Acta Diabetol (2016) 53:683–691
DOI 10.1007/s00592-016-0847-z

REVIEW ARTICLE

The state of the art of islet transplantation and cell therapy in type 1 diabetes

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Received: 15 January 2016 / Accepted: 6 February 2016 / Published online: 29 February 2016

Abstract In patients with type 1 diabetes (T1D), pancreatic β cells are destroyed by a selective autoimmune attack and their replacement with functional insulin-producing cells is the only possible cure for this disease. The field of islet transplantation has evolved significantly from the breakthrough of the Edmonton Protocol in 2000, since significant advances in islet isolation and engraftment, together with improved immunosuppressive strategies, have been reported. The main limitations, however, remain the insufficient supply of human tissue and the need for lifelong immunosuppression therapy. Great effort is then invested in finding innovative sources of insulin-producing β cells. One old alternative with new recent perspectives is the use of non-human donor cells, in particular porcine β cells. Also the field of preexisting β cell expansion has advanced, with the development of new human β cell lines. Yet, large-scale production of human insulin-producing cells from stem cells is the most recent and promising alternative. In particular, the optimization of in vitro strategies to differentiate human embryonic stem cells into mature insulin-secreting β cells has made considerable progress and recently led to the first clinical trial of stem cell treatment for T1D. Finally, the discovery that it is possible to derive human induced pluripotent stem cells from somatic cells has raised the possibility that a sufficient amount of patient-specific β cells can be derived from patients through cell reprogramming and differentiation, suggesting that in the future there might be a cell therapy without immunosuppression.

Keywords β Cell replacement · Islet transplantation · Xenotransplantation · Pluripotent stem cells

Introduction

The International Diabetes Federation (IDF) estimates that 415 million people worldwide have diabetes, a number that is predicted to increase to 642 million by 2040 (http://www.diabetesatlas.org). Type 1 diabetes (T1D), a disease characterized by selective and progressive loss of insulin-producing β cells caused by an autoimmune-mediated destruction, accounts for approximately 10 % of these cases. Administration of exogenous insulin, regular blood glucose monitoring and dietary restrictions are the fundamental means of treating hyperglycemia in all patients with T1D. Although lifesaving, insulin therapy does not restore the physiological regulation of blood glucose [1] and is not able to prevent either the dangerous states of hypoglycemia or long-term complications [2] and the life expectancy of these patients is still shorter compared to that of the general population [3]. Although new technologies like slow-release insulin or insulin pumps have been developed in the last years and have substantially improved glycemic control as well as the quality of life of patients with T1D [4], a fail-safe physiological regulation of systemic blood glucose levels remains challenging. The only possible definitive cure for this disease consists in replacing the destroyed β cell mass capable of sensing blood sugar levels and secreting appropriate amounts of insulin in a glucose-dependent manner. Increasing evidence indicates that β Cell replacement restores protection from severe hypoglycemia,

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reduces levels of glycated hemoglobin (HbA1c) and slows progression of microvascular complications in patients with T1D [5]. So far, the only available clinical approaches able to restore β cell mass in patients with T1D are pancreas or pancreatic islet transplantation, which consists in endocrine cells infusion into the recipient's portal vein and requires only a minimally invasive surgical procedure compared to the complex vascularized pancreas transplantation [6–8]. The field of islet transplantation has evolved significantly over the last three decades thanks to the incredible efforts of the research community worldwide with continuous improvements in islet manufacturing process and transplantation techniques, coupled with better patient management and the development of more effective induction and maintenance immunosuppressive protocols [9]. In addition, islet transplantation represents an excellent platform toward the development of cellular therapies aimed at the restoration of β cell function using alternative sources of β cells like xenogeneic islets or insulin-producing cells derived from the differentiation of stem cells.

This review deals with the state of the art of islet transplantation and the most promising sources of new β cells for functional replacement in diabetes (Fig. 1). Established procedures, ongoing clinical trials (Table 1) and future developments of cell therapies will be discussed.

β Cell replacement with allogeneic pancreatic islets

Pancreatic islet transplantation has recently become an accepted therapeutic option in subjects with unstable T1D. The procedure itself may be performed as islet transplant alone (ITA) in non-uremic patients with T1D, as simultaneous islet-kidney (SIK) in subjects with end-stage renal disease or, if renal transplantation has already undergone, as islet after kidney (IAK) transplantation. Ongoing clinical trials are recruiting 18- to 65-year-old T1D subjects with frequent metabolic instability (i.e., hypoglycemia, hyperglycemia, ketoacidosis) requiring medical treatment despite intensive insulin therapy [10].

