Advanced Drug Delivery Reviews 67-68 (2014) 93–110

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Oxygen supply to encapsulated therapeutic cells ☆

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ARTICLE INFO

Available online 27 February 2014

Keywords:
Encapsulation
Oxygen supply
Immunobarrier
Immunoisolation
Hypoxia
Implanted devices
Cell transplantation

ABSTRACT

Therapeutic cells encapsulated in immunobarrier devices have promise for treatment of a variety of human diseases without immunosuppression. The absence of sufficient oxygen supply to maintain viability and function of encapsulated tissue has been the most critical impediment to progress. Within the framework of oxygen supply limitations, we review the major issues related to development of these devices, primarily in the context of encapsulated islets of Langerhans for treating diabetes, including device designs and materials, supply of tissue, protection from immune rejection, and maintenance of cell viability and function. We describe various defensive measures investigated to enhance survival of transplanted tissue, and we review the diverse approaches to enhancement of oxygen transport to encapsulated tissue, including manipulation of diffusion distances and oxygen permeability of materials, induction of neovascularization with angiogenic factors and vascularizing membranes, and methods for increasing the oxygen concentration adjacent to encapsulated tissue so as to exceed that in the microvasculature. Recent developments, particularly in this latter area, suggest that the field is ready for clinical trials of encapsulated therapeutic cells to treat diabetes.

Contents

1. Introduction

Tissue-engineered immunoisolation devices, which provide a semi-permeable barrier to protect transplanted cells from the recipient's

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Cell encapsulation and drug delivery".

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http://dx.doi.org/10.1016/j.addr.2014.02.007
0169-409X/

immune system without immunosuppressive drugs, have the potential to treat a large range of diseases, including diabetes [1], hemophilia [2], anemia [3], parathyroid disease [4], chronic pain [5], Parkinson's disease [6], Huntington's disease [7], and amyotrophic lateral sclerosis [8]. The therapeutic cells constantly produce a therapeutic protein required for the treatment of most of the diseases listed above. For diabetes treatment, the cells secrete insulin in response to changes in the blood glucose concentration in a feedback-controlled manner.

Cells can be encapsulated at a high, tissue like density or dispersed in an extracellular gel matrix, such as agar, alginate, chitosan, or other hydrogels. The immunobarrier ideally prevents access of immune cells and of the larger humoral immune components but permits passage of smaller secreted products such as insulin. There must be sufficient access to oxygen and nutrients such as glucose and removal of secreted metabolic waste products, such as lactic acid, carbon dioxide, hydrogen ions, and nitrogenous products of metabolism. Encapsulated cells must be supplied with oxygen and nutrients by diffusion from the nearest blood supply, through surrounding tissue, the immunobarrier membrane, and the graft tissue itself.

The issue of oxygen supply to encapsulated therapeutic cells is critically important to their viability and function. Because this issue intersects with all areas of design and performance of devices, we begin this review with a brief discussion of major issues related to the performance of immunobarrier devices, especially as they relate to oxygen supply limitations: (1) device design and materials, (2) supply of tissue, (3) protection from immune rejection, and (4) maintenance of cell viability and function. Most of the literature cited in this review deals with immunobarrier devices used in transplanting islets of Langerhans for type 1 diabetes treatment. The concepts and methods described also apply to other cell therapy applications, especially those involving metabolically active cells. After discussing the major issues, we focus on (1) the existence of oxygen limitations in islet transplantation and its deleterious effect on islet viability and function, and (2) a comprehensive discussion of diverse approaches investigated with encapsulated cell therapy in order to overcome these oxygen limitations. We conclude with the author's perspective on what we have learned about oxygen supply limitations and the challenges that remain for the future. The material presented here builds on previous reviews of the field by the author [9–15] and others [16–23] and highlights recently reported work.

2. Issues in encapsulated cell therapies

2.1. Device designs and materials

Therapeutic cells have been encapsulated in intravascular devices and in extravascular implants.

