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Review

The anterior chamber of the eye as a site for pancreatic islet transplantation

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ABSTRACT

The most viable therapy for curing type 1 diabetes mellitus is pancreatic islet transplantation. However, they are unavoidable in terms of immunogenicity, which is differently affected by transplantation site. Therefore, it is necessary to determine alternate sites to permit successful islet transplantation outcomes. This paper reviews evidence that the anterior chamber of the eye (ACE) could be a good site for islet transplantation when compared to other alternate sites. In addition, this site may be a promising technical platform for noninvasive *in vivo* imaging of transplanted pancreatic islets.

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Introduction

The collaborative islet transplant registry (CITR) reported that clinical islet transplantations are most commonly performed by infusion *via* the portal vein and there have been many improvements in the outcomes of clinical pancreatic islet transplantation

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[1]. Although the liver has been well studied and optimized as a transplantation site, it is not the best site for islet transplantation because the cells are immediately damaged by an instant blood-mediated inflammatory reaction (IBMIR) due to their direct exposure to the bloodstream [2]. Therefore, islet-transplant patients still require insulin protein therapy. In addition, the liver as a transplantation site carries risks for inflammation-related complications, including bleeding and thrombosis. In order to avoid IBMIR, an anticoagulation strategy such as coating the surface of islets with the anti-coagulant heparin is often used [3]. Moreover, it is necessary for recipients to take immunosuppressive drugs after islet transplantation. However, immunosuppressive drugs induce many side effects including glucose intolerance, oral ulcers, renal dysfunction, anemia, diarrhea, fatigue, low-density lipoprotein elevation, hypertension, peripheral edema and weight loss [4]. The long-term administration of expensive immunosuppressive drugs is also a financial burden to patients. Therefore, many experiments have been carried out to identify an immune privileged site for ideal islet transplantation. The most important factor in islet transplantation is revascularization and reinnervation at the transplantation site because these are critical for maintaining islet functionality and survival [5]. This article reviews various immune privileged sites for islet transplantation and is focused on the anterior chamber of the eye (ACE) as an optimal site with respect to revascularization and reinnervation. In addition, we further discuss the additional advantages of the ACE site, such as intravital imaging of islets and noninvasive imaging.

Pancreatic islet transplantation sites for curing diabetes mellitus

Pancreatic islets have been clinically transplanted into the liver through the portal vein. Here, we compared the liver site with other immune privileged sites in terms of certain characteristics for successful islet transplantation outcomes (Table 1).

Portal vein

Pancreatic islet cell transplantation into the liver is a promising cellular therapy for curing type 1 diabetes mellitus. This surgical remedy accounts for 90% of all clinical islet transplant cases. The liver is most commonly used because it is a major site for insulin hormone activity; transplanted islets can quickly secrete insulin *via* direct exposure to the bloodstream and the secreted insulin can rapidly bind to blood glucose to form an insulin–glucose complex that is delivered to hepatocytes for storage as glycogen macromolecules. Therefore, transplanted islets in the liver can quickly and tightly control blood glucose levels in diabetic patients [25]. Unfortunately, 80% of diabetic patients receiving pancreatic islets again require insulin therapy after a limited period due to problems such as surgical complexity and immunological response. From a surgical standpoint, pancreatic islets should be ideally transplanted at a simple operation site for attenuating the physical stress to patients. However, intraportal islet transplantation carries operation-related risks such as hemorrhage, thrombosis, biliary puncture, discomfort, transient rise in serum aminotransferase and arterial–venous fistula [26]. From an immunological standpoint, transplanted islets should not come into contact with the blood. In general, when foreign materials circulate in the bloodstream, platelets in the bloodstream quickly bind to the surface of the implant material to eliminate it from the body. In the case of pancreatic islet transplantation, platelets bind to intraportally infused islets, thereby initiating an instant blood mediated-inflammatory reaction (IBMIR). This IBMIR was first identified through an *in vivo* mimicking system using a heparin-coated polyvinyl chloride (PVC) tube filled with non-anticoagulated ABO-compatible human blood. Thrombotic/inflammatory responses began soon after islets were exposed to human blood in the tube [27]. In other words, IBMIR is a series of destructive early inflammatory reactions that occur between blood and transplanted islets. IBMIR is characterized by platelet development,

Table 1
Immune privileged site comparisons to the clinical site for islet transplantation.

Site	Organ	Quantity of islets required		Characteristics
Clinical site	Liver (portal vein)	Mouse	300 [6]	• Site used for 90% of clinical islet transplantation cases
		Rat	3000 [8]	• Transplanted islets are immediately damaged by IBMIR
		Human	7271 IEQ/kg [9]	• 80% of recipients require additional injections of insulin after 1 year
			11,000 IEQ/kg [10]	• There are many studies on methods to improve therapeutic effects such as encapsulation [7]
Immune privileged sites	Thymus	Mouse	200 [11]	• Site for maturation of T cells or lymphocytes and negative selection
		Rat	600–800 [12]	• Deletion of islet-allograft-specific T cells takes place in the thymus
			2000 [13]	• Various immunological benefits
		Canine	6000 IEQ/kg (50% success) [14]	• A large number of islets are required to maintain normoglycemia
	Brain	Rat	1500 PECs [15]	• Insulin secreted from transplanted islets can cross the BBB
			100 [16]	• Hormones secreted from the transplanted islets play a key role in brain function
			3000 [17]	• Surgical risks
	Testis/Sertoli cells	Mouse	400 [18]	• Sertoli cells play a role in making the testis immune-privileged
		Rat	2000–2500 (10/g) [19]	• Sertoli cells have been studied in a co-transplant model in the kidney capsule
			1900–2600 (13/g) [20]	
	Eyes (the anterior chamber of the eye)	Mouse	10–20 [21]	• Marginal quantity of islets are required for normoglycemia
			30–300 [22]	• Rapid cell revascularization and reinnervation
			125 [23]	• Blood glucose levels are maintained before the eyes are removed
		Baboon	200,000 [24]	• Transplants can be imaged by noninvasive and intravital methods
				• Imaging methods allow investigation of the shape and function of transplanted islets

PECs, single pancreatic endocrine cells; IBMIR, instant blood-mediated inflammatory reaction; BBB, blood–brain barrier.

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