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What's hot and what's new in beta-cell replacement therapy: highlights from the 16th Congress of IPITA

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Introduction

The 16th International Congress of IPITA (International Pancreas and Islet Transplant Association) was held in Oxford, UK, on June 20-23, 2017. The most prominent clinicians and scientists in the field of beta-cell replacement therapies convened and contributed to a stimulating meeting, in which cutting-edge science was presented and discussed, with the fight against type 1 diabetes as the common aim. In this review, we present and discuss the featured topics of the congress. Because this article is based on lectures given at the congress, presenting authors rather than published articles will be cited as references.

Ischemia and hypoxia

Beta-cell replacement therapies currently performed as a clinical procedure include both whole pancreas and islet allogeneic transplantation. Both procedures depend on the quality of a donor pancreas that will be either transplanted as a whole organ or submitted to an islet isolation and purification procedure before transplantation. From the stage of donor management in the intensive care unit, to pancreas retrieval, pancreas preservation and ultimately pancreas digestion in the case of islet transplantation (R. Ploeg, University of Oxford, UK), the organ has to withstand ischemia-reperfusion injury, an insult that is similar in both procedures in the early stages, but becomes islet- or pancreas-specific in the later phases (J. Kerr-Conte, University of Lille, France). *Ex vivo* organ machine perfusion has been shown to be able to salvage marginal kidneys or lungs and is currently explored for the pancreas with very promising results, with the aim to reduce technical failure in whole pancreas transplantation and islet isolation and transplantation outcomes (G. Oniscu, University of Edinburgh, UK). Oxygen persufflation of the pancreas is an intriguing technique in which the organ is perfused with gaseous oxygen during preservation, and for which new data on animal models have shown superiority over conventional cold storage in the preservation of marginal pancreases (K. Papas, University of Arizona, Tucson, AZ, USA).

Worldwide clinical beta-cell replacement activity

In a round table report and discussion, it appeared that pancreas transplantation is actively performed in Europe (J. Casey, University of Edinburgh, UK), North America (J. Markmann, Harvard Medical School, Boston, MA, USA), and Australia (T. Kay, St Vincent Institute, Melbourne, Australia). In Latin America, significant activity is limited to Brazil and Argentina. In Asia, there is activity in Japan and Korea, but it is hampered by the lack of access to donors with brain death (DBD) for cultural reasons, a situation that also affects islet transplantation. Numbers of pancreas transplants have been declining in almost all regions in the past decade. Reasons for this were discussed and seem to be multifactorial: advances in diabetes care, lack of referral, increase in numbers of marginal donors, and risk aversion by transplant surgeons have been cited. Islet transplant activity has been stable in Europe, Canada, and Australia. It has been at a near standstill in the USA while islet transplant centers are waiting for a decision from health authorities to grant licensure and reimbursement for the procedure, in the wake of the CIT trials (J. Markmann, Harvard Medical School, Boston, MA, USA). Results of the first French randomized trial of islet transplantation versus best medical therapy were also presented

(PY Benhamou, University of Grenoble, France). The North American and French trials have clearly demonstrated the safety, efficacy, and superiority of islet transplantation over insulin and should open the way for reimbursement in France and other countries in Europe where the procedure is not yet covered.

Immunosuppression

There has been little in the pipeline recently in terms of new immunosuppressants (IS). Monoclonal antibodies (mAb) and other small biological agents, although not especially novel, are the latest approved drugs that have been tried in beta cell replacement. Alemtuzumab, an anti-CD52, lymphocyte-depleting mAb has been successfully used both in islet and pancreas transplantation as an induction IS and is thought by some to be superior to anti-thymocyte globulin, possibly because of a positive impact on Treg generation and loss of B-cell memory (J. Shapiro, University of Alberta, Edmonton, Canada). Co-stimulatory blockade with the anti-LFA-1 efalizumab mAb or with the CTLA-4-based T –cell activation blocker belatacept, both as induction and as maintenance IS, have achieved remarkable long-term single-donor insulin independence in islet transplantation (P. Stock, University of California, San Francisco, CA, USA). Efalizumab was found to be highly effective, but it is not commercially available any longer because of severe adverse event issues. Tolerance induction strategies were discussed. In terms of autoimmune tolerance, a targeted therapeutic approach was presented - namely peptide immunotherapy (PIT). This strategy is based on the administration of disease-associated peptides, with the aim of restoring antigen-specific immunological tolerance (in this case towards pro-insulin) without generalized immunosuppression (M. Peakman, King's College, London, UK).