The first attempt of islet isolation and transplantation was reported in 1972 by Ballinger and Lacy in chemically induced diabetic rats [11], with Kemp et al. [12] establishing the liver as the most suitable site for islet implantation. Five years later, the first islet infusion in human was performed, with azathioprine and corticosteroid as immunosuppressive drugs [13]. Since then, many efforts and significant progress have been achieved in the field in terms of human islet isolation [14], immunosuppression strategies [15] and setting the optimal number of transplanted islets per kilogram of body weight [16].

Altogether these advances culminated in 2000 with the publication of the Edmonton Protocol achieving a 100 % insulin independence in seven patients with T1D receiving islets from multiple donors and treated with a steroid-free immunosuppression protocol [17]. The Edmonton Protocol represented a fundamental proof-of-concept of the possibility to achieve insulin independence through islet transplantation. Few years later, the same group reported sustained islet function as measured by the presence of C-peptide in 73 % of their transplanted subjects with 15 % insulin independence at 9 years after transplantation [18]. Recently, they reported a further update on long-term follow-up of a cohort of the 36-patient international Immune Tolerance Network trial having persistent graft survival at the end of the clinical study. All patients remained free of severe episodes of hypoglycemia and maintained HbA1c $<$7.0 % showing an overall long-lasting graft function with a gradual decline in C-peptide levels during time. Importantly, the long follow-up showed long-term safety of the procedure with the absence of severe infection, malignancy, hypoglycemia and the stability of renal function [19].

Since the initiation of the Edmonton Protocol, islet transplant programs expanded in North America, Europe and Australia, where alternative protocols for human islet transplantation have been conducted in order to overcome current limitations of the procedure, thus improving the clinical outcome. The most recent report released by the Collaborative Islet Transplant Registry (CITR, www.citregistry.org) analyzes data coming from 864 islet allograft recipients (686 ITA and 178 IAK) and 1679 infusions in the era 1999–2012. A comprehensive report collecting data available for the period 1999–2010 showed that the rate of insulin independence at 3 years remarkably improved during time: 27 % in the era 1999–2002, 37 % in the era 2003–2006 and 44 % in the most recent era 2007–2010. Other parameters indicative of islet graft function like C-peptide $>$0.3 ng/ml, reduction of HbA1c, resolution of severe hypoglycemia episodes and fasting blood glucose stabilization were retained longer in the most recent era [20]. Moreover, successful results were recently reported by numerous European groups: The UK islet transplantation program achieved graft function in 80 % of transplanted patients 2 years after the first islet infusion with a significant reduction in severe hypoglycemic episodes and the achievement and maintenance of HbA1C $<$7.0 % in 70 % of the recipients [21]; the teams of Lille and the Swiss-French GRAGIL Network reached 50 and 75 % insulin independence rate during the 5-year follow-up, respectively [22, 23]. The strong reduction in the rate of islet graft loss during the different periods suggests that new drugs able to improve islet engraftment and survival and to better protect islets from the alloimmune rejection and recurrent autoimmunity have been developed. Specifically, the era 1999–2006 was dominated by the Edmonton Protocol consisting in the administration of IL-2 receptor

