―**Review**―

Allergic Rhinitis and Vascular Endothelial Growth Factor

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Abstract

Vascular endothelial growth factor (VEGF) was identified in 1980s as a protein that increases vascular permeability and induces endothelial cell-specific mitosis. VEGF plays an important role in angiogenesis during the embryonic stage and in angiogenesis and in increasing vascular permeability during postnatal life, both physiologically and pathologically. Great progress has been made in studies of VEGF, mainly in the field of oncology, and VEGF-targeted therapy has been successfully used to treat patients with cancer. In research related to chronic inflammation, several reports concerning rheumatoid arthritis or retinopathy and VEGF have been published. In the lower respiratory tract, increased levels of VEGF have been detected in biological samples from patients with asthma. However, VEGF has not been studied in detail in upper-airway diseases, such as rhinosinusitis. This review article focuses on VEGF and allergic rhinitis to advance studies of VEGF in chronic inflammation of the upper respiratory tract. VEGF levels in nasal secretions and nasal lavage fluid were higher in perennial allergic rhinitis than in nonallergic rhinosinusitis, after, rather than before, the antigen provocation test. The major VEGF isoforms were confirmed to be $VEGF_{121}$ and $VEGF_{165}$ in allergic rhinitis. Expression of VEGF mRNA was higher in serous versus mucous acini. In allergic rhinitis, serous acini produced significant quantities of VEGF, which was hypersecreted after antigen provocation. VEGF seems to play an important role in the pathophysiology of allergic rhinitis. Modulation of VEGF function seems to contribute to the successful treatment of conditions with airway inflammation such as allergic rhinitis.
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Key words: VEGF, VEGF receptor, allergic rhinitis, vascular permeability, angiogenesis

Introductory Summary of Vascular Endothelial Growth Factor

Vascular endothelial growth factor (VEGF) was first identified in 1983 by Senger et al. in secretory components from rodent tumor cell lines as a 34,000– to 42,000-Da protein that increases vascular permeability and was designated a vascular permeability factor[1]. In 1989, Ferrara and Henzel identified a 45,000-Da growth factor in endothelial cell-specific mitogens secreted by bovine pituitary folliculostellate cells and proposed the name VEGF[2]. It was later found that the amino acid sequences of VEGF and vascular permeability factor were essentially identical, and the principal biological activities of both were found to be angiogenesis and increasing microvascular permeability[34]. VEGF plays
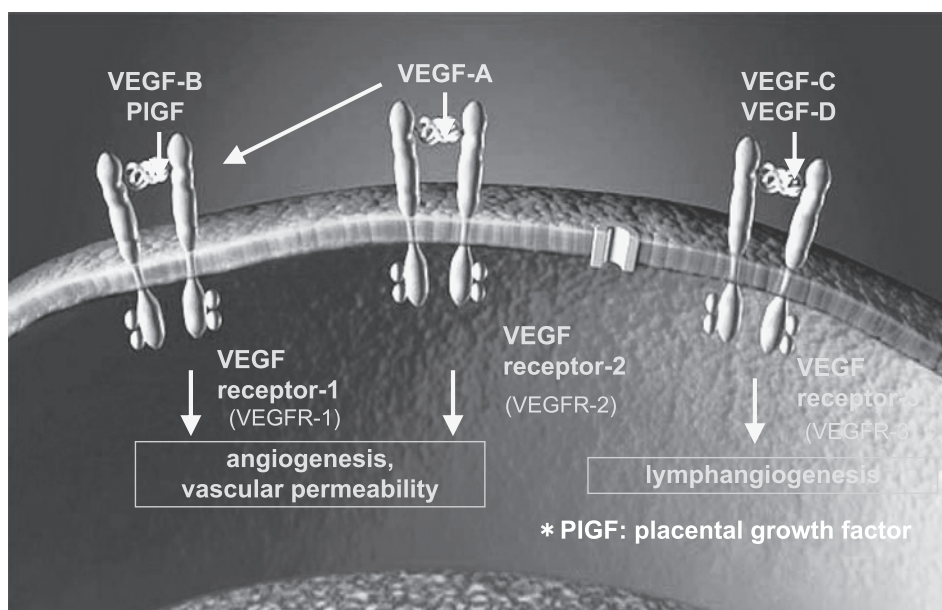
Ferrara N. Nat Med 2003;9:669–76

