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FGF-1 and proteolytically mediated cleavage site presentation influence three-dimensional fibroblast invasion in biomimetic PEGDA hydrogels

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ABSTRACT

Controlled scaffold degradation is a critical design criterion for the clinical success of tissue-engineered constructs. Here, we exploited a biomimetic poly(ethylene glycol) diacrylate (PEGDA) hydrogel system immobilized with tethered YRGDS as the cell adhesion ligand and with either single (SSite) or multiple (MSite) collagenase-sensitive domains between crosslinks, to systematically study the effect of proteolytic cleavage site presentation on hydrogel degradation rate and three-dimensional (3-D) fibroblast invasion *in vitro*. Through the incorporation of multiple collagenase-sensitive domains between crosslinks, hydrogel degradation rate was controlled and enhanced independent of alterations in compressive modulus. As compared to SSite hydrogels, MSite hydrogels resulted in increased 3-D fibroblast invasion in vitro, which occurred over a wider range of compressive moduli. Furthermore, encapsulated soluble acidic fibroblast growth factor (FGF-1), a potent mitogen during processes such as vascularization and wound healing, was incorporated into SSite and MSite PEGDA scaffolds to determine its *in vitro* potential on fibroblast cell invasion. Hydrogels containing soluble FGF-1 significantly enhanced 3-D fibroblast invasion in a dose-dependent manner within the different types of PEG matrices investigated over a period of 15 days. The methodology presented provides flexibility in designing PEG scaffolds with desired mechanical properties, but with increased susceptibility to proteolytically mediated degradation. These results indicate that effective tuning of initial matrix stiffness and hydrogel degradation kinetics plays a critical role in effectively designing PEG scaffolds that promote controlled 3-D cellular behavior and in situ tissue regeneration.

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1. Introduction

Tissue engineering and regenerative medicine focus on the design and development of scaffolds with mechanical and biochemical cues that direct cell behavior aimed towards the *in vitro* construction and the *in vivo* induction of tissue. While scaffolding materials from naturally derived sources possess the structural complexity and functional capacity of a particular tissue of interest, these biomaterials are associated with immunogenicity, batch-to-batch variability, and lack the ability to alter mechanical and degradative properties independent of variations in biochemical composition. As an alternative approach, synthetic polymeric matrices have been extensively investigated as scaffolds in tissue engineering due to their ability to systematically incorporate biofunctional signals of the native extracellular matrix (ECM) and fine-tune mechanical properties in a highly reproducible manner, thus allowing for controlled study of cell–substrate interactions.

Among the classes of synthetic scaffolds, crosslinked poly(ethylene glycol) (PEG) hydrogels have been extensively used in tissue engineering due to their hydrophilicity, biocompatibility, and ability to be biochemically modified. Various approaches have been used to fabricate PEG hydrogels with covalently incorporated ECM signals such as free-radical photopolymerization [1–6], step-growth polymerization such as Michael-type addition [7], combinations of free radical and step-growth chemistries (mixed mode polymerization) [8,9], click chemistry [10], and native chemical ligation [11]. To this end, studies have shown that the incorporation of soluble and immobilized biofunctional cues within these scaffolds as well as their mechanical properties [12] dictate cell behavior *in vitro* [1,13–16] and *in vivo* [13,16,17]. To render these scaffolds susceptible to three-dimensional (3-D) cell adhesion, pro-teolytic degradation, proliferation, migration and matrix deposition, cell adhesion ligands such as RGD as well as cleavable peptide domains sensitive to cell-mediated proteolysis have been covalently immobilized into PEG hydrogels [12,15,16,18]. Studies have also shown that growth factor immobilization enhances adhesion and migration [15,16], and that the presence of both soluble and immobilized growth factors results in enhanced cell-mediated proteolysis [15].

Controlled scaffold degradation is a critical design criterion for successful tissue regeneration. This requires that hydrogel

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