Neuropilin-2 and Neuropilin-1 Are Receptors for the 165-Amino Acid Form of Vascular Endothelial Growth Factor (VEGF) and of Placenta Growth Factor-2, but Only Neuropilin-2 Functions as a Receptor for the 145-Amino Acid Form of VEGF*

Received for publication, November 15, 1999, and in revised form, February 8, 2000

Published, JBC Papers in Press, March 29, 2000, DOI 10.1074/jbc.M909259199

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Neuropilin-1 (np-1) and neuropilin-2 (np-2) are receptors for axon guidance factors belonging to the class 3 semaphorins, np-1 also binds to the 165-amino acid heparin-binding form of VEGF (VEGF<sub>165</sub>) but not to the shorter VEGF<sub>121</sub> form, which lacks a heparin binding ability. We report that human umbilical vein-derived endothelial cells express the a17 and a22 splice forms of the np-2 receptor. Both np-2 forms bind VEGF<sub>165</sub> with high affinity in the presence of heparin (K<sub>D</sub> of 1.3 x 10<sup>-19</sup> m) but not VEGF<sub>121</sub>. np-2 also binds the heparin-binding form of placenta growth factor. These binding characteristics resemble those of np-1. VEGF<sub>145</sub> is a secreted heparin binding VEGF form that contains the peptide encoded by exon 6 of VEGF but not the peptide encoded by exon 7, which is present in VEGF<sub>165</sub>. VEGF<sub>145</sub> binds to np-2 with high affinity (K<sub>D</sub> of 7 x 10<sup>-19</sup> m). Surprisingly, VEGF<sub>145</sub> did not bind to np-1. Indeed, VEGF<sub>145</sub> does not bind to MDA-MB-231 breast cancer cells, which predominately express np-1. By contrast, VEGF<sub>145</sub> binds to human umbilical vein-derived endothelial cells, which express both np-1 and np-2. The binding of VEGF<sub>165</sub> to porcine aortic endothelial cells expressing recombinant np-2 did not affect the proliferation or migration of the cells. Nevertheless, it is possible that VEGF-induced np-2-mediated signaling will take place only in the presence of other VEGF receptors such as VEGF receptor-1 or VEGF receptor-2.

The various growth factors belonging to the VEGF<sub>1</sub> family (VEGF, PIGF, VEGF-B, VEGF-C, and VEGF-D) act as modulators and inducers of angiogenesis in vivo (1–3). The active forms of VEGF are synthesized as homodimers (4, 5) or as heterodimers with other VEGF family members such as PIGF (6). Targeted disruption of the VEGF gene has shown that even in animals containing a single allele of the VEGF gene angiogenesis is severely disrupted, indicating that the maintenance of exact VEGF levels in vivo is critical for the correct development of the cardiovascular system (7, 8). Five splice forms of human VEGF ranging in length from 121 to 206 amino acids (VEGF<sub>121</sub>–VEGF<sub>206</sub>) have been characterized (4, 5, 9, 10). These forms differ primarily in the presence or absence of the heparin binding domains encoded by exons 6 and 7, giving rise to forms that differ in their heparin and heparan-sulfate binding ability (11). The VEGF<sub>121</sub>, VEGF<sub>165</sub> and VEGF<sub>189</sub> forms appear to be abundant and are usually produced simultaneously by VEGF-producing cells (1). VEGF<sub>145</sub> is a rarer and much less studied VEGF form, which was reported to be expressed by cells derived from the female reproductive system (9) as well in other organs such as the skin, penis, and kidney (12–14). It contains the heparin binding domain encoded by exon 6 and binds tightly to the extracellular matrix (9). VEGF<sub>165</sub> contains the heparin binding domain included in exon 7 and binds to heparin with an affinity that is similar to that of VEGF<sub>145</sub>. However, VEGF<sub>165</sub> binds much less tightly than VEGF<sub>145</sub> to extracellular matrix. VEGF<sub>121</sub> lacks both exons and has no affinity for either heparin or for extracellular matrixes. Other VEGF family members such as PIGF and VEGF-B are also expressed in several forms that differ in their heparin binding ability. For example, the peptide encoded by exon 6 of PIGF is found only in PIGF-2 and confers a heparin binding ability to this form while PIGF-1 and PIGF-3 do not bind to heparin (15, 16).

