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Therapeutic cell encapsulation techniques and applications in diabetes ☆

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ABSTRACT

The encapsulation of therapeutic cells permits the implantation of allogeneic and xenogeneic cells for the regulation of certain physiological processes damaged by the death or senescence of host tissues. The encapsulation of pancreatic cells for the treatment of diabetes is emphasized; however, many of the techniques are applicable to a wide array of mammalian cell applications. The summary of both established and novel encapsulation techniques, clinical trials, and commercial product developments highlights the metered but steady pace of therapeutic cell encapsulation towards implementation.

Contents

1. Introduction

The term 'bioencapsulation' generally refers to the entrapment or containment of living cells within a polymeric matrix or membrane. The purpose of this review is to describe the various bioencapsulation techniques developed to encapsulate and thus immunoisolate pancreatic islets or β-cells toward the engineering of a biomimetic endocrine

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pancreas. This will be approached initially by a discussion of the various tissues and cell lines of interest, current pancreas and islet implants, encapsulation technologies for islet immunoisolation, and the properties of alginate, the most commonly implemented encapsulation material. New and novel encapsulation approaches will also be described.

2. Pancreas anatomy and transplantation

The pancreas is predominantly composed of exocrine cells which produce digestive enzymes and buffers for excretion into the duodenum *via* the pancreatic duct. Only about 1% of the pancreas is occupied by endocrine structures known as islets of Langerhans, which are scattered throughout the pancreas and account for roughly two million cells in the average adult human. Islets are heavily vascularized *via* a capillary network supplied by the pancreaticoduodenal and pancreatic arteries, and drained by the hepatic portal vein, which flows directly into the liver [1].

Islets are composed primarily of five endocrine cell types. α-Cells produce glucagon, which raises blood glucose by increasing the rate of glycogen breakdown and hepatic glucose release. β-Cells produce insulin, which lowers blood glucose by increasing the rate of glucose uptake in most cell types. Composing roughly 85% of the cells within an islet, β-cells are the most prevalent [2]. δ-Cells produce somatostatin, inhibiting production and secretion of both glucagon and insulin while slowing the rate of food absorption and enzyme secretion in the digestive tract. F-cells (pp-cells) produce pancreatic polypeptide, which inhibits gallbladder contractions and regulates the production of some pancreatic enzymes. Finally, ε-cells produce the hormone ghrelin to stimulate hunger [2]. Only α and β-cells are sensitive to blood glucose levels, and are therefore the most prominently discussed and observed cells for the purpose of endocrine pancreas engineering [3].

The insulin precursor proinsulin is synthesized by β-cells, which then cleave it into the 51 amino acid, 5808 Da insulin molecule composed of A and B chains joined by disulphide bonds [4]. The byproduct of insulin production, cleaved C-peptide, is often quantified to measure the rate of insulin production. As C-peptide differs between mammalian species, blood levels can be monitored during *in vivo* studies to determine if insulin is being produced by a xenogenic transplant or by residual host pancreatic tissue [5].

Type I diabetes mellitus is a disease resulting from the destruction of pancreatic islets, most importantly the insulin-producing β-cells. When insulin production is absent or insufficient, the concentration of glucose in the blood accumulates, a condition termed hyperglycemia. Chronic hyperglycemia results in serious medical complications including atherosclerosis, kidney failure, blindness, peripheral nerve damage, stroke, coronary heart disease, limb amputation and depression [6,7]. Obversely, low blood sugar, termed hypoglycemia, is also a serious concern for those with diabetes, as unregulated blood glucose levels are highly labile and can fall to low levels with little warning, resulting in unconsciousness, brain damage, and finally death if unresolved [8].

Currently, Type I diabetes is routinely managed by multiple daily insulin injections, blood sugar monitoring, and carefully controlled diet and exercise. However, these non-continuous monitoring and adjustment schemes simply retard the progression of the disease [9]. In addition, insulin therapy to reduce hyperglycemic spikes decreases the risk of complications but increases the risk of life-threatening hypoglycemic episodes [10].

Type I diabetes only accounts for 10% of patients with diabetes, however it develops much earlier, traditionally during adolescence, resulting in an increased number of chronic complications and a 15 year average reduction in life expectancy [11].

The increasing cost of diabetes treatment and the resulting secondary effects have promoted continued effort and funding to combat diabetes and the detrimental effects of labile blood sugar, in a manner which is more controlled and biomimetic. This review will focus on cell-encapsulation based therapies for Type I diabetes, which are an important subset of the diverse and exciting fields of biological and pharmacological therapies for the treatment of diabetes.

2.1. Whole pancreas transplant

When pharmacological alternatives are insufficient, the most direct approach to replacement of endocrine tissue in Type I diabetes is whole pancreas transplantation. Xenogenic pancreas transplantation in part or as a minced injectable, was used as early as 1894, almost 30 years before the discovery of insulin, for the temporary relief of the symptoms of diabetes mellitus, which at the time was inevitably fatal [12]. Allogenic whole pancreas transplantation was first performed in 1966, and since then over 35,000 transplants have been reported to the International Pancreas Transplant Registry [13]. However, unlike heart, lung, and liver transplants, whole pancreas transplantation is not a life-saving operation, but one to improve quality of life. The long-term advantages of glycemic control must be balanced against the severity of the procedure and the side-effects of life-long immunosuppression which is currently required to prevent alloimmunity and autoimmune reoccurrence [14]. In addition, the number of donors with transplant-quality pancreases is very low [15].

Therefore, whole pancreas transplant can only be justified for a small subset of patients and another approach is needed to improve glycemic control in the majority of the population afflicted with Type-1 diabetes. The first step in the engineering of a cell-based treatment for diabetes is to discard the bulk of the pancreas, the superfluous exocrine tissue, and focus on the endocrine islets of Langerhans.

2.2. Islet transplant

Implantation of whole islets, initially proposed by Lacy and Kostianovsky [16], is preferred over whole-pancreas or purified β-cell transplantation, as islets can be easily isolated, quantified, and implanted, while retaining the complex multicellular interactions of the glucose-modulating endocrine pancreas functional subunit [2]. Dividing islets further into their constituent cells and implanting purified insulin-producing β-cells reduces the body's ability to suppress insulin secretion during a hypoglycemic episode. Islet dissociation also eliminates the cell–cell interactions found within the aggregated islet state required for glucose responsiveness and the up-regulation of insulin secretion [17].

Islet implantation sites are typically located such that secreted insulin enters portal venous circulation, either through the hepatic portal vein or through venous drainage of the peritoneal cavity. Hepatic drainage then replicates natural hormone delivery from the pancreas to the hepatic portal vein *via* the pancreatic, pancreaticoduodenal and splenic veins [1]. It is noteworthy that when islets are transplanted into the liver, the insulin is drained into the sus-hepatic circulation and reaches the hepatic cells only through the general circulation.

2.3. Islet isolation

Human islet isolation for transplantation, made famous by the Edmonton Protocol [18] requires the proper collection, digestion, and purification of the pancreas. Freshly procured pancreases are held in chilled organ transplant solution such as ViaSpan®. The pancreatic duct is then infused with chilled protease solution, generally a mixture of collagenases and thermolysin such as Liberase [19], to digest the pancreatic extracellular matrix (ECM). Islets are then separated from the ECM by gentle mechanical dissociation and purified *via* a density gradient of Ficoll–diatrizoic acid in an apheresis system. In place of xenoprotein products, the isolation and purification media for the Edmonton Protocol contains 25% human albumin [18]. In 46% of clinical applications, islets are used without pretreatment, and in the remaining 54% of cases, islets are cultured for 27 h on average, allowing the islet