Bartus et al., 2016; Kang et al., 2019; Kang et al., 2020; Vrillon et al., 2022). Inflammation results in an increase in cytokine secretion and neutrophil survival, resulting in the exacerbation of allergic disorders, including asthma, allergic rhinitis and atopic dermatitis (Holgate, 2008; Kim et al., 2014; Kim et al., 2020; Lee, 2020). IL-6, IL-8, and MCP are inflammation-related cytokines that regulate the survival rate of neutrophils by reducing their apoptosis. In this study, the treatment with TNF-α and IFN-γ was used as inflammatory activators, and human lung epithelial BEAS-2B cells were used as cytokine secreting cells.

First, the effect of NRG-1 on the secretion of IL-6, IL-8, and MCP-1 in BEAS-2B cells was examined. Although NRG-1 alone had no effect on the release of IL-6, IL-8, and MCP-1, co-treatment of TNF-α and IFN-γ with NRG-1 suppressed the secretion of these cytokines enhanced by TNF-α and IFN-γ (Fig. 1). These results indicate that NRG-1 acts as an essential regulator in cytokine expression in an

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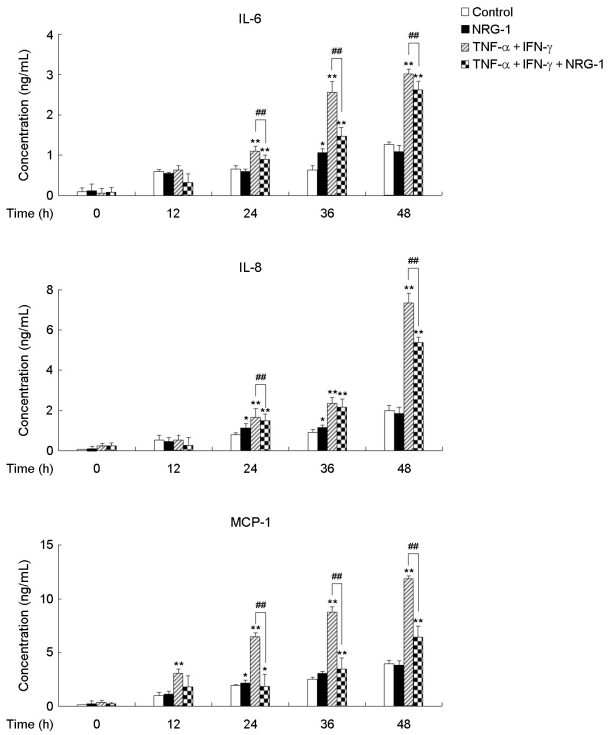

Fig. 1. NRG-1 suppresses IL-6, IL-8, and MCP-1 secretion increased by TNF-α and IFN-γ in BEAS-2B cells. BEAS-2B cells were treated with TNF-α+IFN-γ (10 ng/mL), NRG-1 (10 nmol/mL), and TNF-α+IFN-γ (10 ng/mL)+NRG-1 (10 nmol/mL). The data are presented as the mean ± S.D; **P* < 0.05 and ***P* < 0.01 indicate a significant difference between the control and TNF-α and IFN-γ-treated groups, and ##*P* < 0.01 indicates significant difference between the TNF-α and IFN-γ and TNF-α+IFN-γ+NRG-1-treated groups.

inflammatory state. The study also examined whether the decreased level of cytokines by NRG-1 treatment, such as IL-6, IL-8, and MCP-1, affects the apoptosis of neutrophils and eosinophils. As shown in Fig. 2A, TNF-α and IFN-γ doesn't block eosinophil apoptosis but neutrophil apoptosis. Single NRG-1 had no effect on neutrophil and eosinophil apoptosis. Co-treatment of TNF-α and IFN-γ with NRG-1 did not affect the inhibition of neutrophil apoptosis due to TNF-α and IFN-γ. The supernatant collected from the BEAS-2B cells after treatment with TNF-α and IFN-γ inhibited neutrophil apoptosis (Fig. 2B). However, the supernatant of BEAS-2B cells after co-treatment of TNF-α and IFN-γ with NRG-1 showed a decreased anti-apoptotic effect on neutrophils compared to the effect of the supernatant stimulated with TNF-α and IFN-γ. It has been reported that NRG-1 enhances MUC5AC and MUC5B expression in human bronchial epithelial cells (HBECs) and may result in the aggravation of allergy (Kettle et al., 2010). In contrast to this finding, NRG-1 exhibits a protective role by its anti-inflammatory and anti-oxidative effects on cardiocytes by regulating IL-1, IL-6, IL-8, and IL-10 (Kang et al., 2019). Our results show that NRG-1 by itself has no effect on cytokine secretion and apoptosis in BEAE-2B cells and neutrophils, respectively.