All the VEGF isoforms bind to the tyrosine-kinase receptors VEGFR-1 (flt-1) (17) and VEGFR-2 (KDR/flk-1) (18). The binding of VEGF to VEGFR-2 initiates intracellular signal transduction (1, 19–22) and is correlated with the induction of endothelial cell proliferation and migration, angiogenesis, and permeabilization of blood vessels (1, 23, 24). In contrast the activation of VEGFR-1 does not seem to result in the induction of cell proliferation, angiogenesis, or permeabilization of blood vessels but enhances cell migration (24–26). However, there have also been other reports that indicate that the activation of VEGFR-1 can induce cell proliferation and angiogenesis (27). Both of these receptors have also been shown to play critical roles in embryonic vasculogenesis and angiogenesis (28, 29).

Endothelial cells also contain another type of VEGF receptors possessing a lower mass than either VEGFR-2 or VEGFR-1 (30, 31). It was subsequently found that these smaller VEGF receptors of the endothelial cells are isofrom specific receptors that bind VEGF<sub>165</sub> but not VEGF<sub>121</sub> (32). It was therefore recognized that these receptors are not related to...
the VEGFR-1 or to the VEGFR-2 receptors, which bind to both VEGF isoforms. An additional search revealed several types of prostate and breast cancer cell lines, which express unusually large amounts of these isoform-specific receptors (33). A VEGF<sub>165</sub> affinity column was used to purify the receptors from MDA-MB-231 breast cancer cells, and sequencing of the receptor revealed it to be the product of the gene for np-1 (34). NP-1 is likely to play an important role in the development of the cardiovascular system. Gene disruption studies have indicated that np-1 is probably an important regulator of blood vessel development since mouse embryos lacking a functional np-1 gene die because their cardiovascular system fails to develop properly (35). Subsequent experiments have shown that np-1 also serves as a receptor for the heparin-binding form of placenta growth factor (PIGF), PIGF-2, and for VEGF-B (36, 37). np-1 was previously identified as a receptor for semaphorin-3A (38, 39) and it was demonstrated that the VEGF<sub>165</sub> and semaphorin-3A binding sites on np-1 overlap (40). Semaphorins act as repellers of growing tips of axons, and it was recently observed that semaphorin-3A inhibits migration of endothelial cells causing a collapse of the actin cytoskeleton (41).

NP-1 is part of a receptor family that also contains np-2, a receptor that displays highly similar structural features and is a receptor for semaphorin-3C and for semaphorin-3F. Interestingly, np-1 and np-2 can form complexes (40, 42). NP-2 shares a 44% identity at the amino acids level with np-1. Several alternatively spliced forms of np-2 that can be divided into two broad groups have been identified. Mouse group A variants have insertions of 5, 17, or 22 amino acids at amino acid 809 (42). In humans only one splice form of this group was identified having a 17-amino acid insertion at position 808 (42). Mouse group B isoforms differ in the sequence of the transmembrane and intracellular parts starting from amino acid 809, and two such isoforms have been identified (42). The expression pattern of np-2 differs from that of np-1. Although there are broad overlaps, there are regions in which there is np-1 expression but no np-2 expression. For example, in contrast to np-1, np-2 expression was not detected in the heart or in capillaries but was found in the dorsal aorta colliculus (40). The neuropilins have short intracellular domains and are therefore unlikely to function as independent signaling receptors, and it was indeed shown recently that plexins form signaling complexes with both neuropilins (43, 44).

Since np-1 functions as a VEGF receptor, we sought to determine whether np-2 is also a receptor for VEGF family members. We have cloned the np-2 cDNA from HUVEC. We show that np-2 functions as a splice variant specific VEGF receptor that binds VEGF<sub>165</sub> but not VEGF<sub>121</sub>. However, the two receptors do not behave equally with regard to their interactions with VEGF since np-2 is able to bind VEGF<sub>145</sub>, a VEGF splice form that does not bind to np-1.