Fig. 1   VEGF family and receptors

an important role in angiogenesis during the embryonic stage[5,6] and in angiogenesis and in increasing vascular permeability during postnatal life, both physiologically and pathologically[7,8].

The VEGF family comprises 7 members: VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, VEGF-F, and placental growth factor. All members have a common VEGF homology domain. VEGF-A plays a central role in the physiological and pathological functions of the VEGF family. Recently, isoforms of VEGF-A and its receptors (VEGFRs), along with their mutual specific binding patterns, have been clarified **(Fig. 1)**.

The VEGF-A gene consists of 8 exons that give rise to 7 isoforms of 121, 145, 148, 165, 183, 189, and 206 amino acids through differential splicing. An important biological property that distinguishes the different VEGF isoforms is their ability to bind heparin and heparan sulfate. Although the 3 secreted VEGF splice forms—$VEGF_{121}$, $VEGF_{145}$, and $VEGF_{165}$—induce physiological activities among the 7 VEGF isoforms, $VEGF_{121}$ and $VEGF_{165}$ usually predominate. The production of $VEGF_{145}$ is restricted and occurs in cells derived from reproductive organs. $VEGF_{189}$ contains peptides inducing a higher affinity to heparin and heparan sulfate than do the peptides of $VEGF_{145}$ or $VEGF_{165}$ and is sequestered on heparan-sulfate proteoglycans of cell surfaces and in the extracellular matrix without secretion into the medium of $VEGF_{189}$-producing cells. Among the 7 VEGF isoforms, $VEGF_{121}$ and $VEGF_{165}$ are the dominant secretory forms and have the strongest biological activity in inflammation and tumor growth[8,9].

The biological effects of VEGF are mediated by 3 receptors, VEGFR-1 (flt-1), VEGFR-2 (KDR/flk-1), and VEGFR-3. VEGFR-1 and -2 mediate physiological and pathological angiogenesis and increase vascular permeability[10–12], whereas VEGFR-3 mediate lymphangiogenesis[13]. Expression of the VEGF-A gene can be induced when cells are subjected to hypoxia or hypoglycemia. The hypoxia-inducible protein complex hypoxia-induced factor (HIF)-1 binds to the enhancer sequences of the VEGF-A gene. HIF-1, a heterodimer consisting of HIF-1α and HIF-1 β subunits, is the most important transcription factor for hypoxia-regulated genes. Among growth factors and cytokines, tumor necrosis factor-α tissue growth factor-β, epidermal growth factor, and platelet-derived growth factor BB can trigger or induce VEGF-A messenger (m) RNA expression.

