Human stem cell encapsulation: a promising approach

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Stem cell research is a relatively new area using primitive human cells and developing them into most of the 220 varieties of cells in the human body, including blood, heart and brain cells[1–3]. The recent demonstration of conversion of somatic cells into pluripotent stem cells has opened up new avenues of research in regenerative medicine[4]. Some scientists and researchers expect that stem cell research would uncover treatments and possibly even cures for some of the worst diseases, including heart disease, diabetes and neurodegenerative diseases like Alzheimer's and Parkinson's. Mesenchymal stem cells (MSCs) are effortlessly isolated from adult bone marrow, adipose tissue, cord blood, placenta and umbilical cord, and from foetal organs such as liver, blood, bone marrow and lungs[5]. Stem cells proliferate extensively and generate sufficient quantity of tissue as well as differentiate into the desired cell type(s). They can be expanded *ex vivo* without differentiation or maturation and can be modified genetically to express a variety of genes. Other advantages include survival in the recipient after transplant, integration into the surrounding tissue after transplant, functioning appropriately for the duration of the recipient's life and causing no harm to the recipients[6]. Considering these advantages, human embryonic stem cells will yield information about the complex events that occur during human development and could also be used to test new drugs. Additionally, the most important potential application of human stem cells is the generation of cells and tissues that could be used for cell-based therapies. In order to complement stem cell research for better and effective results, encapsulation of stem cells in a gel matrix has been envisaged which has opened up further avenues to derive maximum utility of stem cells for various medical treatments[6]. These fascinating biological traits, along with their genetic engineering potential for therapeutic applications, make stem cells attractive assets for cell-based therapy, including cell encapsulation[7].

The encapsulation mechanism is based on a process of embedment and trapping of living cells in a nutrient gel. To impart hardness and stability to the gel, various chemicals as complex agents have been suggested which interact with the gel and form cross linked beads. This composition of gel and complex agent form extruding droplets (beads) which ensures sufficient protection to fragile cells embedded in the gel[8]. This encapsulation methodology is exceptional, compared to other cell-based treatment techniques, because it facilitates the liberated exchange of nutrients and oxygen between the entrapped cells and their surroundings, while preventing the break away and removal of the entrapped cells[9]. Microcapsules can be introduced at the transplantation bed, localizing the release of therapeutic factor. This approach avoids systemic side effects and increases patient compliance. These applications require tight control of a number of material properties, including mechanical stiffness, swelling, degradation, cell attachment and binding or release of bioactive molecules. Keeping cells in a microenvironment has given satisfactory results in several cases for which biomaterials derived from natural sources or from synthetic polymers are widely used. These biomaterials available from commercial sources or are freshly synthesized[10]. They have the desirable properties with control over size and shape, and possess tailorable material characters. Cell encapsulation is based on the principle of developing a capsule with sufficient permeability that allows nutrients and oxygen to reach the encapsulated cells. Advantages of encapsulated cells are several fold and have been well established in other types of cells, including microbial and plant cells. In case of human stem cells the encapsulating matrix is often used in conjunction with the therapeutic secreting cells to provide a physical barrier to protect the cells from hostile extrinsic factors and must be restrictive enough to exclude immune cells and antibodies that would cause rejection and destroy the implant, but let outward secretion of essential molecules generated by the cells[11,12] (Figure 1). Additionally, replacement of damaged tissues with stem cells encapsulated to mimic the extracellular matrix restoring the normal control of cell function is being actively pursued using tissue engineering[13]. However, when implanted, encapsulated cells produce cytokines and antigens, which ultimately evoke a host

