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Xenotransplantation: A Revolutionary Option for Diabetes Treatment

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ABSTRACT

Type 1diabetes is a disease that typically occurs in childhood and adolescence and it is caused by the destruction of beta cells in the islets of pancreas resulting in insulin deficiency. Finally, it leads to high glucose levels in the blood. Insulin therapy is easier to maintain the desire blood sugar levels but it has multiple problems. Xenotransplantation has crossed the boundaries of transplanting organs and tissues to another species. Islet transplantation offers an attractive alternative treatment for type 1 diabetes. In this method host beta cells that have been destroyed are replaced by new beta cells in the islets. Transplanted beta cells are able to change in blood glucose levels. Pig is the most likely source of animal organs and cells for transplantation into humans. But this method has not abolished all complications. Hosts are facing mainly two problems one is refusal of the organ and cells, and another is the possibility of launching novel infections into the hosts. For successful implication of this method above problems must be overcome.

Key Words: *Xenotransplantation, Type 1diabetes, Pig.*

INTRODUCTION

The number of organ transplantations has increased slowly due to the shortage of suitable human organs. This is resulting from an increased demand and an inadequate supply. Xenotransplantation could be a solution to overcome this problem. Xenotransplantation means transplant organs from other animal species into humans. Additional benefit of Xenotransplantation is organs would be obtained from healthy animals [1]. Type 1 Diabetes (T1D) affects around 28 million patients worldwide with an increasing incidence and insulin therapy has made Diabetes treatment easier. Insulin therapy has only been able to maintain their

desired blood glucose level but don't reduce the other complexities such as retinopathy, nephropathy and cardiovascular diseases. These severe complexities reduce the life span of the patients with diabetes than non-diabetic persons [2]. The transplantation of pancreatic islets from animals could be a treatment of diabetes mellitus. Patients with type 1 diabetes, whose bodies are unable to make insulin, will be a possible treatment to transplant islets of Langerhans from pigs into patients. These purposes could be achieved by transplanting an entire pancreas [3].

PHYSIOLOGY OF HUMAN ORGANS FOR XENOTRANSPLANTATION

Following physiological factors should be considered for Xenotransplantation.

Size: Differences in organ size is one of the most crucial factors for xenotransplantation. Differences of organ size limit the range of potential recipients of xenotransplants.

Hormone and protein differences: Some proteins could disturb the important regulatory processes. These proteins specially affect the hepatic xenotransplantation. Because liver one of the organ for production of so many proteins [4].

Environment: pig hearts are different than human hearts. Working sites and pressure for Pig heart are different than humans [5].

Temperature: Body temperature favors the activity of important human enzymes. But the body temperature of pigs is greater than human body temperature (2 °C above the average human body temperature). So this difference should be considered for going xenotransplantation [6].

DIABETES

The transplantation of pancreatic islets from animals could be a treatment of diabetes mellitus. Patients with type 1 diabetes, whose bodies are unable to make insulin, will be a possible treatment to transplant islets of Langerhans from pigs into patients. These purposes could be achieved by transplanting an entire pancreas [7]. Type 1 diabetes is a serious chronic disease in which there are high levels of sugar in the blood. Daily injection of insulin is the only treatment for many diabetic patients, but this treatment is not covering the prevention of all complications in the majority of diabetics [8].

For diabetes treatment:

Type 1 diabetes is a common and major health problem throughout the world. Cardiovascular disease, neuropathy, retinopathy and nephropathy are common complications even though administering insulin [9].

The possible potential sites for Islet infusion:

The possible potential sites for Islet infusion are liver, spleen, kidney capsule, testes, brain, peritoneal cavity, and omentum. The liver is most commonly used site because of the early successes with autologous and allografts islet transplants (autologous islets are infused intraoperatively directly into the hepatic portal venous circulation under direct view, islet allografts are infused percutaneously into the portal vein). Bleeding, portal venous thrombosis, and portal hypertension are the potential complications of an infusion into the liver. It is crucial to monitor the portal blood pressure during the procedure. Anticoagulants are used to

prevent clotting as well as promote hepatic bleeding at the sites of the percutaneous needle punctures [10]. To avoid above problems, it is possible to infuse unpurified islet preparations into non-hepatic sites. The benefits of these sites would eliminate the trauma to and losses of islets caused by purification. Peritoneal cavity and omentum, both have been used successfully in animal models and shown to be safe for humans [11, 12].

Appropriate life period for Isolation of pig islets:

There has been great confusion about the appropriate life period of pig islets, whether fetal, neonatal or adult should be used for Xenotransplantation. Reduced *in vitro* and *in vivo* activity has been shown by young adult pigs aged less than two years old due to fragmentation of islets during isolation because of smaller size compared to pigs older than two years [13]. Pigs aged greater than two years, specially retired breeder sows have showed significant promises in case of clinical transplantation. The ideal time limit for *ex vivo* culture of adult pig islets should be between 16 to 48 hours [14,15].