Great progress has been made in studies of VEGF, mainly in the field of oncology, and VEGF-targeted therapy has been successfully used to treat patients
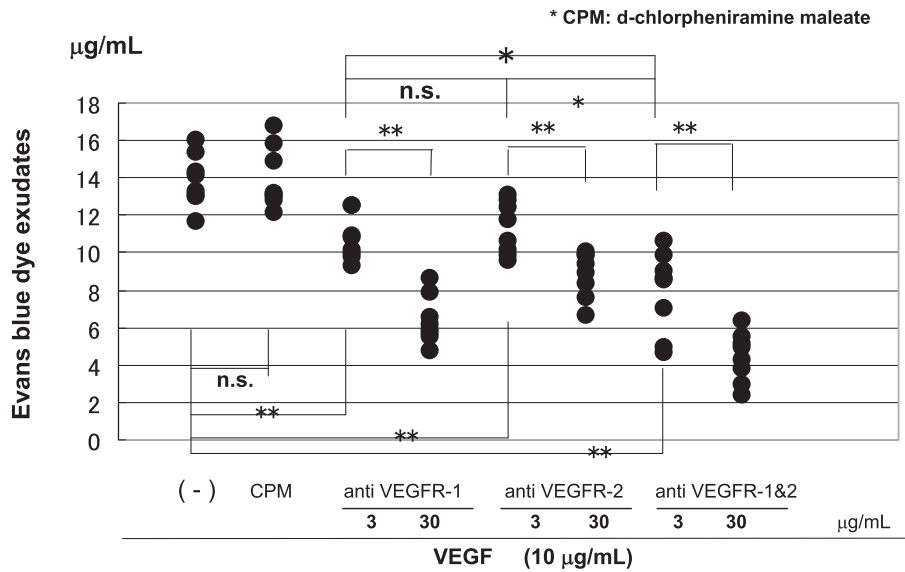
Fig. 2 Inhibition of VEGF-effects by anti-VEGF receptor antibodies in nasal mucosa
―experimental data―

with cancer. In research related to chronic inflammation, several reports concerning rheumatoid arthritis or retinopathy and VEGF have been published[14] . In the lower respiratory tract, increased levels of VEGF have been detected in biological samples from patients with asthma[15,16]. However, VEGF has not been studied in detail in upper-airway diseases, such as rhinosinusitis. This review article focuses on VEGF and allergic rhinitis (AR) to advance studies of VEGF in chronic inflammation of the upper respiratory tract.

## VEGF-A (VEGF_165), VEGFRs, and Vascular Permeability in Normal Nasal Mucosa: Experimental Analysis

The role of VEGF in vascular permeability was examined in the dorsal skin of guinea pigs by Senger DR *et al*; they found that VEGF increases vascular permeability 5×10^4 times as potently, on a molar basis, as histamine[17]. According to our data, in the nasal mucosa of normal guinea pigs, VEGF increases vascular permeability 1.0×10^6 times as potently as histamine on a molar basis. Although the increase in vascular permeability induced by VEGF is not blocked by a histamine receptor 1 antagonist, it is blocked by antibodies against VEGFRs.

Regulating VEGF may be a new therapeutic option for persistent nasal symptoms in AR[18] (**Fig. 2**).

VEGF and AR

In research on AR, the possible importance of VEGF as a mediator was first reported by Benson et al. in 2002; in summary, results of oligonucleotide microarray analysis of nasal biopsy specimens and protein analysis of nasal fluids suggest that VEGF-A is an important mediator in seasonal AR (SAR)[19]. The presence of increased angiogenesis and its relation to angiogenic molecules, namely VEGF, CD34, and FvW, in endothelial cells of the nasal mucosa in patients with SAR were studied with 3 different methods of immunohistochemical analysis[20].

