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CURRENT STATUS OF PANCREATIC ISLET TRANSPLANTATION IN MURINE EXPERIMENTAL MODELS. LITERATURE REVIEW.

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Abstract: **Background**: Global estimates show that by 2,035 we will have about 592 million diabetic patients, with a major impact on low- and middle-income countries. Pancreas and pancreatic islet transplantation are currently the only available therapeutic alternatives capable of restoring the physiological pattern of insulin secretion in diabetic patients. However, because the rate of pancreas transplantation is still very low in the country, a more comprehensive criterion for donor acceptance has been proposed. The therapeutic procedure for transplantation of pancreatic islet is approved in Canada and it is in the approval phase in the United States and in experimental phase in Brazil. Despite the fact that the procedure is minimally invasive, consisting of islet infusion into the hepatic parenchyma by ultrasound-guided transcutaneous catheterization, it was observed that both the function and the survival of the islet deteriorate with time, due to factors related to the revascularization of the grafts. In addition, long-term follow-up allowed the identification of late side effects, such as the development of foci of hepatic steatosis. **Aims:** To investigate the state of knowledge of pancreatic islet transplantation in murine experimental models. **Materials and Methods:** A critical analysis of PubMed®- indexed publications from 2000 to May 2019 was performed, associating the following descriptors: "pancreatic islet transplantation", "proliferation", "beta-cell". **Results**: Of the total of 225 publications, 23 publications were obtained, whose summary or complete access was validated by correlation with the theme. Full articles have been reviewed and references were used to identify other sources of information. **Conclusion:** The state of the art in transplantation of pancreatic islets, in murine experimental models and their translational use, still present pending questions. Researchers advocate the need for well-designed, and statistically significant prospective studies aimed at solving basic and fundamental issues such as immune tolerance. However, it is believed that in the near future, cell replacement therapy will benefit a greater number of diabetic patients.
Keywords: Diabetes Mellitus; Pancreatic Islet Transplantation; Translational Medical research; Rodents

1. INTRODUCTION

The modern history of pancreatic islet transplantation began in 1972, when Lacey was

able, for the first time, to reverse chemical diabetes in rodents. However, only in 1990, Scharp et al. reported having obtained insulin-independence in a patient with Diabetes Mellitus Type I (DMT1) for a period of one month [1]. In a landmark study published in 2000, Shapiro et al. [2]. reported that seven patients treated with islet transplants under the Edmonton protocol (University of Alberta, Canada) maintained insulin independence for 1 year.

Data from the Brazilian Registry of Transplantation (BRT) in 2018, indicate that the rate of pancreas transplantation in the country is still low, 0,7 pmp (numbers per million population). About 70% of these transplants are simultaneous with the renal, 24% after renal transplantation and 6% of the isolated pancreas transplantation [3].

In order to obtain a greater increase in the number of pancreatic donors in Brazil, a more comprehensive criterion for accepting donors was proposed.

Thus, the current acceptance criterion is not restricted only to laboratory values, age, weight and clinical condition of the donor, but mainly to a macroscopic evaluation during the withdrawal of the deceased donor's pancreas [4].

Pancreatic islet transplantation (group of insulin-producing β cells) is considered a non-surgical cell therapy and allows the metabolic control to be obtained without the need for exogenous insulin in approximately 70% of cases, when sufficient numbers of islets can recover from the pancreas. The pancreatic islets represent only 1% to 2% of the cellular mass of the pancreas, the rest of the organ being non-endocrine tissue [5].

The current procedure, considered minimally invasive, consists of the isolation, purification and quantification of pancreatic islets and its infusion into the hepatic parenchyma by transcutaneous catheterization guided by ultrasonography.

However, it has been observed that both the function and the survival of the islets deteriorate with time, due to factors related to the revascularization of the grafts.

Long-term follow-up allowed the identification of late side effects, such as the development of foci of hepatic steatosis, probably due to the environment of hyperinsulinism around the sites where the islets were implanted [6, 7].

In this scenario, other sites have been proposed, such as bone marrow or striated muscle, which have the potential to reveal themselves as alternative sites.

In 2010, Christoffersson et al. reported that allogeneic transplantation of islets in muscle tissue promoted better glycemic control results when compared to the conventional intrahepatic method. The results may be associated with greater viability of the grafts [8]. The angiogenesis is induced during a variety of pathologies, but under physiological conditions it occurs only in the ovaries (during the ovarian cycle), in the placenta (during placental development) and in the muscles (during exercise-stretching mechanical and increased vessel wall tension during exercise may promote increased capillarity due to elevation of vascular endothelial growth factor (VEGF), factor-induced hypoxia-1β and matrix-2 metalloproteinase at the implant sites) [9].

Although the literature reports that only a small proportion of patients remain insulin-free after five years of follow-up, the procedure may represent the frontier in technological innovation for the treatment of a specific group of patients with DMT1.

