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Review

Cell encapsulation via microtechnologies

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ABSTRACT

The encapsulation of living cells in a variety of soft polymers or hydrogels is important, particularly, for the rehabilitation of functional tissues capable of repairing or replacing damaged organs. Cellular encapsulation segregates cells from the surrounding tissue to protect the implanted cell from the recipient's immune system after transplantation. Diverse hydrogel membranes have been popularly used as encapsulating materials and permit the diffusion of gas, nutrients, wastes and therapeutic products smoothly. This review describes a variety of methods that have been developed to achieve cellular encapsulation using microscale platform. Microtechnologies have been adopted to precisely control the encapsulated cell number, size and shape of a cell-laden polymer structure. We provide a brief overview of recent microtechnology-based cell encapsulation methods, with a detailed description of the relevant processes. Finally, we discuss the current challenges and future directions likely to be taken by cell microencapsulation approaches toward tissue engineering and cell therapy applications.

1. Introduction

Technologies for creating living functional tissues in the laboratory for the repair or replacement of damaged organs have emerged as new promising tools for therapeutics. Implanted cells must be protected from attack by the host immune system. Currently, the most common immune protection techniques have involved entrapping therapeutic cells in a polymeric coating using diverse hydrogels [1–4]. Several technological barriers must be addressed before these approaches may be applied practically and widely. The selection of a suitable encapsulating material with appropriate porosity, which can facilitate the transport of nutrients, proteins, DNA, and drugs while blocking attack of antibodies and immune cells, is critical. The capsule must be mechanically stable and easy to handle. These requirements may be satisfied by controlling the pore size and thickness of the encapsulating polymer membrane at the microscale ranges. The cell viability and metabolic status have been shown to be optimal if the encapsulated cells are on the order of one hundred microns in size. [5] Although several encapsulation methods have been developed, the satisfaction of all of these requirements still remains challenging [6].

Advances in recent microfabrication techniques based on photolithography have been widely adopted in the biomedical fields and have enabled the preparation of devices or systems that remove some of the bottlenecks that have historically slowed certain processes in the life sciences. Some of these technologies have faced barriers to adoption in the biomedical fields due to the high costs, long time required for microfabrication processes, limitations on the materials, and requirement of complicated facility and labor skills. Softlithography has circumvented many of the problems associated with conventional silicon-based photolithography processes and has enabled the emerging of strong cell encapsulation tool [7–9]. The microsystems based on softlithography present several major advantages: small quantities of reagents and sample volumes are needed, the experimental timescales are short, the processes are cost-effective, a diversity of materials may be used, and the dimension of experimental platform is reduced enough to be placed in the cell-incubator. The ability to handle small sample volumes using a microscale platform permits precise control over the number and sizes of encapsulated cells, as well as over the shape of the cell-laden polymer structure.

In this review, we describe a variety of methods that have been developed for cell encapsulation based on microscale platforms. Microsystems can encapsulate cells in diverse shapes, including beads, sheets, and fibers, and can finely control the sizes and numbers of encapsulated cells on the microscale. The materials needed for microtechnology-based cell encapsulation and a detailed description of the microencapsulation processes are described. Finally, we discuss the current challenges and future

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opportunities made available by cell microencapsulation for tissue engineering and cell therapy applications.

2. Concept of cell encapsulation and overview of encapsulation techniques based on macro-platforms

Transplanted cells are recognized by host immune cells as foreign substances. Like antigens, transplanted cells tend to trigger an immune response. Activated immune cells, such as macrophages, granulocytes, lymphocytes, and fibroblasts, secrete cytotoxic molecules and cytokines that cause the structural and functional loosing of implanted cells [10,11]. Cells for which a donor shortage exists and that are unable to grow in artificial media, for example, pancreatic islet cells, must be provided from xeno or allo species. A host immune response and the associated functional damage to implanted cells may be avoided by encapsulating the cells in a variety of non-cytotoxic and semipermeable hydrogel. The most important requirements of cell encapsulation is that the cells retain their function and release cytokines or hormones in the capsule, and they are also protected from a patient's immune system (Fig. 1) [12,13]. Therefore, the cell encapsulation method is crucial and encapsulating hydrogel membranes should allow oxygen and nutrients to reach the internal cells, while excreted wastes and therapeutic products may be released. The encapsulation methods could be classified into macro- and micro-platform based method. Macro platform based method involves encapsulation of cells in hollow fiber and bulk hydrogel using macroscale devices. In contrast, micro-platform based method involves the encapsulation of cells in microparticles and microfibers using microfluidic chips and micromolding (Fig. 1). Encapsulation of cells in bulk hydrogels offer the simplest encapsulation method, with a process involving the steps of: 1) suspending cells at a desired density in a pre-gel solution; 2) injecting the suspension into the container; and 3) gelling the pre-gel cellular suspension via a temperature transition, chemical reaction, or photocuring process [14]. The ultrasonication-induced gelation method reported by Wang et al. [15] is an additional process that accelerate gelation kinetics. Synthetic polymers, such as poly (ethylene glycol) (PEG)-based hydrogels, are commonly used as bulky hydrogel encapsulating materials [16–27]. Most of PEG-based hydrogels for encapsulation require a photopolymerization procedure for gelation. Mixtures of monomers, crosslinkers, and photoinitiators are essential components of gel formation [28]. PEG hydrogels that form via a temperature transition have been shown by some studies to display advantages over photopolymerization reactions when applied to areas that permit only limited light penetration [16,17]. Foo et al. reported a two-component molecular recognition gelation method in which cells are encapsulated without environmental condition changes (e.g., temperature, pH, or ironic strength). They developed a crosslinking method that linked multiple repeats of conserved tryptophan residues and proline-rich peptide domains in a sol to form a gel phase upon mixing [29]. The WW domains (named

