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Tunable hydrogel-microsphere composites that modulate local inflammation and collagen bulking

Elena Tous [a], Heather M. Weber [a], Myung Han Lee [b], Kevin J. Koomalsingh [c], Takashi Shuto [c], Norihiro Kondo [c], Joseph H. Gorman III [c,d], Daeyeon Lee [b], Robert C. Gorman [c,d,*], Jason A. Burdick [a,*]

[a] Department of Bioengineering, University of Pennsylvania, Philadelphia, PA 19104, USA
[b] Department of Chemical and Biomolecular Engineering, University of Pennsylvania, Philadelphia, PA 19104, USA
[c] Gorman Cardiovascular Research Group, University of Pennsylvania, Glenolden, PA 19036, USA
[d] Department of Surgery, University of Pennsylvania, Philadelphia, PA 19104, USA

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ABSTRACT

Injectable biomaterials alone may alter local tissue responses, including inflammatory cascades and matrix production (e.g. stimulatory dermal fillers are used as volumizing agents that induce collagen production). To expand upon the available material compositions and timing of presentation, a tunable hyaluronic acid (HA) and poly(lactide-co-glycolide) (PLGA) microsphere composite system was formulated and assessed in subcutaneous and cardiac tissues. HA functionalized with hydroxyethyl methacrylate (HeMA) was used as a precursor to injectable and degradable hydrogels that carry PLGA microspheres (~50 μm diameter) to tissues, where the HA hydrogel degradation (~20 or 70 days) and quantity of PLGA microspheres (0–300 mg ml^{-1}) are readily varied. When implanted subcutaneously, faster hydrogel degradation and more microspheres (e.g. 75 mg ml^{-1}) generally induced more rapid tissue and cellular interactions and a greater macrophage response. In cardiac applications, tissue bulking may be useful to alter stress profiles and to stabilize the tissue after infarction, limiting left ventricular (LV) remodeling. When fast degrading HeMA–HA hydrogels containing 75 mg ml^{-1} microspheres were injected into infarcted tissue in sheep, LV dilation was limited and the thickness of the myocardial wall and the presence of vessels in the apical infarct region were increased ~35 and ~60%, respectively, compared to empty hydrogels. Both groups decreased volume changes and infarct areas at 8 weeks, compared to untreated controls. This work illustrates the importance of material design in expanding the application of tissue bulking composites to a range of biomedical applications.

1. Introduction

Various biomedical and cosmetic applications benefit from the ability to bulk tissue with biomaterials (e.g. dermal fillers) that act as void fillers or to stimulate tissue production. Such approaches have evolved beyond simple volumizing replacements towards stimulatory composites that promote a transient tissue filling effect by inducing a foreign body response (FBR). This promotes collagen production and a gradual increase in tissue bulking, resulting in a natural filling effect over time [1–5]. Most stimulatory fillers comprise two main components: (i) a particle that determines the type of FBR and bulking that is endured and (ii) a carrier material that delivers the particle and is subsequently resorbed [1–5]. The mechanism behind this response relies on the activation and "crosstalk" between macrophages and fibroblasts, which is mediated by particle and carrier design.

When a foreign object is implanted into the body, proteins immediately adsorb to its surface and activate an inflammatory cascade that determines the cellular response and extent of tissue remodeling [6–10]. This entails an initial innate response comprising neutrophil infiltration and macrophage phagocytosis, followed by a more specialized response that relies on macrophage plasticity [11,12]. Macrophages have recently been loosely characterized as having M1 (pro-inflammatory) and M2 (pro-healing) phenotypes [13–17]. Classically activated (M1) macrophages are induced by interferon-γ, lipopolysaccharide and tumor necrosis factor-α and play a dominant role in the initial inflammation, and are characterized as inducing a chronic inflammatory response [14,15]. Alternatively activated (M2) macrophages are stimulated by interleukin (IL)-4, IL-10 and IL-13 cytokines, and are anti-inflammatory because of their ability to facilitate tissue remodeling [13–15]. It is thought that these macrophages, in particular, play a large role in secreting transforming

* Corresponding authors. Address: Gorman Cardiovascular Research Group, University of Pennsylvania, Glenolden, PA 19036, USA. Tel.: +1 267 350 9614; fax: +1 267 350 9627 (R.C. Gorman), tel.: +1 215 898 8537; fax: +1 215 573 2071 (J.A. Burdick).
E-mail addresses: Robert.Gorman@uphs.upenn.edu (R.C. Gorman), burdick2@seas.upenn.edu (J.A. Burdick).

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