Extracellular matrix binding and diffusible pro-angiogenic VEGF isoforms similarly promote ocular neovascularisation in oxygen induced retinopathy

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Oxygen induced retinopathy (OIR) arises when blood vessels in the developing retina regress in response to environmental hyperoxia and regrow abnormally on resolution of hyperoxia, for example, in a subset of premature neonates after their release from an incubator. The oxygen-regulated vascular endothelial growth factor VEGF-A induces blood vessel growth in OIR. Yet, it is not known how each of the three major pro-angiogenic VEGF isoforms, termed VEGF120, VEGF164 and VEGF188, individually contribute to revascularisation of the retinal area with hyperoxia-induced vascular ablation or the formation of pathological vascular tufts, which arise from vessels that have not regressed during hyperoxia.

We have recombined a floxed *Vegfa* allele in mice with the CAGG-CreER^{TM} transgene to selectively knockdown VEGFA expression in mice by tamoxifen administration, either both alleles of *Vegfa* or only one allele of *Vegfa* whilst retaining expression of a single VEGFA isoform. Using these mice in a mouse model of OIR, we found that VEGF is surprisingly dispensable for revascularisation of the retinal areas where hyperoxia causes vascular regression, but VEGF was required, as expected, for neovascular tuft formation from capillaries and veins that had not regressed during hyperoxia. Notably, each of the VEGF isoforms was similarly effective in promoting neovascular tuft formation. These findings suggest that VEGF is required for pathological but not beneficial neovascularisation in the OIR retina. As both diffusible and matrix-bound VEGF isoforms were equally able to drive vascular tuft formation, the VEGF source is likely local to the site of tuft formation.