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Polymers in cell encapsulation from an enveloped cell perspective ☆

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ABSTRACT

In the past two decades, many polymers have been proposed for producing immunoprotective capsules. Examples include the natural polymers alginate, agarose, chitosan, cellulose, collagen, and xanthan and synthetic polymers poly(ethylene glycol), polyvinyl alcohol, polyurethane, poly(ether-sulfone), polypropylene, sodium polystyrene sulfate, and polyacrylate poly(acrylonitrile-sodium methallylsulfonate). The biocompatibility of these polymers is discussed in terms of tissue responses in both the host and matrix to accommodate the functional survival of the cells. Cells should grow and function in the polymer network as adequately as in their natural environment. This is critical when therapeutic cells from scarce cadaveric donors are considered, such as pancreatic islets. Additionally, the cell mass in capsules is discussed from the perspective of emerging new insights into the release of so-called danger-associated molecular pattern molecules by clumps of necrotic therapeutic cells. We conclude that despite two decades of intensive research, drawing conclusions about which polymer is most adequate for clinical application is still difficult. This is because of the lack of documentation on critical information, such as the composition of the polymer, the presence or absence of confounding factors that induce immune responses, toxicity to enveloped cells, and the permeability of the polymer network. Only alginate has been studied extensively and currently qualifies for application.

This review also discusses critical issues that are not directly related to polymers and are not discussed in the other reviews in this issue, such as the functional performance of encapsulated cells in vivo. Physiological endocrine responses may indeed not be expected because of the many barriers that the metabolites encounter when traveling from the blood stream to the enveloped cells and back to circulation. However, despite these diffusion barriers, many studies have shown optimal regulation, allowing us to conclude that encapsulated grafts do not always follow nature's course but are still a possible solution for many endocrine disorders for which the minute-to-minute regulation of metabolites is mandatory.

Contents

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1. Introduction

Encapsulation involves the envelopment of living cells in polymer membranes to protect the cells from immune destruction. The introduction of this technology dates back to 1933, when Bisceglie et al. [1] studied the effect of encapsulation on the survival of tumor cells in the abdominal cavity of pigs. Bisceglie demonstrated that prolonged cell survival can be achieved by enveloping cells in immunoprotective membranes [1]. To achieve this, Bisceglie applied amnion tissue as a membrane but did not recognize the potential of the technology for the treatment of disease. In 1950, Algire et al. [2] introduced the concept of the "diffusion chamber" to graft therapeutic cells. Algire was also the first to emphasize the importance of the application of biocompatible polymers with constant, predictable properties as a prerequisite for therapeutic application [2]. Since then, many groups have demonstrated the principal applicability of encapsulation technology for the treatment of different types of diseases [3]. The number of diseases for which this technology has been proposed is long and includes hemophilia B [4], anemia [5], dwarfism [6], kidney [7] and liver failure [8], pituitary disorders [9], central nervous system insufficiency [10], and diabetes mellitus [11].

Basically, the encapsulation of living cells is applied in two geometries: macro- and microcapsules. In macrocapsules, living cells are enveloped in relatively large diffusion chambers with semipermeable properties. Diffusion chambers have been produced in the form of flat sheets, hollow fibers, and disks [12]. Macrocapsules can be distinguished in intra- or extravascular devices [13]. In intravascular devices, cells are distributed outside of artificial capillaries and connected to the blood circulation as a shunt. The advantage of these devices is that they are in close proximity to the bloodstream, implying the fast exchange of therapeutic molecules and nutrients, such as oxygen [14]. A major disadvantage of this system is that thrombosis may occur with these kinds of devices. This makes the use of life-long anti-coagulation therapy a requirement. For most endocrine diseases for which encapsulation is proposed, this risk of thrombosis makes it an unacceptable alternative for conventional treatment, in addition to its side-effects [15]. For this reason, most groups currently focus on extravascular devices, in which cells are enveloped within semipermeable diffusion chambers and implanted under the skin or in the peritoneal cavity without direct vascular access. The technology is associated with minor surgery and allows easy replacement in case of failure of the graft or when the transplant has to be substituted for other reasons. The numerous reports on the successful application of macrocapsules in experimental animals and humans [16–19] illustrate the potential of the technique. However, there is also a drawback. Macrocapsules are characterized by a relatively large surface-to-volume ratio. This implies that high amounts of nutrients are required to build an adequate diffusion gradient for ingress of the nutrients. This interferes with optimal nutrition for the cells. Another obstacle is that the cell density in macrocapsules should be quite low to guarantee adequate nutrition [13]. Within most applications, the cell density should not exceed 5–10% of the volume fraction [14]. This suggests that if large numbers of cells are required to cure disease [14], then numerous or large devices must be implanted. Current research on macroencapsulation focuses on the development of techniques that increase nutrition for tissues [20–22].

Microcapsules are not associated with surface-to-volume ratio issues. They allow for the fast exchange of therapeutic molecules and have been shown to closely mimic the release of insulin and glucose. Because of this beneficial property of microcapsules, the majority of research groups have concentrated on the development of microcapsules that provoke low or no inflammatory responses for the cure of endocrine diseases [11,23–25]. During recent years, the technology has reached the human stage [26–30].

Before discussing the advances in polymer research, a number of important items should be discussed that influence the functional survival of encapsulated tissue, regardless of the type of polymer that is being applied. As outlined below, encapsulated grafts have several limitations that cannot be overcome by simply applying better, innovative polymers.

2. Functional performance of encapsulated cells

A prerequisite is that the capsules or their materials should not interfere with cellular viability. Encapsulation procedures and the polymers applied, therefore, should not be associated with toxicity. Toxicity is a phenomenon that is rather cell-specific, and the susceptibility of cells to toxic molecules varies considerably [31,32]. Moreover, cells with high proliferation or regenerative capacities are more susceptible to toxicity than cells that derive from cadaveric donors, such as pancreatic islets [32,33]. In the latter case, minimal or no loss should be associated with the encapsulation procedure. These issues are discussed below with regard to the principal applicability of the procedure for mammalian cells.

In addition to optimal viability, an encapsulation system should allow for optimal function. Viability and function are not always directly related (discussed below). Immunoprotected cells are proposed for the treatment of diseases for which minute-to-minute regulation of a metabolite is required. To illustrate its potential, diabetes is currently being treated with multiple daily doses of exogenous insulin. This therapy is associated with fluctuations in the daily glucose profile, with consequently frequent episodes of hyper- and hypoglycemia. In the long-term, this can lead to diabetic complications [34,35], hypoglycemic unawareness, or even the failure of organs, such as the kidneys [36]. This can only be prevented by using an insulin source that regulates glucose levels on a minute-to-minute basis [34]. Immunoprotected pancreatic islets are proposed to be such a source.

Many studies have shown that immunoprotective capsules do not interfere with the free diffusion of glucose and insulin. Until a size of 1 mm is reached, the capsules do not disturb the normal biphasic release of insulin after a glucose challenge [37]. However, this is very different in vivo, in which the same functional, biphasic serological release patterns of insulin as those seen from islets in the normal pancreas may not be expected [38,39]. This can be explained as follows. Conventionally encapsulated islets are transplanted in the peritoneal cavity where they remain free-floating in the peritoneal fluid without direct vascular access. This implies that a number of barriers have to be overcome before glucose-induced insulin release can be observed in the systemic circulation. Glucose must first pass the basement membranes of the capillaries in the peritoneal cavity. This can take up to 5 min after glucose is increasing in blood [40]. The released insulin then must