EXPERIMENTAL PROCEDURES

MATERIALS—The VEGF splice forms and PIGF-2 were produced in sF9 cells using appropriate baculoviruses and purified as described previously (9, 36, 45, 46). LipofectAMINE was bought from Life Technologies, Inc. The pBabePuro plasmid was kindly given to us by Dr. Eyal Ben-Gal from the Technion School of Medicine (Haifa, Israel). BS<sub>3</sub> was generated by co-transfecting PAE cells with the PECE/np-2(a22) expression vectors and the pBabePuro plasmid (49), generated by co-transfecting PAE cells with the PECE/np-2(a17) or PECE/np-2(a22) expression vectors and the pBabePuro plasmid (49), followed by selection with 0.5 μg/ml puromycin (49). Transfection was carried out using LipofectAMINE according to manufacturer's instructions. Stable cell lines were subsequently cultured without puromycin or G418. MDA-MB-231 breast cancer cells were cultured as described previously (33).

RESULTS

NP-2 Is a Receptor for VEGF<sub>165</sub> but Not for VEGF<sub>121</sub>—NP-2 was originally characterized as a receptor for semaphorins 3C and 3F, whereas np-1 was originally identified as a semaphorin-3A receptor (39, 42). NP-1 was subsequently found to be a receptor for VEGF<sub>165</sub> (34). We hypothesized, therefore, that np-2 may also act as a VEGF receptor. Northern blot analysis revealed np-2 mRNA transcripts in HUVEC (data not shown). RT-PCR led to the isolation of two cDNA species encoding two splice forms of human np-2 from HUVEC-derived mRNA. These correspond to the previously identified a17 and a22 splice forms (42). The full-length cDNAs encoding these np-2 forms were stably expressed in PAE cells. <sup>125</sup>I-VEGF<sub>165</sub> was subsequently bound and cross-linked to the PAE/np-2(a22) cells. The binding was strongly enhanced by heparin, and two <sup>125</sup>I-VEGF<sub>165</sub>/np-2 cross-linked complexes of ~140 and ~160 kDa could be observed (Fig. 1A, lane 2). The binding was specific since <sup>125</sup>I-VEGF<sub>145</sub> did not bind to parental PAE cells, even though heparin was added during the binding (Fig. 1B, lane 3). Similar results were obtained when PAE/np-2(a17) cells were used (data not shown). It was previously observed that the related receptor encoded by the np-1 gene binds VEGF<sub>165</sub> but not VEGF<sub>121</sub> (34, 36). It seems that np-2 behaves similarly since cells expressing the recombinant np-2 forms were not able to bind <sup>125</sup>I-VEGF<sub>121</sub> (Fig. 1A, lane 4), even though the <sup>125</sup>I-VEGF<sub>121</sub> used bound efficiently to recombinant VEGF-1 receptors that were expressed in PAE cells (Fig. 1B, lane 2). The affinities of np-1 and np-2 toward VEGF<sub>165</sub> were compared using Scatchard analysis. The dissociation constant of VEGF<sub>165</sub> from np-2 found to be 1.3 × 10<sup>-11</sup> M<sub>2</sub>, while the dissociation constant of VEGF<sub>165</sub> from np-1 was 1.8 × 10<sup>-10</sup> M<sub>2</sub> (data not shown). The dissociation constants are thus very similar.

NP-2 Is a Receptor for PIGF-2—NP-2 was also found to function as a VEGF-B receptor and a receptor for the heparin-
Neuropilin-2 is a VEGF<sub>165</sub> and VEGF<sub>145</sub> Receptor

![FIG. 1. NP-2 is a splice variant-specific VEGF receptor.](image)

**Panel A**

| Cell Type | PAE/np-2 | PAE/np-1 | HUVEC |
|-----------|----------|----------|-------|
| Heparin:  | 165      | 165      | 165   |
| 100 ng/ml | +        | +        | +     |
| 0 ng/ml   | -        | -        | -     |

**Panel B**

![FIG. 2. NP-2 is a receptor for PlGF-2.](image)

![FIG. 3. VEGF<sub>145</sub> binds to np-2 but not to np-1.](image)

**Panel A**

| Lanes | 1 | 2 | 3 | 4 |
|-------|---|---|---|---|
| 125I-VEGF<sub>145</sub> | + | + | + | + |
| VEGF<sub>145</sub> solution | - | - | - | - |

**Panel B**

| Lanes | 1 | 2 | 3 | 4 |
|-------|---|---|---|---|
| 125I-PlGF-2 | + | + | + | + |
| VEGF<sub>145</sub> solution | - | - | - | - |