Islet autotransplantation

Because of the temporary decline in islet allotransplantation activity, the field of islet autotransplantation is thriving in the USA. This is a procedure that was originally designed for patients with chronic pancreatitis (CP) who had to undergo total pancreatectomy, in order to prevent or at least control surgical diabetes. Surgical diabetes might not be as difficult to control as thought in the past, because of lack of glucagon counter-regulation, but is nonetheless characterized by total absence of insulin production (A. Lumb, University of Oxford, UK) and is amenable to islet autotransplantation, in a setting where there is neither rejection nor autoimmunity. A large series from Minneapolis has even applied this procedure with great success to children with hereditary forms of CP (M. Bellin, University of Minnesota, Minneapolis, MN, USA). Recently, islet autotransplantation has been offered to patients undergoing total pancreatectomy for benign and even malignant tumors of the pancreas (L. Piemonti, San Raffaele Institute, Milan, Italy). Islet isolation is of course performed on a portion of the pancreas from which the tumor has been removed. In spite of obvious fears, this form of islet autotransplantation has not been associated with an increased incidence of liver metastases; on the contrary, the group observed decreased morbidity in comparison to the classic Whipple procedure.

Islet and beta-cell biology

Interactions between α-, β- and δ-cells within islets of Langerhans is an intriguing phenomenon that deserves more in-depth study. Insulin and glucagon secretion have been proposed to be regulated by autocrine and/or paracrine mechanisms, two modes that are not mutually exclusive. Both hormone secretions are also regulated by somatostatin, which inhibits both α- and β-cell functions. The cross-talk, or lack thereof, between these islet cell types is essential in the counterregulatory mechanisms that take place both in physiology and in situations of hypo- or hyperglycemia in diabetes (P. Rorsman, University of Oxford, UK). The arrangement of β cells within islets of Langerhans is critical for insulin release because the β cell population *in situ* is operationally heterogeneous. Mapping of islet functional architecture revealed the presence of hub cells with pacemaker properties, able to release insulin in a rhythmic fashion. These hub cells exhibit failure when subjected to pro-inflammatory stimuli, contributing to altered insulin secretion patterns – for example in the situation of islet transplantation (G. Rutter, Imperial College, London, UK). Intriguing phenomena have been observed in the arrangement of individual islet cell types from the end of the isolation procedures through the weeks after transplantation. The arrangement of endocrine cell within islets is completely disrupted after isolation. The architecture is progressively corrected *in vivo* to a physiologic one after transplantation, emphasizing the functional importance of endocrine cell interaction in islets of Langerhans

(D. Bosco, University of Geneva, Switzerland). The islet extracellular matrix is another important player in cellular interactions within the islet and has more than a simply structural role. Matrix molecules, such as laminins, collagens, and proteoglycans, play an important immunomodulatory or activating role in the pathogenesis of type 1 diabetes. In a phenomenon similar to endocrine cells, their composition is significantly altered during islet isolation to slowly recover after transplantation (C. Simeonovic, Australian National University, Canberra, Australia).

Stem-cell-derived islets for transplantation

Protocols have now been established that allow the differentiation of human embryonic stem cells (hESC) or human induced pluripotent stem cells (hiPSC) into specific pancreatic lineage cells. These protocols are based on a stepwise approach, in which stem cells are expanded and differentiated by culturing in media enriched with various growth factors, cytokines and small molecules. Different protocols allow stem cells to give rise to polyhormonal or monohormonal insulin- and/or glucagon-producing cells, or multipotent pancreatic progenitors with the potential to generate all pancreatic lineages, including non-endocrine cells, *in vivo*, after transplantation into immunodeficient mice (MC Nostro, University of Toronto, Canada). Evidence from murine transplantation models indicated that undifferentiated syngeneic iPSC can be immunogenic and can be rejected *in vivo*. This has tempered the enthusiasm about using such cells for autologous cell therapy purposes. On the other hand, it was shown that after initiation of differentiation, as early as from the stage of embryoid bodies, or after differentiation into cells of any of the 3 embryonic germ layers, iPSC-derived cells did not stimulate T-cell proliferation *in vitro* or rejection *in vivo*. The immunogenicity of iPSC-derived tissues or cells remains an open issue (A. Boyd, University College, London, UK). The recent advent of simple, efficient and cost-effective genome-editing tools has recently opened a number of seemingly endless opportunities to manipulate the genome of hESCs or hiPSCs for a variety of purposes. This technology involves the use of endonucleases, the most efficient and utilized being the CRISPR/ Cas9 system, targeting the genes of interest, to remove, insert or modify them as needed. Applications of this technology to the stem cell field could include, but are by no means limited to, insertion of suicide genes in order to kill stem cell-derived tissue undergoing malignant transformation, modification or deletion of MHC molecules in order to abolish rejection of allogeneic stem cells, or insertion of immunomodulatory genes such as CTLA-4. Such strategies, if successful, are likely to boost the field and bring regenerative medicine for type 1 diabetes closer to clinical application by providing safer, more efficient and immunologically accepted stem cell-derived insulin-producing cells or tissues (J. Odorico, University of Wisconsin, Madison, WI, USA).