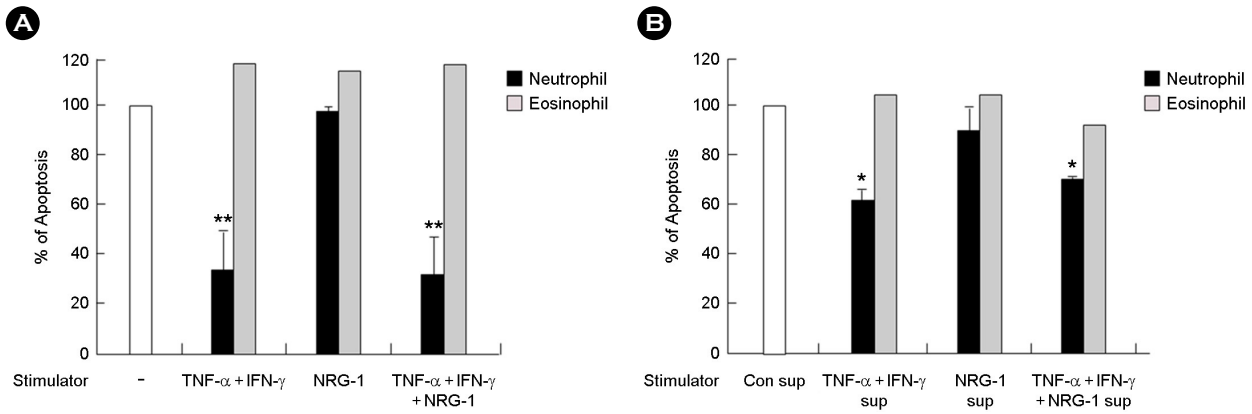

Fig. 2. BEAS-2B cell supernatants treated with TNF-α, IFN-γ and NRG-1 suppresses anti-apoptotic effect of the supernatants exposed to TNF-α and IFN-γ on neutrophils. (A) Neutrophils (n=3) and eosinophils (n=3) were isolated and incubated for 24 h or 48 h in the absence or presence of TNF-α+and IFN-γ (10 ng/mL) or/and NRG-1 (10 nmol/mL). (B) BEASE-2B cells were treated with TNF-α+IFN-γ (10 ng/mL) or/and NRG-1 (10 nmol/mL). The supernatants were collected and used for treatment of neutrophils (n=3) and eosinophils (n=3). The supernatant-treated cells were incubated for 24 h (neutrophils) or 48 h (eosinophils) Apoptotic cells were evaluated using annexin-PI staining. Data are presented as mean ± SD relative to the control, which was set to be 100%. **, *P* < 0.01 and *, *P* < 0.05, significant differences between non-treated and stimulator-treated groups.

In an inflammatory state, NRG-1 exhibits a protective effect that reduces IL-6, IL-8, and MCP-1, which connects with the reversal of neutrophil apoptosis decreased by TNF-α and IFN-γ. Previous studies have reported the close relation of allergy with cytokine secretion and neutrophil apoptosis (Hong et al., 2021; Jeon et al., 2021). Based on these findings, NRG-1 may play a critical role in the protection of exacerbations of allergies as well as other inflammatory diseases. This study has limitations with respect to the number of normal subjects and the absence of subjects suffering from specific inflammatory diseases. Hence, further studies are required to unveil the clear mechanism of the anti-inflammatory action induced by NRG-1 in specific inflammatory diseases.

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CONFLICT OF INTEREST

The authors have no conflicts of interest, financial or otherwise, to declare.

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