Engineering biosynthetic cell encapsulation systems

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9.1 Introduction

Polymeric hydrogels have been a rapidly developing group of biomedical materials since the 1960s. Traditionally, hydrogels were utilised for applications *adjacent* to cells, such as contact lenses and absorbable sutures (Langer and Peppas, 2003), and used synthetic polymeric materials such as polyhydroxyethyl methacrylate (e.g. contact lenses). Natural hydrogels were also explored in addition to synthetic hydrogel materials. For example, Yannas et al. designed natural hydrogels based on collagen and glycosaminoglycans for burn dressings (Yannas and Burke, 1980). These simple, preliminary biomedical polymers were hydrophilic (i.e. water soluble), nontoxic, and could be tailored for biodegradability or stability depending on the application.

As the advantages of polymer hydrogels for biomedical applications became recognised, more advanced chemistries and applications have been explored. It was soon realised that there was great potential if cells could be encapsulated *within* the hydrogel materials. The delivery of cells as newly engineered tissues and organs is often necessary clinically due to insufficient organ donors and the inability of any transplanted organs to function adequately. The first use of hydrogels for cell encapsulation was pioneered by Lim and Sun. They created calcium alginate microspheres for the encapsulation of islet cells as an approach to treat diabetes and were able to correct the diabetic state of rats for several weeks (Lim and Sun, 1980). This work truly demonstrated the potential for cell encapsulation within hydrogel biomaterials for the first time and has ongoing contributions to the development of advanced hydrogels for the transplantation of therapeutic cells. As a result, researchers around the world have focused on using natural, synthetic and biosynthetic hydrogels for the local and controlled delivery of therapeutic products and cells for a variety of defects and diseases. Examples of areas of research include treatment of diabetes, liver disease (Maguire et al., 2006), myocardial infarction (Yu et al., 2010), cancer (Hao et al., 2005) and numerous diseases of the central nervous system (e.g. Parkinson's disease, glioma, Huntington's disease) (Kim et al., 2005; Read et al., 2001; Emerich et al., 1997).

Despite the groundbreaking work from Lim and Sun in the 1980s, cell encapsulation within biomaterials still poses many challenges for researchers today. If the

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use of functionalised CS has been as a component of hydrogels for cartilage tissue engineering (Bryant et al., 2004; Steinmetz and Bryant, 2012).

Heparin

Heparin is a linear polysaccharide with the highest charge density of any biological molecule. Its heterogeneous structure is made up of α-L-iduronic acid, β-D-glucuronic acid and a-D-glucosamine repeat units. The high charge density of heparin makes it attractive for cell encapsulation in applications using growth factors and cytokines, because heparin helps to localise and stabilise these proteins (Bhatia, 2012). Physically and chemically crosslinked heparin hydrogels have been used for a variety of biomedical applications including the encapsulation of fibroblasts (Wieduwild et al., 2013), differentiation of stem cells (Seto et al., 2012) and liver tissue-engineering applications (Kim et al., 2010). In spite of these advantages, heparin is degraded in vivo by heparanase, and as such, caution must be taken when using heparin for biomaterials, as it is a potent anticoagulant and can cause bleeding (Lever et al., 2012; Melloni et al., 2008).

Hyaluronan

Hyaluronan (HA) hydrogels are one of the most prominent materials for cell encapsulation (Burdick and Prestwich, 2011). Hyaluronan is found in nearly all animal tissues, but is particularly prevalent in joints and the wound healing cascade because of its role in tissue hydration, nutrient diffusion and proteoglycan organisation (Peppas et al., 2006; Alberts, 1994). A variety of cell-surface proteins, including intercellular adhesion molecules (ICAM-1), cluster of differentiation (CD 44) and the receptor for hyaluronan-mediated motility, are known to enable binding to HA and promote cell adhesion and proliferation (Toole, 2004). The repeating dissacharide of HA is comprised of 1,4-linked β-D-glucuronic acid and *N*-acetyl-β-D-glucosamine units, of which the primary and secondary hydroxyl groups, glucuronic acid carboxylic acid, and the *N*-acetyl group (following deamidation) have been targeted for modification. Common modifications include carbodiimide-mediated reactions, esterification, amidation, etherification, addition of thiols, hydrazide derivation, divinylsulphone crosslinking and methacrylate crosslinking (Burdick and Prestwich, 2011). Native enzymes (i.e. hyaluronidase) can degrade hyaluronan hydrogels, allowing the cells in the body to locally regulate clearance of the hyaluronan. However, for HA hydrogels there is a fine balance between forming gels with weak mechanical properties and rapid, uncontrollable degradation versus forming mechanically robust hydrogels that have reduced capability for enzymatic degradation because of too much modification. Additionally, enzymatically degraded HA fragments from hydrogels can regulate ECM production (Nuttelman et al., 2008), and low-molecular-weight hyaluronan oligomers can be pro-inflammatory (Noble, 2002).

9.2.2.3 Deoxyribonucleic acid

Deoxyribonucleic acid (DNA) is composed of two polynucleotide chains held together by weak intermolecular forces. DNA has been probed for its ability to form hydrogels (Um et al., 2006). Hydrogels made from DNA can efficiently self-assemble into