2.1.1. Intravascular devices

Blood flows from artery to vein through the lumen of a tube encased in a chamber. The tube is an immunoisolating membrane, on the outside of which cells or tissues are cultured, thereby maximizing the effectiveness of oxygen, nutrient, waste, and therapeutic protein transport because diffusion distances are relatively short. The presence of blood flow in close proximity to tissue provides a good arrangement for oxygen supply from the bloodstream. On the other hand, this device is an arteriovenous shunt that disrupts the patient's vascular system, thereby leading to a greater risk of complications such as thrombosis.

Work with intravascular devices began more than four decades ago by Dr. William Chick together with a multidisciplinary team, culminating in the first paper that demonstrated normalization of a disease state (hyperglycemia) with a tissue-engineered device containing encapsulated therapeutic cells [24]. In that study, islets were cultured outside of very small diameter hollow fibers through which anticoagulated blood flowed in an ex vivo arrangement. Subsequently, a single large-diameter tube was used to eliminate the need for systemic anticoagulation.

Additional papers using this approach have been described in an earlier review [10]. In one study [25] in which two devices were implanted in each of 10 diabetic dogs, exogenous insulin was completely supplanted in six animals. Even with the favorable oxygen transport conditions arising from blood flow through the tube, each device contained more than 50% of nonviable islets when examined after explantation. In these experiments, islet surface density was about 2670 islets/cm^2 tubular surface area and dose was 19,400 islets/kg body weight, which was nearly four times the 5000 islets/kg required for satisfactory blood glucose control in a canine autotransplant [26]. Because canine islets have an average diameter of 122 μm compared to 150 μm for an islet equivalent (IE, volume 1.77×10^{-6} cm^3), the volume of canine islets is reduced by a factor of 1.86 compared to an IE. When put on the same volumetric basis of a human IE, the surface density and dose were about 1440 IE/cm^2 and 10,400 IE/kg, respectively.

Work on the intravascular approach progressed successfully to the point where more than 360 successful implantations in diabetic dogs had been carried out, and a human clinical trial of a tubular intravascular device for islet transplantation was being planned. The planning was suspended by the FDA because of a mechanical failure of a cannula in one dog. By the time the cannula was redesigned, resources of the small company that championed this approach were depleted, and the work has never been resumed. This type of device is not currently under study. Surprisingly, designs involving blood flow through hollow fibers [27], akin to the original concept [24], and blood flow through narrow channels [28] have been proposed in the past decade without recognition of their clinical impracticality for chronic use because of the need for chronic systemic anticoagulation.

2.1.2. Extravascular implants

Extravascular implants differ in geometrical characteristics and also in the way the effects of oxygen supply limitations are manifested. Diffusion in a spherical geometry is privileged because, at any radial position away from the center of a sphere, the available surface area for diffusion relative to the volume of tissue contained within that radius is the highest; conversely, the surface to volume ratio is the lowest for the slab. In addition, the presence of an external layer, such as fibrotic tissue arising from the foreign body response, through which diffusion must also occur decreases the available driving force for diffusion within the tissue. This decrease has the smallest relative effect for a spherical geometry, whereas the effect is largest for a planner slab. The mass transfer resistance of a layer outside a sphere reaches a maximum asymptotic value as the thickness of the layer increases. Conversely, as the region outside of a slab thickens, its mass transfer resistance grows without bound. For these reasons, the mass transfer effectiveness of each geometry decreases in the order sphere > cylinder > planar slab.

2.1.2.1. Microcapsules. Beginning with the work of Lin and Sun with islets microencapsulated in alginate [29], small spherical hydrogel beads containing usually 1 or 2 islets and ranging in diameter from 200 μm for thin coatings to 1000 μm or more have become the most extensively studied approach for encapsulated islet transplantation to treat diabetes. The larger beads [30–33], sometimes called macrocapsules or macrobeads, have received less attention. The peritoneal cavity is the most common implantation site because there is ample space for the capsules, and, if the capsules are able to float freely, immune responses are less aggressive than at other implantation sites, such as the subcutaneous space where immune cells can more easily attach to the surface. Microcapsules may aggregate and may be located far from the blood supply; under these conditions, the islets have very limited oxygen supply, which further degrades tissue survival. The feasibility of intraportal injection (used for naked human islet transplantation) has been examined to enhance microcapsule proximity to the blood supply, but there is an increased immune response, which requires short-term immunosuppression [34].