The Application of Bioinspired Surface Treatments to Cardiovascular Biomaterials: *In Vitro* and *In Vivo* Considerations and Comparisons

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The wide spread use of synthetic materials for cardiovascular devices has a modern history extending back some 60 years. The materials used have largely been derived from commercial/commodity materials modified to demonstrate acceptable toxicology. Such materials (examples: silicone elastomers, fluoropolymers, polyurethanes and Dacron) have advantages of desirable mechanical properties and biodurability, though generally their biological performance is sub-optimal. Particular problems are chronic (low level) inflammation, fibrosis, thrombosis, calcification and infection.

The response of the body to such materials implanted in most tissue spaces is a fibrotic, avascular capsule walling the material from the body[1]. Furthermore, this response is characteristic a of chronic inflammatory reaction with activated macrophages, even years after implantation. There similarities (and differences) between the classic foreign body reaction and blood reaction to biomaterials. Similarities include the initial adsorption of proteins and the involvement of leucocyte cells in the early stages of reaction. If we believe that all tissues in the body (including blood) interact with commonalities with materials, perhaps it is no surprise that materials perform problematically in blood -- our synthetic materials induce clotting unless anticoagulation is used and calcification and poor endothelialization are common complications.

The central ideas behind this talk are (1) use biorecognition mechanisms (or biomimics) to "talk" to the biology in a physiologically compatible manner and (2) inflammation must controlled and coordinated. Concerning point (2), recent ideas that macrophages exist in an "M1" and an "M2" phenotype, where M1 is tissue destructive and M2 is tissue remodeling, suggest that controlling the macrophage will permit control of healing.

Three projects will be presented that were guided by the points above. These projects were funded by the NSF under the University of Washington Engineered Biomaterials (UWEB) Engineering Research Center.

Osteopontin on heart valves (with C. Giachelli, R. Ohri and S. Martin)

Calcification of tissue heart valves is still a significant problem leading to valve failure and need for replacement. Osteopontin (OPN), a matricellular protein, will inhibit ectopic calcification. However, if the OPN signals are delivered correctly to the organism, the molecule can be more efficacious. In this study, OPN was immobilized by first immobilizing collagen type I onto pericardial leaflets of the type used in heart valves. Then, the natural binding affinity of collagen I for OPN could be exploited by dipping the heart valve leaflet in OPN solution. OPN presented on collagen I was found to be much more effective in inhibiting calcification (as measured in a mouse knock-out model) than other ways to deliver OPN to the leaflet[2].

Blood compatible surfaces *(with I.C. Gonçalves, M.C.L. Martins, M.A. Barbosa)*

The search for blood compatible materials has been ongoing since the early 1960's. Materials widely used clinically include silicones, polyethylene, plasticized poly(vinyl chloride) and polyurethanes. Systemic anticoagulation is essential for critical or longer term applications in the blood stream. It has long been hypothesized that a surface that is passivated with albumin will be non-reactive to blood. The surface must adsorb blood albumin and inhibit fibrinogen adsorption. Also, the albumin should be exchangeable with fresh albumin from the bloodstream. Such a surface was engineered on gold using self-assembled monolayers with oligoethylene glycol chains and C18 n-alkane chains. The surface was shown to be relatively non-adhesive to platelets, and those that adhered were not activated[3].

Inflammation control by sphere templated porous materials (with A. Marshall)

Unique healing in soft tissue has been seen with porous implants since the 1960's. However, the effect of pore size has never been clarified because porous materials available have broad distributions of pore sizes. By precisely tuning pore size using sphere templating, materials have been created that exhibit enhanced angiogenesis and reduced fibrosis in implant sites as diverse as subcutaneous soft tissue, skin (percutaneous) and cardiac muscle[4,5]. We believe these materials function by sending the macrophage down a reconstructive (M2), as opposed to a destructive (M1), pathway.

References

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