The affinity of VEGF<sub>145</sub> toward np-2 is about 5 fold lower than that of VEGF<sub>165</sub> as is revealed by binding/competition experiments (Fig. 4B). Thus the dissociation constant of VEGF<sub>145</sub> is around 7 x 10<sup>-10</sup> M as compared with 1.3 x 10<sup>-10</sup> M for VEGF<sub>165</sub>. However, even 4 µg/ml VEGF<sub>145</sub> were not sufficient to inhibit significantly the binding of 125I-VEGF<sub>165</sub> to np-1, indicating that the affinity of np-1 to VEGF<sub>145</sub> is at least 100-fold lower (Fig. 4A).

Because VEGF<sub>145</sub> differentiates between the two neuropilin types, we have also looked at the expression of np-2 on the surface of several cell types using VEGF<sub>145</sub> binding to differentiate between the two receptors. Our experiments indicate that HUVEC express functional np-2 receptors on their surface since VEGF<sub>145</sub> is able to bind to a receptor with a mass corre-

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NP-2 binds VEGF165 and VEGF145 with high affinity, but is unable to bind VEGF121. Furthermore, np-2 is also a receptor to PIGF-2. Thus, except for the VEGF145 binding ability, which is unique to np-2, these two receptors appear to behave very similarly with regard to their interaction with various VEGF family members. We have also shown here that the selective binding ability of VEGF145 can be used to distinguish between np-1 and np-2 receptors on various cell types. The neuropilin receptors of MDA-MB-231 cells bind VEGF165 and PIGF-2 (34, 36). By using VEGF145 binding, we see clearly that these cells have a very low or no functional np-2 receptors at all on their surface, and that their splice variant-specific receptors are almost exclusively np-1 receptors, indicating independently that np-1 is indeed a PIGF-2 receptor.

VEGF165, VEGF145, and PIGF-2 are all heparin-binding proteins, and their heparin-binding domains are well defined (1, 3). The heparin-binding domains of VEGF165, VEGF145 and PIGF-2 contain clusters of highly charged basic amino acids that presumably interact with charged sulfate groups on heparin-like molecules. However, it is difficult to detect other common sequence motifs in the heparin-binding peptides encoded by exon 6 of PIGF and exons 6 and 7 of VEGF. This observation argues for the participation of heparin-like molecules in the mechanism that regulates the binding of these VEGF and PIGF forms to neuropilins. However, this is not the only cue that regulates binding to neuropilins since heparin-binding factors such as bFGF fail to bind to neuropilins (data not shown) and since VEGF145, despite its heparin binding ability fails to bind to np-1. Nevertheless, when a heparin-binding factor binds to a neuropilin, heparin potentiates the binding. It is possible that heparin-like molecules may directly assist the binding of heparin-binding VEGF forms to neuropilins by changing the conformation of VEGFs so as to enable their binding to neuropilins. This hypothesis predicts that heparin-binding VEGF forms bind to neuropilins through a domain that is distinct from the heparin-binding site. Indeed, if neuropilins were to bind to the heparin-binding forms of VEGF by interacting directly with their heparin-binding domain, than neuropilin would have been expected to inhibit the binding of VEGF165 to neuropilins through steric interference. This hypothesis needs to be tested. However, because iodinated VEGFs had been used, it is also clear that part of the observed effect of heparin on VEGF165 binding is the result of a chaperone-like effect. VEGF165 loses part of its biological activity following exposure

DISCUSSION

np-1 had been characterized as a receptor for semaphorin-3A/collapsin-1, while np-2 was initially characterized as a receptor for the related semaphorin-3F. Both receptors play an important role in nerve guidance during embryonic development and repel growing axons in response to the binding of their respective ligands (40, 50, 51). The identification of receptors that interact with VEGF165 but not with VEGF121 in endothelial cells (32) was followed by the identification of tumorigenic cells that express large amounts of such receptors (33). Affinity purification of membrane extracts from MDA-MB-231 cells on VEGF165 affinity columns identified np-1 as the splice variant specific receptor (34). NP-1 does not bind VEGF121, a VEGF form lacking a heparin binding ability, but the heparin-binding VEGF165, and the heparin-binding form of PIGF (36) as well as VEGF-B (37) bind to this receptor.