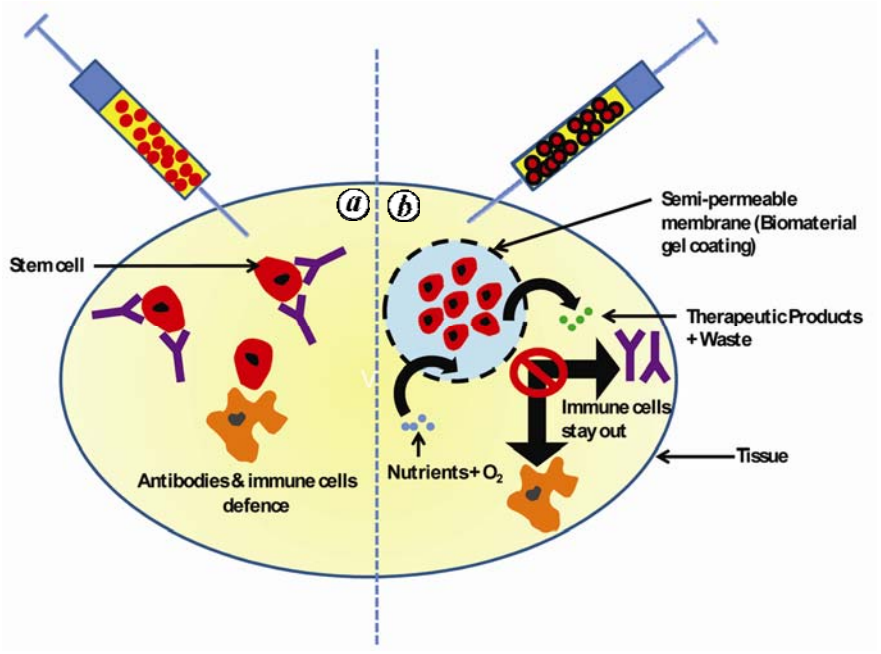

Figure 1. Schematic overview of stem cell. ***a***, Non encapsulated; ***b***, Encapsulated.

immune response causing an inflammatory tissue adjoining the microcapsules. This inflammatory reaction leads to cell suffocation and decreased encapsulated cell viability. One promising solution to reduce host immune reaction is the administration of anti-inflammatory drugs along with the therapeutic system.

A number of polymeric encapsulation systems have been developed or are being tested in clinical trials. Attempts have been made to use polysaccharide hydrogels, chitosan, calcium or barium alginate, and a layered matrix of alginate and polylysine for preparing the encapsulating matrix[11]. Among the various hydrogels used, alginate hydrogels are proving to have applicability as biomaterials[11,13,14]. Reports have indicated their efficacy as scaffolds for tissue engineering, as delivery vehicles for drugs, and as model extracellular matrices for basic biological studies. The efficiency of the gels is controlled by several factors, as listed by Santos *et al.*[13], including composition and purification of the natural source, viscosity, cation used, pH, temperature and methodology adopted. According to Augst *et al.*[15], it is necessary to have a firm control over the various material properties of alginate gel, such as mechanical stiffness, swelling, degradation, cell attachment and binding or release of bioactive molecules.

Several novel innovations and modifications are underway for reinforcing the nutrient gel for effective results[12]. Goren *et al.*[16] demonstrated encapsulation of MSCs using alginate and poly-L-lysine which retained stem cell properties, long-lasting viability and proliferation inside the microcapsule, and suggested that microencapsulation can serve as a platform for an uninterrupted long-term release of therapeutic factors. A novel microencapsulation technique was developed producing self-assembled collagen–MSC microspheres. These microspheres were found to serve as excellent cell-delivery devices as they were stable, injectable and provided a protective, growth and migration-supporting matrix to the MSCs[15–18]. Chan *et al.*[19] showed that MSCs could preserve their stem cell nature upon microencapsulation and easily be localized with retained viability upon *in vivo* implantation. These microspheres present novel cell-delivery devices with optimal biological and functional profile that may facilitate clinical applications of MSC-based therapy. The use of PEG hydrogel system having peptide sequences allowing better sustained viability of the encapsulated cells has been explained[20]. Another study illustrated a two-component protein engineered with physical hydrogels for cell encapsulation having desirable properties such as shear thinning, injectable and self-healing, which may make them suitable for use in a wide range of experimental and clinical cell encapsulation applications[21].

Although the cells encapsulated significantly improve the therapeutic efficacy of transplanted cells, there have been no successful products commercialized based on these technologies[13]. Currently, infusing or implanting living cells – in a free state or in polymeric capsules – into patients is under intense study in animal models and in promising human clinical trials with potential to dramatically change the treatment of human diseases[18,22].

The recent advancement, as discussed here, in stem cell research and encapsulation of cells technology will radically change the conceptual framework of drug delivery, tissue engineering and regenerative medicine. The knowledge obtained to mimic stem cell microenvironment and the interface of stem biology and biomaterial science is now reasonably advanced. These developments when complimented with conventional medical research hold the solution to assuring both sustainability and workability of the future medicinal treatments. Undoubtedly, this research is in its early stages, but as has been confirmed by a number of reports, there is an enormous prospective in using biomaterials for stem cell biology applications.

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