We analyzed the relationship of VEGF and the pathophysiology of AR in detail; VEGF levels in nasal secretions and nasal lavage fluid were higher in perennial AR (PAR) than in nonallergic rhinosinusitis (**Fig. 3**), after, rather than before, the antigen provocation test (**Fig. 4**). The major VEGF isoforms were confirmed to be VEGF_121 and VEGF_165 in AR (**Fig. 5**). Expression of VEGF mRNA was higher in serous versus mucous acini (**Fig. 6**). These results are consistent with immunohistochemical results (**Fig. 7**). In AR, serous acini produced
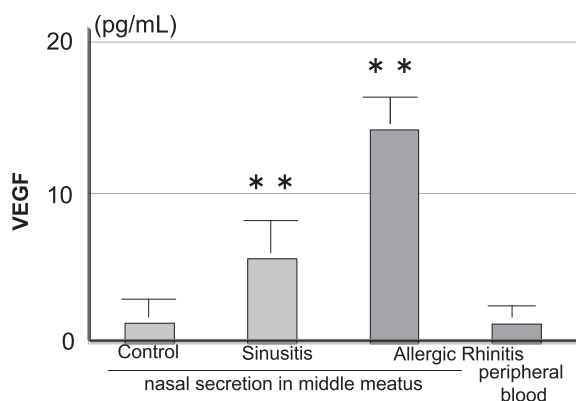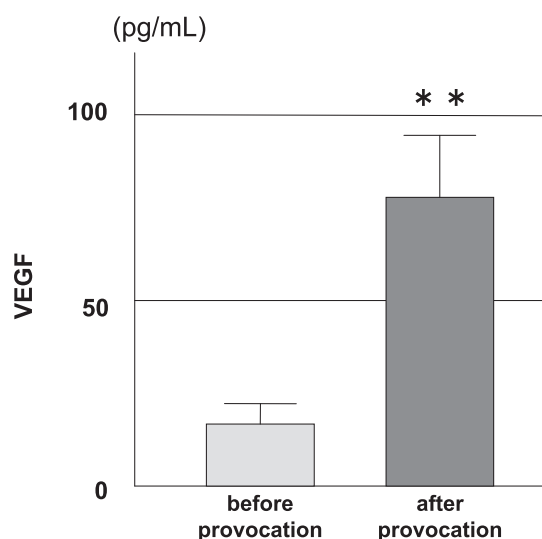
Matsune S *et al.* Am J Rhinol. 2008.

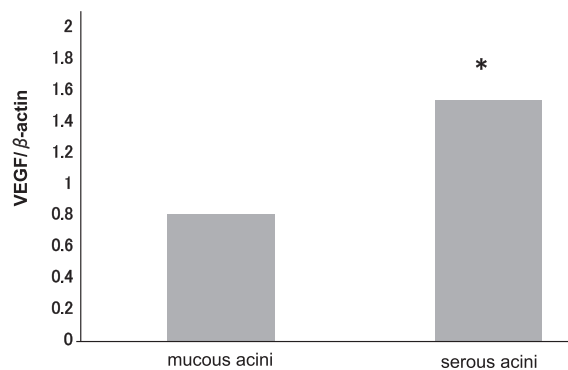Fig. 3 VEGF in nasal secretion from rhino-sinusitis patients
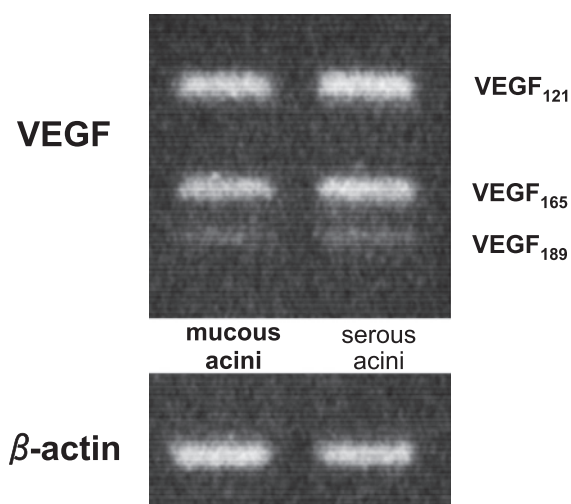
Matsune S *et al.* Am J Rhinol. 2008.

Fig. 5 VEGF subclass in mucous and serous acini of nasal glands of allergic rhinitis patients

Matsune S *et al.* Am J Rhinol. 2008.

Fig. 4 VEGF in nasal lavage before and after the nasal provocation test
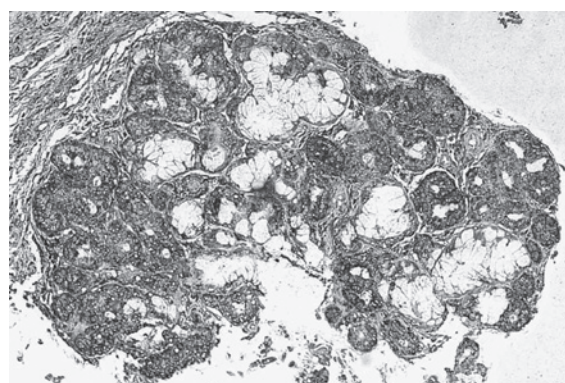

Matsune S *et al.* Am J Rhinol. 2008.