Derivation of Pig Islets from different age groups:

Islets derived from neonatal pigs are preferred for various reasons, for example their ability to resist hypoxia [16]. It is generally more favorable to rescue the pancreas during the early first week of life [17,18] than to maintain the pigs for around two years in a controlled environment, which requires high space, time and cost maintenance. The success of operation may depend pn the storage condition specially cryopreservation of neonatal islets. The neonatal islet cells should be cultured for minimum seven days for proliferation after isolation from donor, which is required mostly after transplantation [18]. Studies prove that, fetal pancreatic cell excised at around 42 days of life can result in successful transplantation into NHPs [18] , though they need up to 5 months to become completely active which requires patients to continue insulin and immunosuppressive therapy. Additionally to produce normoglycemia in one single adult Human,it is necessary to excise minimum 60 fetal pig pancreas(extrapolated from NHP recipients studies [19]. The exact number of islets to cure diabetes in human is unknown, but with the numbers of pig islet equivalents (IEQ)/kg, which is around 10 to 15 thousand IEQ/kg in NHP and also with the yield of 40 thousand IEQ per adult pig [13], a number of adult pigs to provide islets may be required to cure a single patient. Nonetheless, neonatal islets may still proliferate even after transplantation, which creates the scope to excise smaller number of islets still proving a active islet mass [18]. A newer technology which uses pig islets encapsulated in Alginate (30 thousand IEQ/kg) loaded in to a macrodevice and placed subcutaneously reversed diabetes in NHPs [20]. The approach shows great promise, as it does not require immunosuppressive therapy for survival. Although number of problems need to be solved to increase its' potential to cure diabetes. They are- i) Degeneration of Alginate capsule with time, ii)Lowered life span of islets inside the capsule due to constricted nutrients, iii) Generation of anti-pig antibodies and lastly iv) Humoral rejection.

Inflammatory reactions after Xenotransplation:

The first problem faced by islets are initiated after transplantation into portal vein is instant blood mediated inflammatory reaction (IBMIR), which results in potential eradication of islets within very short period of time. Transplanted islets can generate tissue factor, which start up the coagulation process. For that reason, the islets are filled with neutrophils and macrophages due to the activation of platelets and cytokine complements [21]. The greater level of tissue factor expression by islets lower the success rate of Xenotransplantation respectively [22]. Islet damage can be prevented in vitro by inhibition of tissue factor expression [23, 24], although in case of *in vivo* transplantation, IBMIR can't be blocked completely by anticoagulation [21].

DISCUSSION

Xenotransplantation can be regarded as an essential element for diabetes treatment. Although there is presence of scientific challenges and controversy over the acceptance of xenotransplantation, work continues to solve the cases. One attempt, which has gained new exposure, is conducted by *ex vivo* intromission through animal livers [25]. The fruitful results of this special effort finalized the future exploration of it. In opposition to transplation of whole organs attempts also been directed at xenografting cells in suitable situations. For example, efforts have been made by doctors to insert fetal pig islet cells into human diabetic patients. One attempt by Swedish investigators came out to be successful in the endurance of the pig cells in notably one patient and also the generation of porcine C-peptide [26]. Moreover, a serious problem for the successful use of xenotransplantation is persistence of the xenografts. Though porcine organs have achieved growing significance in this application, there is scarce knowledge about their survival and also their primate keeper over the first month after implantation. The main improvement approach for the better future of xenotransplantation technology is to overcome the fight against xenografts rejection. One Intriguing way is to use of gene therapy using retrovirus to stop the production of Xenosensitive antibodies to inhibit the hyperacute and delayed types of rejection.An interseting study reveals that the production of this antibody can be stopped by developing animal model containing genetically modified bone marrow, which produces an enzyme that supplies an epitope, called α Gal Epitope.The genetically modified animal becomes unresponsive to xenograft rejection because of the production of this specific epitope. One futuristic approach to overcome the difficulty of short longevity of hosts can be the use of specific cells in place of whole organ for veroius severe diseases. One current study proves the success of using immortalized human liver cells in experimantally induced acute liver failure rats [27], which approach is worth trying in later time. Developing encapsulation technology can supplement these approaches, where as using carriers like agarose/polystyrene sulfonic constucts and such will widen the spectrum of cell used for these purposes. Another approach which has been tried by researchers is to develop genetically modified Pig donors with absence of potential epitope responsible for xenograft rejection. To achieve success, the pursuit is directed to develop animals with genetically engineered bone marrow,which renders them tolerant by providing underexpression or complete absence of such antigens [28]. More advanced innovations for example using gene therapy to modify xenotrantasplant organs are being developed ,which would provide better immunity, competency and as a result endurance of the organs and their hosts, thus providing better achievement for the xenograft technology [29].

CONCLUSION

Xenotransplantation has recently received attention as a result of promising clinical efforts. It can reduce the burden on both the patient and the healthcare system. Xenotransplantation treatment has the potential for sustained benefit in human type 1 diabetics by avoiding other infections.

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