Colloidal microgels for neovascularization

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Statement of Purpose: Over the past few decades, there has been extensive research using micro and nano-sized polymeric particles as drug delivery vehicles because of their non-invasive drug delivery, and controlled and sustainable drug release (1). For tissue regenerative therapies, it is common to inject particles encapsulating various regenerative medicines (e.g. nucleic acids, growth factors, and cytokine) into a target tissue defect to stimulate host and/or transplanted cells (2,3). However, particles implanted in a tissue experience mechanical deformation and subsequently scatter throughout the tissue. Therefore, the use of drug-encapsulating particles for tissue regenerative therapies results in a loss of drug molecules at the implant site, which leads to a significant decrease in regenerative efficacy. In this study, we demonstrate that a colloidal gel formed from electrostatic attraction between micro-sized hydrogel particles (i.e. microgels) remains stable in the implant site because of a significant increase of viscosity and viscoelasticity. We further demonstrate that the colloidal gel system improved the efficacy of angiogenic growth factor towards stimulating neovascularization.

Methods: PEGDA microgels containing charged polymer, either sodium acrylate (SA) or (vinylbenzyl)trimethyl ammonium chloride (VTMA), were made through a single emulsion process using dichloromethane as a solvent. Oppositely charged microgels were mixed at varied volumetric ratios to form colloidal gels. We examined the morphology and surface potential of individual microgels and the rheological properties of unary microgel suspensions and binary mixtures of SA and VTMA microgels. Microgel mixtures, characterized to have the highest modulus, were loaded with vascular endothelial growth factor (VEGF) and examined for their angiogenic potential using a chorioallantoic membrane (CAM) assay. Histological analysis of CAM cross-sections were visually examined and quantified for blood vessels density.

Results: As expected, mixing of VTMA and SA microgels resulted in a significant increase in viscosity and storage modulus indicating the formation of a colloidal gel structure between VTMA and SA microgels. The rheological properties were further controlled with polymer concentration of microgel particles and volume fractions of microgel suspensions. Proteins encapsulated in the microgel particles were released at the same rate, independent of the rheological properties of the microgel suspension. Implantation of microgels into a tissue showed that unary microgel suspensions were readily scattered away after one day of implantation, while the binary microgel mixture was still visible. Subsequently, the use of binary microgel mixtures as an encapsulation vehicle of vascular endothelial growth factor (VEGF) resulted in the significant increase of blood vessel density as compared with implantation of unary microgel suspension (Fig. 1).

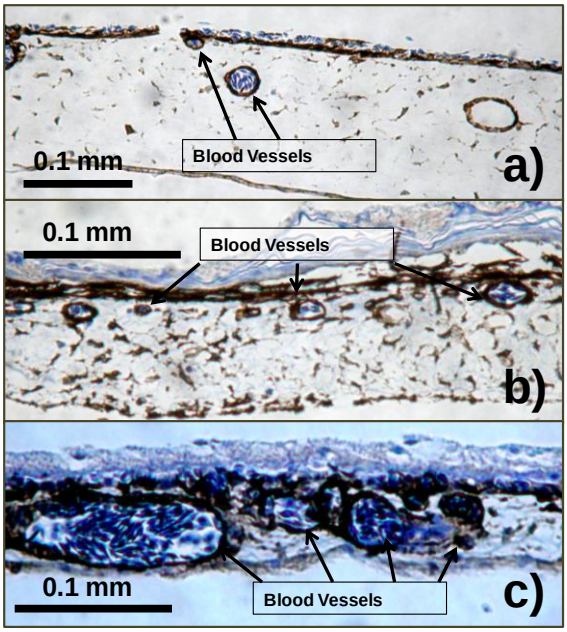

Figure 1. αSMA stained CAM cross-sections for a control (a), implantation of VEGF loaded unary microgel suspension (b) and implantation of VEGF-loaded binary microgel mixture (c).

Conclusions: In this study, we demonstrated that the electrostatic interaction between microgels created a colloidal gel system for use as a proangiogenic drug delivery vehicle. The colloidal microgel system improved the efficacy of VEGF in stimulating neovascularization as compared with implantations of unary microgel suspensions. These colloidal microgel systems will be broadly useful for improving the growth factor efficacy of stimulating tissue regeneration.

References:

(1) Jilek S. Adv D Del Rev. 2005; 57:377-340.
(2) Nishiyama N. Pharm Ther. 2006; 112: 630-648.
(3) Griffith LG. Acta Mat. 2000; 48: 263-277.