Currently, islet transplantation is a therapeutic procedure approved in Canada, undergoing approval in the United States and experimental in other countries, including Brazil [10].

When in 1980 Lim & Sun [11] first showed that intraperitoneal grafts of allogeneic pancreatic islets from rats containing alginate-poly-lysine microcapsules reversed hyperglycemia in non-immunosuppressed diabetic rats, a new era in diabetes cell therapy had begun, however still outstanding issues remain over microencapsulation.

The finding of Ricordi et al., in 1989 [12], enabled an automated method in the isolation of human pancreatic islets stimulating a large number of subsequent researches on islet transplantation.

Hirabaru et al. (2015) [13] reported a method of islet transplantation using islet cells and islet cell membranes (MSCs) that overcame the issue of low vascularization at subcutaneous sites and managed to reverse DM in a murine model.

However, the laboratory development of differentiated stem cells, better techniques for induction of immune tolerance and immunoisolation may still in the near future make cell replacement therapy applicable to a larger number of patients [8].

Considering that pancreatic and pancreatic islet transplantations are currently the only available therapeutic alternatives capable of recovering the physiological pattern of insulin secretion in diabetic patients [14], the study aims to investigate the state of knowledge regarding the transplantation of pancreatic islets in experimental models. In addition, the study can help in the improvement and development of new hypotheses, concepts and paradigms.

2. MATERIALS AND METHODS

A critical analysis of publications indexed in the PubMed® database was performed from January 2000 to May 2019, was perfomed associating the following descriptors: "pancreatic islet transplantation", "proliferation", "beta-cell ".

3. RESULTS

From the total of 225 publications, 23 publications were obtained, who's summary, or complete access, was validated by correlation with the theme. Full articles have been reviewed and references have been used to identify other sources of information.

4. DISCUSSION

To date, islet transplantation is the only safe cell replacement therapy capable of reversing Type I Diabetes Mellitus (DMT1) [11]. A prospective, cross-over and cohort study indicated a decreased progression of microvascular complications, including nephropathy, retinopathy, and polyneuropathy, compared with intensive medical therapy [15]. However, this clinical application is impaired by the low efficacy of β-cell replacement and absence of adequate donors [3].

As a result of deficiency or functional impairment of pancreatic insulin-producing β cells, alone or in combination with insulin resistance, the replacement or regeneration of these cells could reverse the progression of diabetes. A priori, this seems to be the case in humans and rodents. The use of stem cells to transdifferentiate (direct transformation of an adult cell phenotype into a second adult cell phenotype), reprogram non-β-cells into β-cells or discover of molecules or compounds that induce the proliferation of human β-cells has been investigated by several laboratories showing promise, but difficult to implement [16].

In spite of the fact that several murine models (Figure 1) have helped to understand the processes of islet and β-cell development in function, differentiation, survival and stress responses [17], it is necessary to consider differences between nutritional and metabolic needs, functions of β-cells and patterns of gene expression.

The insulin gene, located on the short arm of chromosome 11, region 11p15, consists of two codon exons separated by a single intron [18]. Rodents have two insulin genes (INS1 and INS2), while humans have only one insulin gene (INS). Another striking difference is related to the fact that cellular membranes are not permeable to glucose, forcing the presence of transporter proteins. In rodents, the main glucose transporter in their β-cells is GLUT-2, while in humans GLUT-1 is the predominant form. [19]. In addition, the MAfB transcription factor absent in rodent β cells is present in adult human β cells, being this transcriptional factor involved in the control of several developmental processes, differentiation and tumorigenesis [20].

Characters	Name	Species
Type I DM		
Spontaneous models	NOD	Mouse
	BB	Rat
Type II DM		
	ob / ob	Mouse
	db / db	Mouse
Obesity model	*fa / fa*	Rat
	Goto Kakizaki	Rat
	OLETF	Rat
Type I and II DM		
Drug-induced model	Alloxan	*
	STZ	*
Pancreatic DM		
Pancreatectomized model	Pancreatectomy	**
Others		
Transgenic animal model	Insulin Knockout	Rat
	IRS 1 Knockout	Rat
	IRS 2 Knockout	Rat

*All experimental animals are available.
**All experimental animals are available but larger animals tend to be used.

Fig.1 Animal models of DM. Source: Sakata et al. (2012) [22].

A controversial issue concerns the architecture of pancreatic islets. About 80% of β-cells in rodents are located in the nucleus of the islets, whereas in *anima nobile*, they represent only about 50% of the islet cells with diffuse location [21].

A relevant aspect is that most of the regenerative β-cell research has been performed on juvenile rodents between 2 and 3 months of age. In contrast, human β cells available are almost exclusively from individuals aged 40 to 50 years, leading us to conclude that the age factor decreases the regenerative capacity of the pancreas in rodents, just as the adult human endocrine pancreas loses its regeneration potential over the years [16].

Regardless of the differences, the vast majority of cell proliferation inducers (whether through animal interventions, use of growth factors or small molecules) have not significantly increased human β-cell proliferation [23].

