Surface Self-Assembled PEG Hydrogel Particles to Control Bacteria-Biomaterial Interactions

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Purpose: The fact that desirable tissue cells and undesirable bacteria compete for the surface colonization of an implanted biomaterial is now well recognized (1). When bacteria win this competition, the resulting infection usually leads to failure of the implanted device with substantial consequences to both the patient and the health-care system. To help solve the infection problem, we are developing poly(ethylene glycol) [PEG] -based hydrogel particles with which to modify surfaces and differentially control their interactions with both eukaryotic and bacterial cells. In particular, we are interested in modulating the surface cell adhesiveness at micro/nano length scales with the goal of reducing staphylococcal bacterial adhesion while still enabling the adhesion, spreading, and proliferation of desirable eukaryotic cells. To this end, we have exploited surfactant-free inverse emulsion polymerization to synthesize a family of anionically charged PEG-acrylic acid (AA) copolymer gel particles and used a bottom-up electrostatic self-assembly approach to modify an otherwise cell-adhesive surface with these cell-repulsive gel particles at various particle densities. By assessing bacterial/tissue cell response to these surfaces, we are optimizing the gel properties and spatial distribution to confer an antibiotic-free method of reducing bacterial adhesion while maintaining good tissue-cell integration.

Methods: An emulsion polymerization process was used to synthesize PEG hydrogel particles. 200 µl of PEG 575 diacrylate, 20 µl acrylic acid and 10 µl Darocur 1173 photoinitiator were dissolved in 1 ml of dichloromethane, and then dispersed in 10 ml of DI water by sonication for 20 min. The resulting emulsion was then exposed to UV light to drive the free-radical polymerization during 15 min of additional sonication. SEM/AFM imaging, dynamic light scattering, and zeta potential measurements were used to characterize the as-synthesized particles. After purification and passage through a 1 µm filter, the gel particles were electrostatically deposited onto poly(l-lysine) [PLL] treated Si wafers. By changing the concentration of gel particles in suspension and the deposition time, we could control the density of PEG gel particles on the substrate surface. We compared in static monoculture the response of *S. epidermidis* bacteria and human osteoblast cells (hFOB 1.19, ATCC) to each of four surfaces: unmodified Si; PLL-primed Si; and PLL-primed Si modified by various surface concentrations of PEG gel particles. We used immunofluorescence/confocal and SEM imaging to assess the short-time cell response to each of these surfaces.

Results: Zeta potential measurements at pH 7.4 confirm that this particular set of particles has a net negative charge because of the copolymerized acid groups. SEM imaging and dynamic light scattering indicate that the gel particle diameters range from ~10's to ~ 100's of nm The SEM image of fig. 1 shows PEG hydrogel particles self assembled on a PLL-primed Si surface. The average (dry) particle diameter in this case is ~150 nm, and their area density is ~ $2.5*10^6$ particles/mm^2 (Fig. 1).

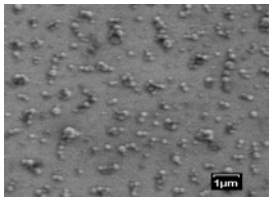

Figure 1. PEG particles modified surface.

Fig. 2 shows that, relative to unmodified Si and PLL primed Si, PEG-modified Si has lower bacterial coverage (*S. epidermidis*) after innoculation and 4 hours of culture consistent with previous studies using e-beam patterned surfaces (2). Despite the fact that the PEG-modified surfaces contain cell-repulsive character, they nevertheless remain adhesive to osteoblasts. Confocal imaging of PEG-modified surfaces after 4 days of osteoblast culture (fig. 3a) shows good spreading and cell proliferation, and SEM imaging (fig. 3b) indicates that the osteoblasts grow over the cell-repulsive gel particles while presumably adhering to the cell-adheisve surface in the inter-gel spaces.

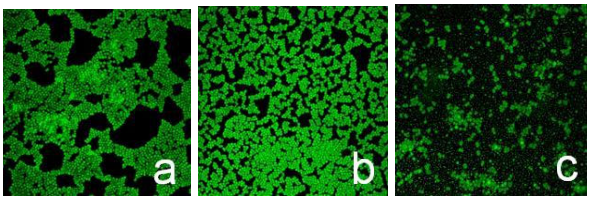

Figure 2. FITC stained *S.epi* on (a) unmodified Si; (b) PLL-primed Si; and (c) PEG particle-modified Si.

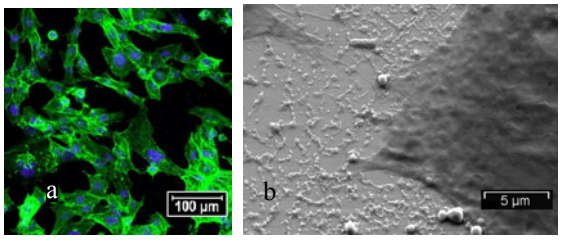

Figure 3. Osteoblasts grow on PEG particle-modified Si: (a) confocal image; (b) SEM image.

Conclusions: Modulating cell adhesiveness at micro length scales using nanoscale features can reduce the adhesion/proliferation of S. epidermidis bacteria while still enabling osteoblast adhesion, spreading, and proliferation. This finding suggests that such surfaces may be useful in reducing the susceptibility of biomedical devices to bacterial infection.

References:

1. A. Gristina, Science 1987, V237, 1588-1595.
2. P. Krsko, Acta Biomaterialia 2009; 5(2):589-596.