Xenoislets for transplantation

Porcine islets are a potential «unlimited» source of β-cell grafts in the current context of donor organ shortage. Preclinical pig-to-primate studies have shown that discordant xenogeneic porcine islet grafts could function in a non-human primate for several months. On the flipside, these studies have revealed as yet unresolved problems, mostly the immunosuppression burden of controlling immune xenorejection, and the issue of zoonosis, and in particular porcine endogenous retroviruses (PERV). Such issues could be tackled with the use of genetically modified pigs. As an example, pigs knocked-out for the αGal gene or transgenic for hCD46 have been generated, with some success in pig-to-primate transplant experiments. However the number of genes to be manipulated is likely to be quite large, and in this respect the newly available CRISPR/Cas9 technology is accelerating the process of generating animals able to provide safer islets (G. Korbutt, University of Alberta, Edmonton, Canada). Evidence was shown that islets transplanted from genetically engineered pigs can be transplanted with reduced immunosuppressive therapy (CG Park, National University College of Medicine, Seoul, Korea). Refinements in encapsulation techniques, for example by incorporating immunomodulatory chemokines in the capsule material, are also expected to play a role in allowing to decrease or altogether avoid systemic immunosuppression after transplantation of xenogeneic islets (M. Poznansky, Harvard Medical School, Boston, MA, USA).

Novel technologies for beta-cell replacement

Stem cell-derived or xenogeneic islets have been competing for the pole position in the race to find an unlimited source of insulin-producing tissue. Both strategies have come long ways and seemed

to be close to reaching clinical reality, but none has convincingly gone beyond successfully reversing diabetes in animal models. Novel strategies and technologies have been developed in the meantime, and are closing in on conventional stem-cell or xeno options in terms of experimental results. Most of these cutting-edge strategies are largely based on techniques and achievements from the stem-cell and/or xeno fields, but pushed to a further level. Detergent decellularization of animal organs, performed to use the acellular matrix as a scaffold for the engineering of vascularized bioartificial organs, has been successfully explored in recent years. Data were presented showing that human pancreases could also be utilized for this purpose. They maintain their vascular structure and can accommodate human endocrine cells and exhibit intriguing immunomodulatory properties (G. Orlando, Wake Forest University, Winston-Salem, NC, USA). A similar strategy was presented in a rat model, in which decellularized lungs were repopulated with rat islets and epithelial cells through the airways and endothelial cells through the vessels, and produced a functional vascularized lung/islet hybrid organ (P. Moser, H. Ott, Harvard Medical School, Boston, MA, USA). Interspecies organogenesis is able to generate organs from one animal species, in animals from another species, by blastocyst complementation with pluripotent stem cells (PSCs). Using this technology, Pdx-1-deficient mice (mice with a lethal mutation that impairs pancreas development) were complemented with rat PSCs and were able to develop a fully functional rat pancreas. Islets isolated from these mouse-rat chimeras were able to reverse diabetes after transplantation into STZ-treated rats. These data provide a proof-of-principle for the therapeutic potential of PSC-derived islets generated by blastocyst complementation in a xenogeneic host. Application to a pancreas-deficient porcine model complemented with human iPSCs will have to overcome ethical concerns, as well as phylogenetic hurdles (H. Nakauchi, University of Tokyo, Japan). In recent years, the use of a simple inkjet technology for cell printing has triggered tremendous interest in the field of 3D bio-fabrication or 3D organ bioprinting. A key challenge has been the development of printing processes able to preserve cell and tissue viability and functions. In one of the most intriguing lectures of the meeting, data were presented on the fabrication of alginate-encapsulated islets using a 3D-bioprinting technology (W. Shu, Heriot-Watt University, Edinburgh, UK). Finally, pure technology is still a major player in the fight against diabetes, and much progress has been made in the development of the closed loop, glucose sensor- and insulin pump-based, artificial pancreas. Algorithms for real time insulin delivery are gaining in sophistication and may be closing in on beta-cell replacement therapies (R. Hovorka, University of Cambridge, UK).

Where will beta-cell replacement be in 10 years time?

The meeting came to its conclusion with a session asking predictions on where the field would be in a rather short period of time. Although the stem cell or xenogeneic islet research is progressing at a fast pace, and in spite of the need to find a source of insulin-producing tissue for a majority of diabetic patients, rather than the unlucky few who deal with complicated diabetes, it was thought that pancreas and islet transplantation would still be the first forms of beta-cell replacement therapy in 10 years. In order to offer a minimally invasive approach to larger numbers of recipients, the islet transplantation field must solve issues of regulations and health care coverage that are plaguing its development (T. Berney, University of Geneva, Switzerland). Islets are still likely to be transplanted into the liver, although there is a growing interest on research for alternative sites. Islet transplantation in the omentum seems promising, but it may present challenges due to an inflammatory microenvironment. Other options could include deviceless strategies with resorbable scaffolds that could be placed subcutaneously or in other alternative sites (C. Ricordi, University of Miami, Miami, FL, USA). Together with such strategies, immunosuppression-free transplantation, achieved either by immune tolerance or immunoisolation, is an absolute prerequisite in a perspective of offering an islet transplant for all patients with type 1 diabetes, including children (P. Johnson, University of Oxford, UK).

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