Diabetes research funding organizations and the scientific community of β-cells themselves have reiterated the need to address basic issues such as the difference in replicative potential of β-cells between species and the validation of agents in murine and human systems [24, 25].

Several clinical trials are underway to verify the safety and efficacy of an alternative transplant site and, among them, bone marrow has been targeted.

A recent approach, using a resorbable generated biological support in situ, showed the potency of the islets implanted in the omentum of rats (*Rattus norvegicus*) and non-human primates (NHP) [26]. It is emphasized that the omentum is highly vascularized, easy to access and drains into the portal system.

Figure 2 summarizes the process of langerhans islet transplantation and factors contributing to its loss.

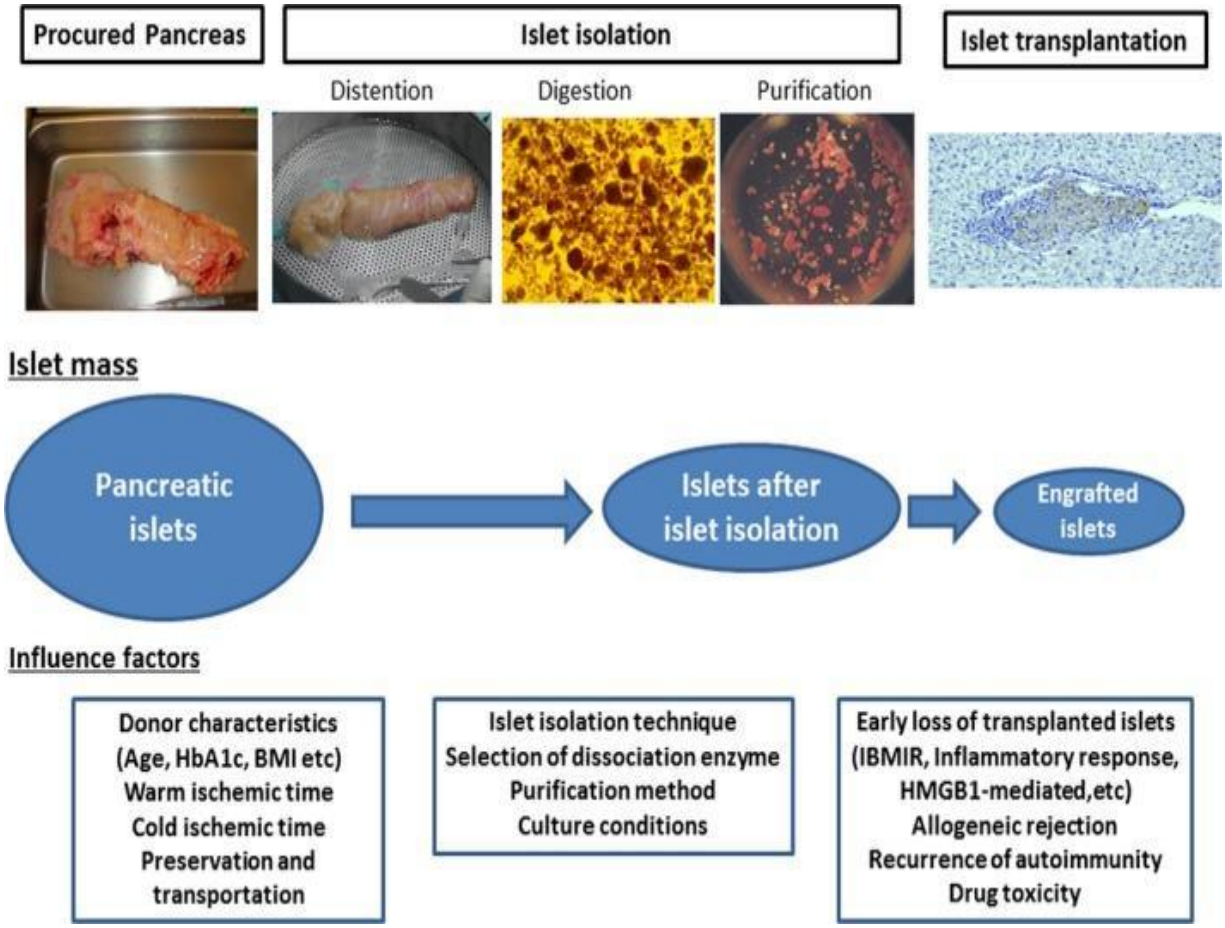

Fig.2. Islet transplantation process and factors contributing to its loss.
Source: Anazawa et al. (2018) [27].

5. CONCLUSION

The state of the art in transplantation of pancreatic islets, in murine experimental models and their translational use, still present pending questions.

Researchers advocate the need for well-designed and statistically significant prospective studies aimed at solving basic and fundamental issues such as immune tolerance. However, it is believed that in the near future, cell replacement therapy will benefit a greater number of diabetic patients.

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