Fig. 6 VEGF mRNA in mucous and serous acini in nasal glands of allergic rhinitis patients

significant quantities of VEGF, which was hypersecreted after antigen provocation. VEGF seems to play an important role in the pathophysiology of AR[21]. Choi et al have also reported increased VEGF production in nasal lavage fluid from patients with PAR after the nasal provocation test, especially during the early response. Additionally, nasal VEGF secretion in response to allergen exposure is thought to augment eosinophilic inflammation in the nasal mucosa of patients with PAR[22].

Levels of VEGF and interleukin (IL)-5 mRNA were significantly higher in patients with AR and airway hyperresponsiveness (AHR) than in patients with AR and no AHR but were lower than those in

Matsune S *et al.* Am J Rhinol. 2008.

Fig. 7 Immunohistochemistry of VEGF in nasal glands of allergic rhinitis patients

patients with asthma. Numbers of eosinophils were significantly higher in patients with AR and AHR and in patients with asthma than in patients with AR and no AHR. However, levels of IL-4, IL-13, and interferon γ were not higher in patients having AR with or without AHR than in patients with asthma. Both VEGF and IL-5 are thought to be important determinants of the development of AHR in patients with AR[23].

There is a difference in the extent of remodelling in AR and asthma. This difference may be attributed to a difference in the local tissue response to inflammatory cytokines including VEGF. The angiogenic factor VEGF and its receptor foetal liver kinase (Flk)-1 was found with immunohistochemical studies to be increased in the inferior turbinate mucosa of patients with SAR. A similar increase in VEGF in SAR with or without asthma, despite higher Flk-1 levels, in patients with SAR and asthma may be a possible explanation for the presence of angiogenesis in the airway walls of patients with asthma but not in those with pure SAR[24].

This evidence seems to show that VEGF is an important cytokine in the pathology of AR.

VEGF Levels after Chemotherapy for AR

The importance of VEGF has been demonstrated in the pathophysiology of AR, which makes the VEGF level a useful indicator to analyze the effects of chemotherapy on AR.

Studies of experimental rhinitis induced by toluene-2,4-diisocyanate in rats have shown that the administration of the histamine receptor-1 antagonist olopatadine suppresses sneezing and the increases in histamine, nerve growth factor, and VEGF production in nasal lavage fluid. These results suggest that the suppression of the increase in nerve growth factor and VEGF are involved in the improvement of signs of nasal allergy by treatment with olopatadine. Early treatment with olopatadine is expected to have stable effects[25]. A selective second-generation histamine receptor 1 antagonist, carebastine, inhibits VEGF-induced proliferation, migration, and angiogenesis of human umbilical vein endothelial cells and human pulmonary artery

endothelial cells in a dose-dependent manner in vitro. Overall, these data provide the first evidence regarding the antiangiogenic activity of ebastine and suggest its potential use as an antiangiogenic molecule, in addition to its antihistaminic activity for the treatment of allergic diseases in which angiogenesis takes place[26].

Conclusion

Whereas the major biological functions of VEGF are inducing angiogenesis and vascular hyperpermeability, other interesting properties of VEGF have been reported in the field of asthma research: these include the possibility of activating antigen-presenting cells, such as dendritic cells, and the regulation of VEGF levels through cysteinyl leukotriene receptors[27,28]. It is true that asthma now precedes AR in the study of VEGF, and more basic and clinical evidence must be accumulated in AR. However, modulation of VEGF function seems to contribute to the successful treatment of conditions with airway inflammation, such as AR and asthma.

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