Islet Transplantation

Subjects: Others

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Islet transplantation is considered as a promising and reliable cellular replacement therapy for severe diabetes mellitus patients with unstable condition of blood glucose level despite intensive insulin therapy, especially for insulin-dependent type 1 diabetes mellitus patients. The therapeutic outcomes of islet transplantation have gradually, but dramatically, improved through innovations in technology regarding islet isolation, transplantation procedures, and immunosuppressants [1].

Keywords: Islet Transplantation ; Diabetes Mellitus ; Transplant Site

1. Introduction

The most recent report from the Collaborative Islet Transplant Registry indicated that the insulin-independence (no necessity to use daily insulin injections) rate at 3 years after islet transplantation was 44% [2], and that approximately 80% of the recipients who received 600,000 or more total islet equivalents (IEQs) achieved insulin independence [3]. Furthermore, a phase III study for elucidating the therapeutic effects of clinical islet transplantation in type 1 diabetes mellitus (CIT-07) performed at eight centers in the United States until 2017 revealed that 87.5% and 71% of the diabetic participants achieved a hemoglobin A1c (HbA1c) level of less than 7.0% and prevention of severe hypoglycemic events at 1 and 2 years after the first islet transplantation, respectively [4]. Although islet transplantation is recognized as a useful therapy that enables an appropriate physiological supply of insulin responding to the changes of blood glucose levels and prevents severe hypoglycemia and life-threatening complications related to micro- and macroangiopathy, including cardiomyopathy, nephropathy, retinopathy, and neuropathy, it still involves some problems that compromise the therapeutic effects.

2. Data

One of the problems surgeons face is the unsatisfactory transplant efficacy, which depends on the difficulty in engraftment of transplanted islets. Many transplanted islets fail to engraft in a couple days after transplantation [5] because they suffer from harsh environmental factors of immunity [6], inflammation triggered by the innate immune system [7], and ischemia [5], which are affected by the transplant site. For instance, the liver is a major clinical transplant site for islets. However, the liver is not the best site in terms of immunity (owing to liver-resident macrophage (Kupffer cells) and natural killer cells [8][9][10]), inflammation (instant blood-mediated inflammatory reaction [IBMIR], an acute thrombotic and inflammatory reaction that causes damage to transplanted islets [11]), and hypoxia (owing to embolization of the peripheral portal vein by the transplanted islets themselves [5][12]). To date, various organs, including the renal subcapsular space [13], gastrointestinal tract [14], bone marrow [15], spleen [6][16], and muscle and subcutaneous tissue [17], have been examined to assess their characteristics as alternative sites for islets in an effort to establish the ideal transplant site (Table 1). Though they offer various attractive advantages, all of these sites have also limitations, which become obstacles for use in the clinical setting [6][17][18].

Table 1. Candidates for transplant site for islets and their characteristics.

	Advantages	Disadvantages
Liver	• ✓ Representative transplant site for clinical islet transplantation • ✓ Largest abdominal organ, which enables the storage of a high volume of islets • ✓ Physiological insulin delivery • ✓ Comparatively little invasion in the transplant procedure	• ✓ Immunity • ✓ IBMIR • ✓ Difficulty in monitoring • ✓ Risk of portal thrombosis and hypertension
Kidney	• ✓ Preventing direct contact of blood flow (diminishing the risk of IBMIR) • ✓ Best transplant efficacy in small animal studies	• ✓ Difficulty of transplant procedure in clinical • ✓ Systemic insulin delivery
Spleen	• ✓ Rich vascularity • ✓ Physiological insulin delivery • ✓ Regulation of immunity • ✓ Islet regeneration	• ✓ Risk of IBMIR • ✓ Risk of bleeding following transplant procedure
Muscle/ subcutaneous tissue	• ✓ Minimized invasion • ✓ Safety • ✓ Preventing risk of IBMIR	• ✓ Hypoxia • ✓ Hypovascularity • ✓ Immunity
Omentum (white adipose tissue)	• ✓ Physiological insulin delivery • ✓ Capacity to involve a large number of islets (omental pouch)	• ✓ Possibility of surgical complications, including adhesion ileus
Mesentery (white adipose tissue)	• ✓ Physiological insulin delivery	• ✓ Necessity for bowel resection in the case of graft removal

IBMIR, instant blood-mediated inflammatory reaction.

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