

P004 Spatially-restricted patterning cues provided by heparin-binding VEGF isoforms control blood vessel branching

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We study the development of mice expressing only the VEGF₁₂₀ isoform of Vascular Endothelial Growth Factor (VEGF). This isoform lacks the ability to bind the VEGF receptor Nrp1 and cannot bind heparan sulphate proteoglycans (HSPGs). We observed reduced microvessel branching in several developing organs of VEGF_{120/120} mice. This defect was not due to isoform-specific differences in stimulating endothelial cell proliferation, and it was not similar to the defect caused by loss of VEGF-signaling through Nrp1. Rather, changes in the extracellular localization of VEGF resulted in an altered distribution of endothelial cells within the growing vasculature. Instead of being recruited into new branches, nascent endothelial cells were preferentially integrated into existing vessels to increase lumen caliber. The disruption of the normal VEGF concentration gradient also impaired the extension of endothelial tip cell filopodia, suggesting that heparin-binding VEGF normally provides spatially restricted stimulatory cues that guide sprouting endothelial cells to initiate branch formation. VEGF_{120/120} mice also show an abnormal migration of facial branchiomotor neurons. However, this defect is due to loss of Nrp1 binding by VEGF, rather than a defective distribution of VEGF in the extracellular matrix. We now wish to examine whether a deficiency in HSPG composition of the extracellular matrix alters VEGF distribution and reproduces vascular defects caused by loss of heparin-binding VEGF