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Therapeutic Engineered Hydrogels Postpone Capsule Formation at the Host-Implant Interface

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Biomedical devices are implanted to improve or restore function in mammalian tissue; however, these outcomes are inhibited by the ensuing foreign body response (FBR). Eventually, the implant is encapsulated in dense connective tissue, composed mainly of type I collagen. This dense collagen layer can detrimentally alter the configuration of soft tissue implants or inhibit the implant from responding to the local microenvironment. Initially, cellular debris and platelet aggregation from the implantation process triggers an inflammatory reaction that includes the infiltration of neutrophils and macrophages and to the surface of the implant. As the FBR processes, fibroblasts are induced to migrate onto the surface of the implant and begin depositing the collagenous extracellular matrix that will form a capsule surrounding the implant walling it off from the surrounding host tissue. Some of these fibroblasts differentiate into myofibroblasts, which begin capsular contraction. Once the FBR is initiated, it is inevitable; thus, early and localized interference offers the greatest opportunity to regulate the multifaceted progression of events. Previous research in this field concentrated on alterations to the implant's surface contour or chemical composition; nevertheless, none of these approaches have altered capsule formation. In addition, systemic administrations of drugs known to affect cellular response are inadequate or too systemically toxic [1]. In this study, we designed implants coated with an engineered, therapeutic hydrogel to determine if it could alter the progression of capsule formation in a rat model of the foreign body reaction. Our hydrogel exploits the host's innate cellular mechanisms to deliver therapeutic agents directly to the implant microenvironment.

Previously, we have developed a fabrication technique to coat implants with an engineered, therapeutic collagen hydrogel to control host responses, improving the implant microenvironment and implant function [2]. Briefly, a three-dimensional PLA printed mold is utilized to fabricate 1mm thick hydrogel-coated silicone discs. Several therapeutics can be incorporated into out degradable hydrogel, allowing for a multifaceted, local approach to regulate the post implantation foreign body response; thus, promoting successful integration and function of the implant. In this present study, two therapeutic agents were incorporated into the collagen hydrogel, which was implanted submuscularly. The first agent, dexamethasone, is a corticosteroid known to prevent the release of substances that cause inflammation. The other was an antibody against the receptor for interleukin 8, which has been shown to inhibit inflammatory cell activation and recruitment. Initial characterization indicates therapeutic-containing hydrogels exhibit very few inflammatory cells at the host-implant site up to and including the one-week time point as compared to silicone only controls (Figure 1). The controls demonstrate the expected stages of the FBR including massive cellular infiltration, Type I collagen deposition, and the presence of foreign-body giant cells at the implant site by the two-week time point. However, by two weeks, the therapeutic

hydrogels exhibited fibroblast infiltration but with limited inflammatory and foreign-body giant cells at the implant interface (Figure 2). In conclusion, the present study indicates that these engineered hydrogels can delay the FBR up to one week. Future work includes utilizing cytokine profiles to determine the activity and effectiveness of dexamethasone in our model system.

References:

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[2] KA Harmon *et al*. The Use of a Degradable Biomaterial to Regulate Fibrosis at the Implant-Host Interface. Microscopy and Microanalysis. 22 (S3): 1052-1053. 2016.
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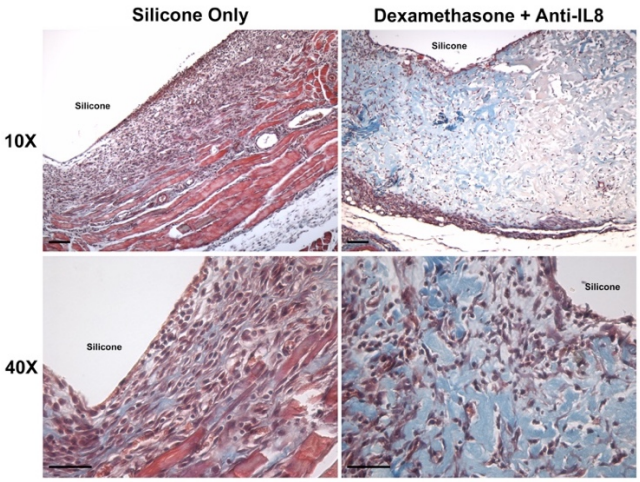

Figure 1. Engineered hydrogels delay foreign body response at one week. Fewer inflammatory cells at the host-implant site was observed in hydrogel coatings containing dexamethasone and inhibitory IL-8 antibody as compared to silicone only controls.

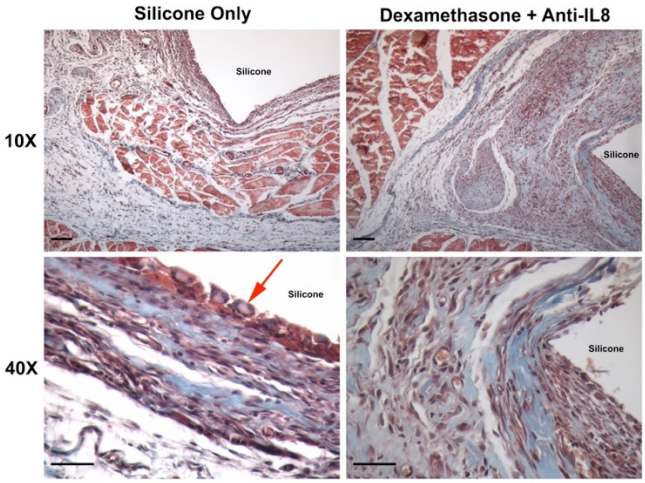

Figure 2. Hydrogels exhibit stages of the foreign body response at two weeks. Therapeutic hydrogels lack the presence of foreign-body giant cells when compared to controls, but demonstrate cellular infiltration. Controls exhibit cellular infiltration, collagen deposition, and the manifestation of foreign body giant cells (indicated by red arrow).

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