A novel vascular endothelial growth factor encoded by Orf virus, VEGF-E, mediates angiogenesis via signalling through VEGFR-2 (KDR) but not VEGFR-1 (Flt-1) receptor tyrosine kinases

ID 156047
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Year 1999
Title A novel vascular endothelial growth factor encoded by Orf virus, VEGF-E, mediates angiogenesis via signalling through VEGFR-2 (KDR) but not VEGFR-1 (Flt-1) receptor tyrosine kinases
Journal The EMBO journal
Volume 18
Number 2
Pages / **Article-Number** 363-74
Keywords angiogenesis, Flt-1, KDR, Orf virus, VEGF

The different members of the vascular endothelial growth factor (VEGF) family act as key regulators of endothelial cell function controlling vasculogenesis, angiogenesis, vascular permeability and endothelial cell survival. In this study, we have functionally characterized a novel member of the VEGF family, designated VEGF-E. VEGF-E sequences are encoded by the parapoxvirus Orf virus (OV). They carry the characteristic cysteine knot motif present in all mammalian VEGFs, while forming a microheterogenic group distinct from previously described members of this family. VEGF-E was expressed as the native protein in mammalian cells or as a recombinant protein in Escherichia coli and was shown to act as a heat-stable, secreted dimer. VEGF-E and VEGF-A were found to possess similar bioactivities, i.e. both factors stimulate the release of tissue factor (TF), the proliferation, chemotaxis and sprouting of cultured vascular endothelial cells in vitro and angiogenesis in vivo. Like VEGF-A, VEGF-E was found to bind with high affinity to VEGF receptor-2 (KDR) resulting in receptor autophosphorylation and a biphasic rise in free intracellular Ca2+ concentration, whilst in contrast to VEGF-A, VEGF-E did not bind to VEGF receptor-1 (Flt-1). VEGF-E is thus a potent angiogenic factor selectively binding to VEGF receptor-2. These data strongly indicate that activation of VEGF receptor-2 alone can efficiently stimulate angiogenesis.

Publisher Nature Publishing Group
ISSN/ISBN 0261-4189
edoc-URL http://edoc.unibas.ch/dok/A5259039
Full Text on edoc No;
Digital Object Identifier DOI 10.1093/emboj/18.2.363
PubMed ID http://www.ncbi.nlm.nih.gov/pubmed/9889193
ISI-Number WOS:000078345000009
Document type (ISI) Journal Article