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Islet transplantation 30 years after the first transplants

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Abstract. – First clinical islet allotransplantation in patients affected by type 1 diabetes mellitus was performed about 30 years ago. Despite the progressive improvement of the success rate, the clinical indication to the islet allotransplantation remains limited to selected patients affected by brittle type 1 diabetes mellitus. The burden of the immunosuppression therapy still represents the main critical issue but other areas might be subject to further improvements, such as the islet production, islet engraftment and long-term function. Several strategies have been proposed to increase the success rate of pancreas digestion and islet purification or to facilitate islet engraftment by reducing islet hypoxia and the inflammatory reaction occurring in the site of transplantation. The co-transplantation of progenitors of beta cell together with the islets has expected to contribute to prolong graft function. Clinical trials are expected soon. Scientific advances, as well as economical efforts, are required to make this procedure a real therapeutical option for patients with type 1 diabetes mellitus.

Key Words:
Islet transplantation, Islet engraftment, Islet culture, Immunosuppression therapy.

Introduction

Thirty years ago, the Ricordi method for human isolation was introduced [1] and hence the first clinical islet allotransplantations were performed in patients affected by type 1 diabetes mellitus[2,3]. The first clinical islet transplantations induced great expectancy among physicians and patients. The possibility to become free from the insulin therapy as well as from glucose auto control appeared to be the solution for a disease that is a burden for the patients impairing their quality of life and that is responsible for severe chronic complications. Along the years many clinical trials have been completed, many research activities have been performed and many islet centers have been created[4]. Nowadays more than 1,000 islet transplantations have been performed. The overall clinical outcome is progressively improved and, in the well experienced centers, islet transplantation outcome matches insulin independence rates of solitary pancreas transplantation[5,6]. In several countries, including Canada, Australia, the United Kingdom, France, Switzerland, Norway, Sweden, and other parts of Europe, islet transplantation is funded as 'non-research' standard clinical care[4]. The improvement of islet production, the choice of a proper immunosuppression therapy, the strategies to improve islet engraftment and to reduce the inflammatory reaction toward islets appeared to be the responsible for the most significant improvement in clinical outcome occurring over time[7]. However, clinical indication to islet transplantation still remains limited to selected patients affected by brittle type 1 diabetes mellitus. The burden of the immunosuppression therapy still represents the main critical issue but other areas might be subject to further improvement, such as the islet production, islet engraftment and long-term function.

The Burden of the Immunosuppression Therapy

The need of the immunosuppression therapy is justified for the prevention not only of the rejection, but even of the recurrence of autoimmunity. An effective immunosuppression therapy has been considered one of the main reasons responsible for the recent progressive improvement of the success rate of islet transplantation. Long-term insulin independence was achieved in about half of recipients given T cell-depleting induction immunotherapy[5]. Maintenance immunosuppression has also been shown to have a significant impact on long term graft function and currently is based on Tacrolimus and Mycophenolate mofetil[8,9] The use of Belatacept maintained a high rate of insulin independence, suggesting that the main effect of the immunosuppression drugs may fall into the early post-transplant phase and new therapeutical schemes are expected in the next few years. In the

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near future the introduction of cotransplantation of mesenchymal stem cells (MSCs) or Treg cell or islet macroencapsulation and microencapsulation will represent the strategies to make the procedure safer[10-13]. However, the first clinical trials in encapsulated islet transplantation were unsuccessful[14].

Islet Production

Islet production is based on efficient islet isolation and purification process, and on efficient islet culture. The recent trial sponsored by NIH aimed to identify standardized procedures and represents the result of much time and efforts spent by many researchers[15-17]. Some critical issues still remain, such as the need of standardized enzyme blends[18-20], the lack of methods to assess collagenase efficacy in islet isolation[21-23], the variable islet purification due to the variable organ condition and the imprecise assessment of islet mass[24] and the lack of a really fully automated method. Not all the isolations succeeded, so that islet yield is sometimes still unpredictable. The consequences are that: 1) islet production is still a very expensive activity requiring a high level of experience and very specialized organization; 2) the business plan of an islet cell factory is sustainable with some difficulties.

Islet culture represents an area of possible significant improvement[25]. Many molecules and strategies have been proposed to favor *in vitro* islet survival and function. Anti-apoptotic molecules, such as JNK inhibitor[26] or p38 activation[27] or the addition of collagen type IV, VI, laminins and other ECM molecules via the combinations of integrin α/β heterodimers on islet cells were shown to facilitate tissue repair after isolation[28]. Alternatively, the use of growth factors can improve pre transplant islet quality (survival and function)[29-31]. Co-culture of islets with mesenchymal stem/stromal cells showed trophic effects on beta cells, enhancing viability and function[32]. However most of these strategies remain at the experimental stage. Moving such developments through regulatory agencies is likely to be complex, because they involve cellular products. Scientific international organizations should engage in facilitating discussions with regulatory bodies to make these developments possible.

Islet Engraftment

Poor islet engraftment still represents an unresolved problem: most of the transplanted islets are lost early after transplantation[33]. The islets release several pro inflammatory molecules that trigger a local inflammation[34,35] thus inducing beta cell death and, in some cases, activating islet rejection. In the site of implant many factors contribute to cell death: the activation of the coagulatory cascade and of the complement[36,37], the release of cytokine and chemokines inducing leukocyte infiltration[38], hypoxia[39,40] and innate immunity[41]. The inflammation might lead to beta cell damage, but at the same time induces tissue remodeling and hence the revascularization. Several anti-inflammatory strategies have been proposed[42-44], including treatments to promote local oxygenation and engraftment[45-49], to promote a local immunoprotection, or with regulatory T cells[50] or incorporating CXCL12 or by a depletion of the leukocytes infiltration[51,52]. Different anti-inflammatory treatments have been moved to clinical trials[5,53-55]. None of the anti-inflammatory strategies that have been proposed are able to fulfill all the requirements for preventing beta cell loss in clinical trials.

Long-Term Function

Long-term islet graft function is still limited. Although anecdotal case report showing long term function[56-58], islet function generally decreases progressively: the overall number of insulin independent recipients has remained small in the long term with just over 1000 patients worldwide[5]. The insulin independence of patients is usually lost within 10 years from the transplant, even if partial graft function is maintained longer[4]. Islet transplantation can be repeated, but usually not more than three times. Islet might be progressively destroyed by a chronic rejection and a new early biomarkers are expected to anticipate a proper anti-rejection treatment[59-62]. In addition the islets in the liver are exposed to a high concentration of immunosuppressive drugs and to the phenomenon of glucotoxicity, which could, in the long term, contribute to the exhaustion of islet function[63,64]. New strategies have been proposed to preserve beta cell mass[65-68]. The possible presence of islet progenitor cells could also contribute to new β-cell mass through posttransplant differentiation[69,70]. The real advance is expected due to the use of stem cells, that might solve the problems of the scarce islet mass as well as of the long-term function[71-73]. Clinical trials are expected soon.

Conclusions

The success of islet transplantation is still facing many obstacles and many efforts are needed

to overcome the present limitations. In the meantime, islet isolation has become a highly regulated procedure in most countries thus contributing to the high costs of an islet program. The hope is that the regulatory activity will guarantee the safety of the solutions and hence of the patients without a delay in the progression of the science.

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Conflict of Interest
The Authors declare that they have no conflict of interest.

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