We have noticed that the np-2 mRNA is also expressed in HUVEC. We have therefore suspected that np-2 may also function as a VEGF receptor. Our experiments reveal that np-2 does indeed function as a splice variant-specific VEGF receptor. NP-2 binds VEGF165 and VEGF145 with high affinity, but is unable to bind VEGF121. Furthermore, np-2 is also a receptor to PIGF-2. Thus, except for the VEGF145 binding ability, which is unique to np-2, these two receptors appear to behave very similarly with regard to their interaction with various VEGF family members. We have also shown here that the selective binding ability of VEGF145 can be used to distinguish between np-1 and np-2 receptors on various cell types. The neuropilin receptors of MDA-MB-231 cells bind VEGF165 and PIGF-2 (34, 36). By using VEGF145 binding, we see clearly that these cells have a very low or no functional np-2 receptors at all on their surface, and that their splice variant-specific receptors are almost exclusively np-1 receptors, indicating independently that np-1 is indeed a PIGF-2 receptor.

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to oxidants such as those used during iodination. The binding of oxidized 125I-VEGF165 to heparin or to cell surface heparan-sulfate glycosaminoglycans such as glypicancan-1 can restore its receptor binding ability (32, 52). Thus, it is logical to assume that at least a part of the observed effect of heparin is due to this effect.

What are the biological roles of np-1 and np-2 in the vascular system? Targeted disruption of the np-1 gene has revealed that np-1 participates in embryonic vasculogenesis and angiogenesis and plays an important role in the maturation of blood vessels (35). However, similar data are not yet available with regard to np-2. Furthermore, this type of data does not reveal much about the mechanism by which np-1 affects blood vessel maturation. It was observed that the binding of VEGF165 to np-1 does not induce cell migration or cell proliferation by itself (34). It was further reported that np-1 enhances the binding of 125I-VEGF165 to the VEGFR-2 receptor and it was suggested, based on these observations, that the np-1-enhanced binding of VEGF165 to VEGFR-2 potentiates VEGFR-2-mediated cell migration (34). However, recent experiments performed in our laboratory failed to confirm these data.

There is therefore no clear-cut evidence indicating that the binding of VEGF family members to np-1 or to np-2 results in signal transduction in endothelial cells or in any other cell type. However, VEGF165 competes with semaphorin-3A for binding to the semaphorin-3A binding site of np-1 (40). It is thus possible that the function of VEGF binding is mainly inhibitory. It was shown that the binding of semaphorin-3A to PAE cells was used (53). It was also shown that semaphorin-3A inhibits the np-1-mediated activity of axon repulsion, indicating that neuropilins results in any direct biological effects.

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The intracellular domain of np-1 is apparently not required for the np-1-mediated activity of axon repulsion, indicating that neuropilins form signaling complexes with other cell surface proteins (54). Furthermore, it was recently shown that np-1 and np-2 form signaling complexes with plexins (43, 44). It is possible that neuropilins may also be able to associate with the tyrosine kinase receptors of VEGF, VEGFR-1 or VEGFR-2 (1), to form signaling complexes responsive to VEGF binding. This possibility is currently under investigation. These observations do not mean that the intracellular domains of neuropilins are superfluous. The discovery of NIP, a PDZ domain containing intracellular protein that binds to the tail end of np-1 (55), and the discovery of np-2 splice forms that differ in their intracellular domains (42) indicate that the intracellular domains of neuropilins are likely to be important for their full function.

To conclude, we have shown here that np-2 behaves like a splice variant VEGF receptor. It behaves like np-1 in that it is able to bind PIGF-2 and VEGF165 but not VEGF121. However, np-2 binds VEGF165, a heparin-binding VEGF form that does not bind to np-1. This last result indicates that a heparin binding ability may be required, but not sufficient, for the np-1 binding ability of VEGF splice forms.
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J. Biol. Chem. 2000, 275:18040-18045.
doi: 10.1074/jbc.M909259199 originally published online March 29, 2000

Access the most updated version of this article at doi: 10.1074/jbc.M909259199

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Vol. 275 (2000) 18040–18045

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The title was printed incorrectly and should read as shown above.