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Review

Immunoisolating semi-permeable membranes for cell encapsulation: Focus on hydrogels

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ABSTRACT

Cell-based medicine has recently emerged as a promising cure for patients suffering from various diseases and disorders that cannot be cured/treated using technologies currently available. Encapsulation within semi-permeable membranes offers transplanted cell protection from the surrounding host environment to achieve successful therapeutic function following *in vivo* implantation. Apart from the immunoisolation requirements, the encapsulating material must allow for cell survival and differentiation while maintaining its physico-mechanical properties throughout the required implantation period. Here we review the progress made in the development of cell encapsulation technologies from the mass transport side, highlighting the essential requirements of materials comprising immunoisolating membranes. The review will focus on hydrogels, the most common polymers used in cell encapsulation, and discuss the advantages of these materials and the challenges faced in the modification of their immunoisolating and permeability characteristics in order to optimize their function.

Contents

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1. Introduction

The transplantation of encapsulated cells is fast becoming a promising approach for the treatment of various diseases and disorders that cannot be cured or treated using technologies currently available. This powerful technique allows for the local and controlled delivery of therapeutic products to specific physiological sites in order to restore lost function due to disease or degeneration. Possible targets of this approach include disorders of the endocrine system (diabetes, hypoparathyroidism) [1] and central nervous system (Parkinson's and Alzheimer's) [2–5], as well as conditions such as heart disease [6], and cancer [7–10] (Table 1). A major obstacle to cellular transplantation is host rejection and attack [11–13]. In this regard, encapsulation offers transplanted cell protection from the surrounding host environment which is critical if they are to achieve successful therapeutic function following *in vivo* implantation. This can be achieved by encapsulating cells within permselective (semi-permeable) membranes, a process termed immunoisolation. Immunoisolation was initially attempted in 1933 by Bisceglie who successfully replaced the endogenous pancreas of rats with human insulinoma cells [14]. The cells were enclosed into a membranous sac and implanted into the abdominal cavity to study the effects of lack of vascularization on the survival of the tissues. The concept of immunoisolation was experimentally developed in 1943 by Algire who demonstrated that graft viability could be prolonged by encapsulating tissues (from the same species (allogenic) and different species (xenogenic)) in diffusion chambers before transplantation [15,16]. The term “artificial cells” was introduced 20 years later by Chang in 1960s, to describe the technique of encapsulating cells for immunoprotection [17,18]. Since then, numerous studies have highlighted that the encapsulating membrane material must serve two vital functions. First, it must allow the inward diffusion of

Table 1
Examples of encapsulated cells targeting various diseases, showing their immunoisolating membrane materials and device configurations.

Encapsulated cells	Targeted disease	Encapsulation device	Membrane material	Ref
Pancreatic islets	Diabetes	Conformal coating	Nanothin-PEG	[21]
			PVA/PEG	[22]
			Polyion complex	[23]
			Chitosan/alginate/chondroitin sulfate	[24]
		Macrocapsule	PEG	[25,26]
			Chondrocyte cell sheet	[27]
			Agarose	[28]
			Polysulfone	[29]
			PVA	[30]
			PVA/PAA	[31]
			Polyurethane	[32,33]
		Microcapsule	Alginate	[34–36]
			Alginate/PEG	[37]
			Biodritin (alginate/chondroitin sulfate)	[38]
			Agarose	[39,40]
			Cellulose sulfate	[41]
Parathyroid cells	Hypoparathyroidism	Microcapsule	Alginate	[42]
PC12 cell line	CNS/Parkinson's	Macrocapsule	Polyurethane	[43]
293 cell line	CNS/Glioma	Microcapsule	Alginate	[44]
BHK cell line	CNS/Huntington's	Macrocapsule	PAN-PVC	[45]
			Alginate	
BHK cell line	CNS/Amyotrophic lateral sclerosis	Macrocapsule	Poly-ether-sulfone	[46]
293 cell line	Pancreas cancer	Microcapsule	Cellulose sulfate	[47,48]
G8P2B5 hybridoma cells	Retroviral neurodegeneration	Microcapsule	Cellulose sulfate	[49]
J558/TNF-alpha cells	Cancer	Microcapsule	Alginate	[9]
HEK 293 cells	Cancer	Microcapsule	Alginate	[50]
CYP2B1 cells	Cancer	Microcapsule	Agarose	[51]
Hepatocytes	Liver failure	Macrocapsule	PEG	[52]
			Polyacrylonitrile-sodium methallylsulphonate	[53]
		Microcapsule	Poly-L-lysine	[54]
			Polyelectrolyte copolymer/modified collagen	[55]
			Alginate-chitosan	[56]
Mesenchymal stem cells	Myocardial infarction	Microcapsule	Alginate	[57]

Abbreviations
PEG: poly (ethylene glycol).
PVA: poly (vinyl alcohol).
PAA: poly (acrylic acid) PAN-PVC.
PAN-PVC: poly (acrylonitrile vinyl chloride) copolymer.