**Re-engineering Cellular Interfaces with Cell Surface-Supported Polyelectrolyte Multilayer Thin Films**

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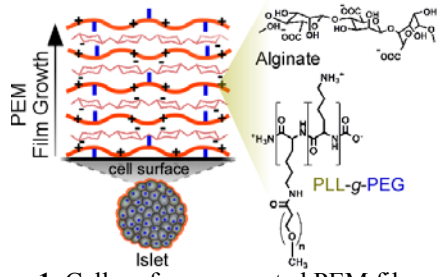
**Statement of Purpose:** Polyelectrolyte multilayer (PEM) films have emerged as a versatile approach to coating diverse materials with thin films of tailored properties. Hence, the ability to assemble PEM films directly on cells and tissues may offer unique possibilities for cell surface engineering. However, the cytotoxicity intrinsic to most polycations poses a significant molecular hurdle to the realization of this potential. The objective of this research is to develop cytocompatible, cell surface-supported PEM films on pancreatic islets through layer-by-layer deposition of poly(L-lysine)-*graft*-poly(ethylene glycol) copolymers and alginate (Scheme 1).




**Scheme 1.** Cell surface-supported PEM film

**Methods:** A structural library comprised of nineteen poly(L-lysine)-*g*[D]-poly(ethylene glycol)$_n$ (PLL-*g*[D]-PEG$_n$) graft copolymers of variable PEG chain length (n) and degree of grafting (D) was synthesized. The cytotoxicity of copolymers towards murine pancreatic islets was assessed via ethidium homodimer and calcein AM. PEM film growth and properties were investigated on planar supports using solid-state spectroscopy, ellipsometry, and AFM. Film formation and localization on cell surfaces were assessed using confocal microscopy. Islet function was characterized by measuring insulin secretion in response to a step-change in glucose concentration. *In vivo* function and engraftment of coated islets was assessed in a murine allograft model of intraportal islet transplantation.

**Results:** The cytotoxicity of PLL-*g*-PEG copolymers tended to decrease as PEG grafting (D) and PEG length (n) increased, and a critical degree of grafting, $D_c$, was identified below which copolymers exerted significant cytotoxicity (Fig.1). Copolymers at $D_c$ facilitated growth of films with exponential-like growth patterns, and eight bilayer films ranged in thickness between 30 nm and 135 nm depending on the copolymer employed, demonstrating the potential to tailor film properties through control of copolymer structure. Moreover, AFM characterization revealed that resultant films were significantly smoother than those assembled using PLL. To determine if PEM films could be assembled on islets, fluorescein-labeled alginate (Alg-F) was used. Islets coated with eight bilayer PLL-*g*[$D_c$]-PEG$_n$/Alg-F films (Fig. 2A) demonstrated discernibly greater fluorescent emission than those coated

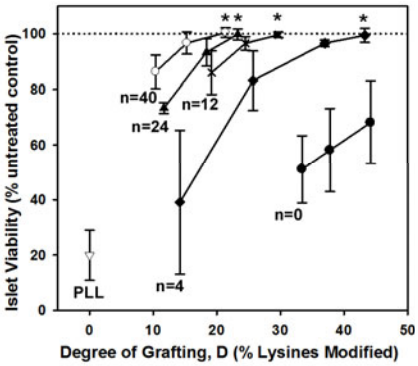



**Figure 1.** Islet viability after exposure to PLL and PLL-*g*[D]-PEG$_n$ copolymers of variable n and D. Cytocompatible variants are indicated by * and were explored as polycations for assembling PEM films.

with a single bilayer (Fig. 2B), and film assembly was localized on extracellular cell surfaces (Fig. 2C). Film assembly did not adversely influence islet viability, and the function of islets coated with a selected film was not compromised (Fig. 3). Upon intraportal transplantation, PEM coated islets tended to increase the fraction of mice that converted from diabetic to normoglycemic (47%) to a greater extent than non-coated islets (25%).

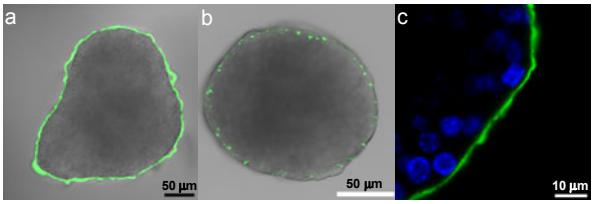



**Figure 2.** Islet coated with eight bilayers (a) or a single bilayer (b). (c) PEM films assemble on cell surfaces.

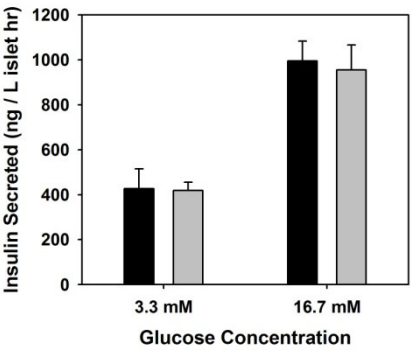



**Figure 3.** Insulin secretion by untreated (grey bar) and PEM coated (black bar) islets in response to glucose.

**Conclusions:** Cell surface-supported PEM films assembled through layer-by-layer deposition of cytocompatible PLL-*g*-PEG copolymers and alginate provide a novel and versatile approach for re-engineering cell surfaces. Through appropriate control of structural variables, PLL-*g*-PEG copolymers could be rendered cytocompatible while simultaneously facilitating the assembly of a unique class of PEM films with tunable properties. These investigations have helped establish a conceptual framework for the rational design of cell surface-supported thin films and offer an opportunity to translate the diverse biomedical applications of PEM films to cellular interfaces.