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Title: Differential VEGF signalling in the lung

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Body: VEGF undergoes alternate splicing producing isoforms with differing functions. The most commonly studied form is VEGF165. Recently an isoform that causes inhibition of endothelial proliferation, migration and permeability induced by VEGF165, namely VEGF165b has been identified. We have previously investigated the downstream signalling mechanisms in response to VEGF165 in pulmonary and systemic endothelial cells and have now compared these to the effects of VEGF165b HUVEC and Human Lung Microvascular Endothelial Cells (HMVEC-L) were treated with both VEGF isoforms. Phosphorylation of VEGFR-2 (tyr1175 and tyr1214) was measured along with phosphorylation/activation of pMEK1/2, p44/42MAPK (regulating cell proliferation) and eNOS protein (involved in cell permeability). The downstream effects of VEGF165/ VEGF165b on cell permeability was assessed by Endohm, Electrical Cell-Substrate Impedance Sensor (ECIS) and FITC-BSA passage and changes in VE-cadherin cell distribution was determined by immunofluorescence VEGF165 induced maximal phosphorylation of VEGFR-2 at tyr1175 and tyr1214 between 5 and 10min (>10fold increase), VEGF165b induced less than 5 fold increase compare to control. Comparable results for both isoforms were seen for activation of pMEK1/2, p42/44MAPK and eNOS. All three permeability assessments showed an increase due to VEGF165 (HUVEC $p<0.001$) (HMVEC-l $p<0.01$) which was inhibited by VEGF165b. This may be reflected by the differential changes in the cellular distribution of VE-cadherin induced in both cell types by VEGF isofroms VEGF165b induces a different response to VEGF165 in HUVEC and HMVEC-L. These observations suggest different pathways for the regulation of mitogenesis or permeability identifying potential therapeutic targets.