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Direct cell encapsulation in biodegradable and functionalizable carboxybetaine hydrogels

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ABSTRACT

Hydrogels provide three-dimensional (3D) frames with tissue-like elasticity and high water content for tissue scaffolds. They were commonly prepared from macromers such as poly(ethylene glycol) diacrylate (PEGDA) via free radical polymerization and used to encapsulate cells. Here, we report the direct encapsulation of cells into hydrogels using a low-toxic and water-soluble monomer, carboxybetaine methacrylate (CBMA), via redox polymerization. A disulfide-containing crosslinker was added to form a biodegradable carboxybetaine (CB) hydrogel, which can be self-degraded as cells grow or degraded in an accelerating way via adding of a cysteine-contained medium NIH-3T3 cells encapsulated in the CB hydrogel formed spherical aggregates that were recovered from hydrogel erosion. Furthermore, an RGD-containing peptide was also added to improve cell adhesion on the two-dimensional (2D) hydrogel surface and promote cell proliferation in the 3D hydrogel. The non-cytotoxic and biodegradable CB hydrogel with additional cell-adhesion moieties provides an excellent 3D environment for cell growth as tissue scaffolds.

1. Introduction

Three-dimensional (3D) scaffolds in tissue engineering serve as a temporary support for cell accommodation and growth [1,2]. Hydrogels have been attractive candidates for tissue engineering scaffolds due to their tissue-like elasticity and high water content, mimicking the interstitial tissue environment. Cell encapsulation during hydrogel formation *in situ* is a popular strategy, with which a minimally invasive operation is possible [2]. The requirements for such a strategy include hydrogel materials whose precursors and final products are non-cytotoxic, and an innocuous process of cell encapsulation [1]. In designing a suitable hydrogel for cell encapsulation, several criteria must be taken into consideration. First, because organic solvents usually damage cells, a water-based process along with water-soluble precursors is needed. Secondly, reactions for gelation must be mild and not impair cell physiology. The structure and chemical properties of hydrogels must be suitable for cell proliferation and tissue formation. Furthermore, hydrogels must degrade at a rate matching tissue growth, and degraded products of hydrogels must not have adverse effects on encapsulated cells [1].

Poly(ethylene glycol) (PEG)-based hydrogels have been the most widely used synthetic materials for cell encapsulation [3–7]. PEG-based hydrogels provide a highly swollen environment similar to native tissues and possess a low background level of non-specific protein adsorption [5,8]. Precursors of PEG hydrogels used in cell encapsulation are “macromolecular” monomers such as PEG diacrylate or dimethacrylate [3,7] because short oxyethylene chains with less than 14 repeating units showed high cytotoxicity [9]. Cell encapsulation is usually completed through radical chain polymerization of PEG monomers to form high-molecular-weight interconnected network to entrap cells [3,10].

Recently, a series of water-soluble zwitterionic molecules, such sulfobetaine and carboxybetaine, were developed to create ultra-low-fouling substrates [11]. Highly hydrated layers surrounding the opposing charges of zwitterionic compounds creates a high-energy barrier to non-specific protein adsorption [12]. We previously showed that a surface coated with polyzwitterionic polymers was ultra-low fouling to restrain protein adsorption to 5 ng/cm^2 even from undiluted blood plasma and serum. The zwitterionic substrates were also resistant to the adhesion and growth of cells or bacteria [11]. The functionalizable property of carboxybetaine provides an advantage to create non-fouling hydrogels with

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