Tailoring the interface of methacrylic terpolymer biomaterials for endothelialization

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Statement of Purpose: The function of many blood contacting biomedical devices is compromised by thrombus development at the biomaterial/blood interface. No surface except a healthy endothelium is fully blood compatible. However, a confluent and functioning endothelial cell layer on a biomaterial surface has not yet been successfully achieved in humans. In this research we attempt to understand the mechanical, topographical, chemical, and biological features of polymeric biomaterial surfaces which promote the development of a confluent and functioning endothelial cell layer.

Methods: In previous work, we have developed a biostable methacrylic terpolymer copolymerized from hexyl-methacrylate (HMA), methyl methacrylate (MMA), and methacrylic acid (MAA). The physical properties of the biomaterial system can be tailored by controlling the molar ratio of HMA to MMA incorporated into the polymer backbone. MAA was incorporated in small quantities (2 mole %) to allow post synthesis derivatizations. The biological properties of the polymer system are modified through the incorporation of topography using electrospinning and the covalent attachment of cell specific ligands. Furthermore, non-specific biological interactions can be minimized through the copolymerization of methacrylate monomers which contain non-fouling pendant groups: poly(ethylene glycol) methacrylate (PEGMA) and sulfobetaine methacrylate (SBMA).

Results: By varying the ratio of HMA and MMA in the polymer backbone, the glass transition temperature of the material can be specified. We have illustrated that variations in the stiffness of the substrate has minimal impact on the adhesion and growth of human umbilical vein endothelial cells (HUVECs). However, when these materials are electrospun they produce scaffolds with very distinct topographical features as observed in Figure 1. Furthermore, electrospinning onto a rotating collector allows scaffolds with aligned fiber architectures to be produced. In static culture, HUVECs showed enhanced cellular proliferation and metabolic activity and a more spread cellular morphology on materials with small pores and low void percents (panel B) and the morphology of HUVECs on the aligned fiber scaffolds (panel D) was elongated in the direction of fiber orientation illustrating that scaffold topography plays an important role in determining adherent EC behavior.

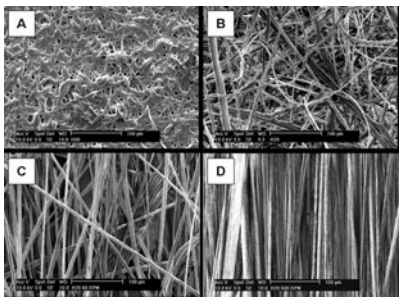

Figure 1. Morphology of electrospun polymer scaffolds: (a) slightly porous, (b) highly porous, (c) partially aligned, and (d) highly aligned

The chemical nature of the biomaterial is also an important characteristic. We have illustrated that copolymerization of PEGMA and SBMA produces materials resistant to fibrinogen adsorption and platelet adhesion.

In addition to mature ECs we are also interested in human blood outgrowth endothelial cells (HBOECs) which are circulating adult stem cells with high proliferation capacities and rates. In previous work, we have developed novel peptide ligands which specifically bind HBOECs. The polymer has been functionalized with RGD to promote mature EC adhesion and the novel ligands to promote HBOEC specific attachment as illustrated in Figure 2.

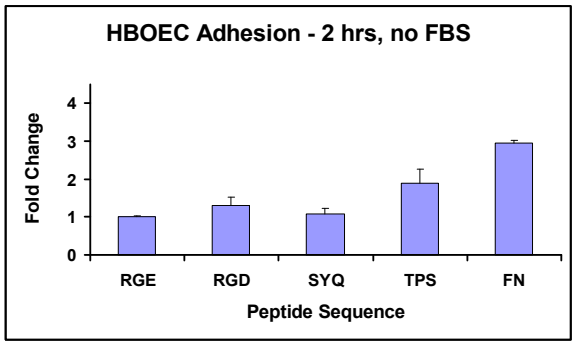

Figure 2. Up regulated attachment of HBOECs to materials functionalized with the novel TPS peptide ligand

Conclusions: This research illustrates how scaffold topography, chemical derivatization, and biofunctionalization can be controlled in order to tailor the specific interactions of the scaffold with HUVECs and HBOECs. We hope this research will be useful in the design of blood compatible biomaterials.