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The effect of nitric oxide surface flux on the foreign body response to subcutaneous implants

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ABSTRACT

Although the release of nitric oxide (NO) from biomaterials has been shown to reduce the foreign body response (FBR), the optimal NO release kinetics and doses remain unknown. Herein, polyurethane-coated wire substrates with varying NO release properties were implanted into porcine subcutaneous tissue for 3, 7, 21 and 42 d. Histological analysis revealed that materials with short NO release durations (i.e., 24 h) were insufficient to reduce the collagen capsule thickness at 3 and 6 weeks, whereas implants with longer release durations (i.e., 3 and 14 d) and greater NO payloads significantly reduced the collagen encapsulation at both 3 and 6 weeks. The acute inflammatory response was mitigated most notably by systems with the longest duration and greatest dose of NO release, supporting the notion that these properties are most critical in circumventing the FBR for subcutaneous biomedical applications (e.g., glucose sensors).

1. Introduction

The foreign body response (FBR) is a major impediment toward the development and long-term functionality of most implanted biomedical devices. Implantation disrupts the native tissue, initiating the FBR with the adhesion of proteins and other biomolecules to the device surface [1,2]. This process continues with the infiltration of inflammatory cells that attempt to phagocytose the foreign object [1,2]. Within a few weeks, the cells create a relatively avascular collagen-rich encapsulation, effectively sequestering the implant from the surrounding tissue [3]. Macrophages undergo cell fusion to form multi-nucleated foreign body giant cells (FBGCs) that remain at the implant surface and enhance its degradation, often leading to device failure or performance mitigation [4,5]. In the case of implanted glucose sensors, this isolation blocks the diffusion of glucose from surrounding tissue, inhibiting accurate measurements.

Efforts to improve the fate of subcutaneous implants have largely focused on developing materials with chemical and physical properties that mitigate the FBR and allow better tissue integration. The use of natural materials (e.g., collagen [6,7]) and synthetic polymers [8,9] to alter the tissue–sensor interface has slightly improved tissue integration of such devices. However, complete avoidance of the FBR has yet to be achieved and the field of biomaterials has evolved to include the design of coatings that actively release FBR mediators [10]. For glucose sensors, the focus has been on materials that release anti-inflammatory (i.e., dexamethasone) and/or pro-angiogenic (i.e., vascular endothelial growth factor (VEGF)) mediators [11–14]. Unfortunately, reports on the combined use of dexamethasone and VEGF have been controversial, possibly due to the molecules acting in an antagonistic manner [13–16].

Other work has focused on the design of interfaces that release nitric oxide (NO), an endogenous signaling molecule that plays multiple roles in the immune response including cytokine production [17,18], collagen deposition [19–22], angiogenesis [23], and anti-microbial activity [24]. Hetrick et al. [25] examined the subcutaneous in vivo response to NO-releasing *N*-diazeniumdiolated xerogels coated onto rectangular silicone rubber substrates. These coatings released ~1.35 μmol/cm^2 of NO over 72 h with 50% of the NO payload exhausted within 5 h. A >50% decrease in collagen capsule thickness was observed after 3 weeks of implantation [25]. Furthermore, NO release reduced the chronic inflammation at 3 and 6 weeks while enhancing angiogenesis adjacent to the implant after only 1 week of implantation [25]. In a separate study, mitigation of the FBR with NO release was evaluated by quantifying glucose diffusion to NO-releasing microdialysis probes

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