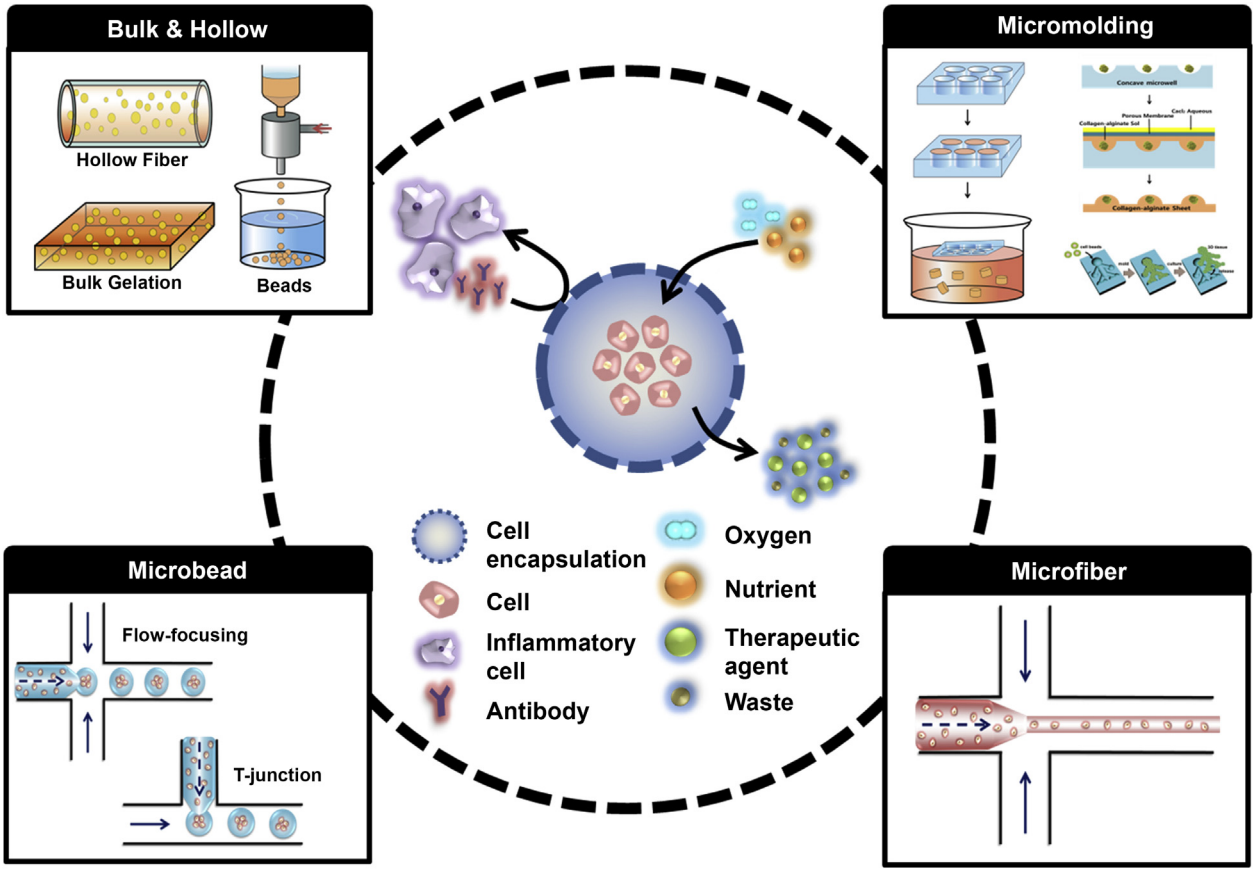

Fig. 1. Schematic diagram and a list of the major methods used to achieve cell encapsulation: Cellular encapsulation sequesters the encapsulated cells from inflammatory cells and antibodies without impeding the inward diffusion of oxygen and nutrients and the outward diffusion of therapeutic agents and wastes. (Inspired by Orive et al. [12]) The major methods used for cell encapsulation are the macro platform (mainly nozzle-based platforms), micromolding (The figure on the left was inspired by McGuigan et al. [84] and the upper figure on the right was inspired by Lee et al. [89]. The bottom figure was reprinted from Matsunaga et al. [86]: Molding cell beads for rapid construction of macroscopic 3D tissue architecture. Advanced Healthcare Materials. 2011. 23. H90–H94. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission), microfluidics-based microbeads, and microfibers.