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Perspective

The Bioartificial Pancreas – How should We Address the Issue of Oxygen Delivery?

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INTRODUCTION

Diabetes mellitus represents a growing burden both on health-care expenditures and the quality of life of the afflicted individuals. Current estimates for the prevalence of diabetes indicate a global prevalence of about 285 million people [1]. Type 1 diabetes is a significant cause of morbidity and mortality in young adults. Secondary diabetic complications include a quadrupled risk of heart attack and stroke and a significant decrease in life expectancy. The economic impact of diabetes is tremendous across the world, with a projected impact of over $200 billion in direct annual costs in North America in 2010 and an estimated 25% of U.S Medicare annual in-patient care expenditures being attributed to the treatment of diabetes and its associated complications [2].

The current standard treatment for Type 1 diabetes is daily injections of exogenous insulin to control blood sugar. An alternative treatment modality for Type 1 diabetes is the replacement of the missing β-cells through transplantation of whole pancreas, which in contrast to insulin administration, is capable of achieving normoglycemia along with the prevention and even reversal of certain secondary diabetic complications, such as nephropathy and atherosclerosis [3]. The advantageous effects of β-cell replacement therapy on diabetic complications compared to insulin treatment may be attributed to the role played by the byproduct of pro-insulin cleavage, named C-peptide, during insulin processing in the β-cell [4-7]. However, the benefits of the β-cell replacement may be masked by collateral risks associated with the use of immunosuppressive drugs to prevent transplant rejection in transplant recipients [3].

While whole pancreas transplantations have been performed, it is a complex surgical procedure that is fraught with significant morbidities and challenging technical issues including the drainage of exocrine secretions from the transplanted pancreas [3]. Successful islet transplantation in diabetic patients remained elusive [8] until the introduction of the glucocorticoid-free immunosuppressive regimen by the Edmonton group, and this protocol has successfully led to insulin independence in a limited number of diabetic patients transplanted with isolated human islets [9,10]. In a few cases, insulin independence has been achieved for several years [11,12], thus showing islet transplantation to be a viable therapeutic option for patients with Type1 diabetes. Still, the need to use immunosuppressive drugs to prevent graft rejection and the severe shortage of human islets remain two major barriers to clinical islet transplantation [12-16].

An attractive strategy to overcome these two obstacles to routine use of islet transplantation is the technique of immunoisolation by microencapsulation of islets prior to transplantation, as it could potentially solve the problem of islet shortage by opening up the possibility of using islets from non-human sources while obviating the need for longterm immunosuppression of transplant recipients [13,16-24]. However, there are a number of issues that need to be resolved before microencapsulated islet transplantation can become a clinical reality. A major obstacle of this approach is the death of large proportions of the encapsulated islet grafts owing to severe hypoxia, resulting in the need for large quantities of islets to achieve normoglycemia in experimental diabetic animals.

Why is Oxygen So Important?

Although islets constitute approximately 1% of the pancreas, they receive about 6-10% of the blood flow to this gland [25,26], indicating a disproportionate level of perfusion in which islets receive and consume oxygen. The unusually high oxygen requirement of islets is interrupted during the process of islet isolation and processing for transplantation, and studies have shown that hypoxia has significant deleterious effects on the survival and function of islets [27-29]. In the immediate post-transplant period, isolated islet transplants are forced to depend upon diffusion of oxygen and nutrients through peripheral perfusion from the surrounding tissue within the site of transplantation [30], until the islet transplants are revascularized by angiogenesis, a process that requires 7 – 10 days [28]. As a result most studies with encapsulated islets have used extraordinarily high doses of these cells to achieve variable effects on blood glucose levels in large animals and human subjects [20,31-35]. Using more cells and hoping enough survive is an inefficient and counterproductive approach because more cells mean more oxygen demand for a limited supply. This may inadvertantly select for islets with the lowest metabolism in the struggle for surival possibly leading to a less effective therapy.

To achieve the goal of maintaining normal blood glucose levels through islet transplantation, a key factor for producing high quality of islets is the prevention of oxidative stress during islet preparation [36,37] and a sufficient oxygen supply during the immediate post-transplant period [30]. How do we get oxygen to islets and how do we overcome the challenges associated with its delivery?

Significant cell death can occur during the process of isolating islets. One should consider the oxygen tensions during the islet isolation process. Culture and transport of islets could be performed in gas-permeable devices such as silicone rubbers or hollow fibers bioreactors [38]. A factor to consider in using these processes would be the need to avoid aggregation or accumulation of islets to ensure optimal oxygenation of the cells.

Once implantation occurs, oxygen delivery becomes an even more significant requirement during the time window between implantation and establishment of the support vascularity. In general, while there are mechanical means to deliver oxygen (e.g. perfusion pumps with oxygen carrier solutions), one must also consider that after implantation having to perform any second procedures to remove an oxygen-delivery system would be highly undesirable. There is therefore a crucial need for a more elegant solution for oxygen delivery in the immediate post-transplantation period. One approach could involve incorporation of oxygen delivery systems into the microencapsulation process that would be exhausted in due time without adverse events in the body.

Having the ability to co-encapsulate islets with a source of oxygen rich materials may fulfill this goal. Investigators have microencapsulated islets in barium-alginate with perfluorocarbon (PFC) emulsion. After low oxygen culture for 2 days, islets in control alginate capsules without PFC lost substantial viable tissue and displayed necrotic cores, whereas most of the original oxygen consumption rate was recovered with the oxygen-supplying PFC in the microcapsules [39]. The PFC can carry, through adsorption, oxygen at much greater concerntrations than water. However, other investigators have noted that reformulation of the PFC emulsion is required to reduce toxicity to the islets, and it has also been shown that PFC emulsions may have little or no benefit to encapsulated β-cells in culture [40].

An alternative to perfluorocarbons that involves taking advantage of chemical reactions which allows for greater densities of oxygen to be stored and delivered subsequently may work. Co-encapsulation of islets with micro- or nano- particulate oxygen generators that can chemically generate oxygen to help bridge to revascularization seems to be a particularly attractive option [41]. Solid peroxides, such as sodium percarbonate or calcium peroxide, can potentially deliver 100 times the amount of oxygen that can be stored in an equivalent amount of water. Of course, too much of a good thing can be detrimental and so the oxygen delivery systems need to be designed to provide oxygen at a therapeutic dosage. Yet such an approach should be practical as our own bodies have developed strategies to keep oxygen and reactive oxygen species under control.

SUMMARY AND CONCLUSION

With the impact of diabetes mellitus continuing to grow, there is an urgent need for creating effective strategies to treat this disease. For those patients who could most benefit from islet transplantation, developing approaches which enhance islet cell survival during the periods of isolation, encapsulation, and implantation, as well as during the period of integration to systemic circulation is critical. Optimal oxygen delivery during these processes is critically important. From the brief review above there are several potential approaches which may provide the needed boost to enhance the delivery of oxygenin the development of the bioartificial pancreas. Further development and evaluation of the efficacy of these approaches are needed for successful use of the bioartificial pancreas in diabetic animals and humans.

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