An engineered heparin-binding form of VEGF-E (hbVEGF-E) : biological effects in vitro and mobilizatiion of precursor cells

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Vascular endothelial growth factor (VEGF-A) is the founding member of a family of angiogenic proteins with various binding abilities to three cognate VEGF receptors. Previously, a gene encoding from the genome of parapox orf virus (OV) with about 25% amino acid identity to mammalian VEGF-A was named VEGF-E and shown to bind and specifically activate the vascular endothelial growth factor receptor VEGFR-2 (KDR/flk-1). Here, we have generated a novel heparin-binding form of VEGF-E by introducing the heparin-domain of the human VEGF-A(165) splice variant into the viral VEGF-E protein. Recombinant heparin-binding VEGF-E (hbVEGF-E) is shown to stimulate proliferation and sprout formation of macro- and microvascular endothelial cells to a similar extent as the parental OV-VEGF-E but fails to activate peripheral mononuclear cells. However, hbVEGF-E is more potent in binding competition assays with primary human endothelial cells when compared to the OV-VEGF-E. This can be explained by our finding that binding of hbVEGF-E but not of parental OV-VEGF-E to the VEGFR-2 is strongly increased by the addition of neuropilin-1 (NP-1), a cognate co-receptor for VEGF-A. The engineered hbVEGF-E was compared with the VEGFR-1 selective and also heparin-binding form of placenta growth factor (PlGF-2) in vivo. Both heparin-binding homologues induced mobilization of endothelial progenitor cells from the bone marrow and gave rise to similar colony numbers of myeloic cells in a colony-forming assay. These findings suggest that both VEGFR-1 and VEGFR-2 are involved in stem cell mobilization.

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