Effects of VEGF Temporal and Spatial Presentation on Angiogenesis

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Introduction

Therapeutic angiogenesis relies on the delivery of angiogenic factors capable of reversing tissue ischemia. Polymeric materials that can provide spatial and temporal over vascular endothelial growth factor (VEGF) presentation provide clear benefit, but the influence of VEGF dose, temporal, and spatial presentation on the resultant angiogenic process are largely unknown. The influence of these variables on angiogenesis in in vitro models of angiogenesis and ischemic murine limbs was analyzed in this study.

Materials and Methods

The temporal effects of VEGF presentation on endothelial cell (HMVEC-d) activation were tested via an in vitro fibrin 3D sprouting assay. A VEGF delivery system capable to recapitulate this temporal presentation locally in vivo was fabricated from alginate, a polysaccharide. Alginate gels were a combination of the high molecular weight and low molecular weight polymers at a ratio of 75:25. Both alginate (low and high molecular weight) polymer chains were oxidized - 1% of the sugar residues. This injectable system was used to test the therapeutic angiogenic effects of different VEGF doses (ranging from 3, 5 and 10 ug/animal) and distinct spatial distributions (single injections vs dual injections) in a hypercholesterolemic ApoE / mice model subjected to femoral artery and vein ligation to create severe hindlimb ischemia. Regional blood flow was measured using laser doppler perfusion imaging (LDPI), and immunohistochemistry with blood vessel quantification, were used to decipher and analyze the therapeutic angiogenic effect of the VEGF temporal and spatial presentation.

Results

A profile consisting of a high VEGF concentration initially, followed by a decreasing concentration over time was found to yield optimal angiogenic sprouting in vitro (Fig.1).

Discussion and Conclusions

Determining the optimum dose of VEGF clearly remains a critical factor in controlling angiogenesis in vivo. This work showed that the appropriate therapeutic dose distributed in a binary spatial fashion resulted in superior regional blood perfusion and neovascularization. Overall, these findings suggest that material systems capable of controlling and regulating the temporal and spatial presentation of VEGF maybe useful to achieve a robust and potent therapeutic angiogenic effect in vivo.

References

N/A

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Disclosures

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