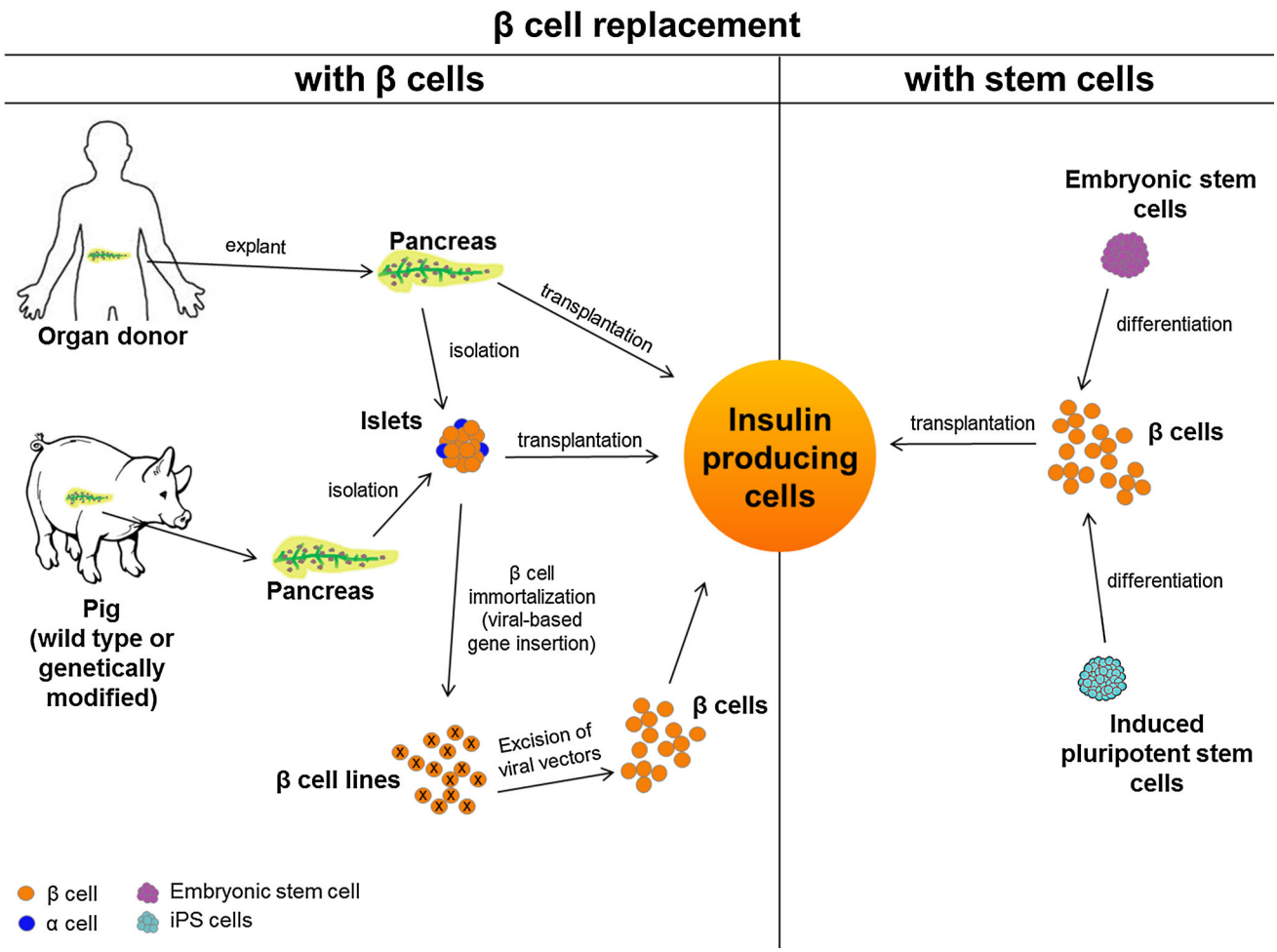

Fig. 1 Schematic representation of the most promising sources and the related strategies currently studied in order to obtain a large amount of transplantable β cells

Table 1 Clinical studies testing safety (Phase 1) and efficacy (Phase 2) of different sources of insulin-producing β cells

Source of β cells		Study type	Study locations	Status
Allogeneic pancreatic islets	Islets isolated from brain-dead organ donors	Clinical routine	Every hospitals performing pancreatic islet transplantation	
Xenogeneic pancreatic islets	Neonatal pig islets	Phase 1/2	Hospital Infantil de Mexico, Mexico	Completed, [45]
Xenogeneic pancreatic islets	Neonatal pig islets	Phase 1/2	Third Xiangy Hospital, China	Completed, [46]
Xenogeneic pancreatic islets	Neonatal pig islets	Phase 1/2	Hospital Interzonal General de Agudos Eva Peron Buenos Aires, Argentina, and Centre for Clinical Research and Effective Practice Auckland, New Zealand	Completed, results not yet published
ESC-derived insulin-producing cells	Human ESC-derived insulin-producing cells	Phase 1/2	University of California, San Diego, USA, and University of Alberta Hospital, Alberta, Canada	Ongoing

antagonist (i.e., daclizumab) for induction and a mammalian target of rapamycin (mTOR) inhibitor (i.e., sirolimus) in combination with a calcineurin inhibitor (CNI, i.e., tacrolimus) for maintenance immunosuppression. In the most recent era (2006–2010), the immunosuppressive regimen shifted to a T cell depleting antibody with or without a TNF-α inhibitor (i.e., etanercept) administered peri-transplant [24, 25] and an mTOR inhibitor or an

inosine monophosphate dehydrogenase inhibitor (IMPDH, i.e., mycophenolic acid) combined with a CNI for the maintenance therapy [26, 27]. Besides, an efficient protocol of induction based on the use of alemtuzumab for lymphocyte depletion was associated with promising longer-term function [28]. Moreover, a CNI-free immunosuppressive schedule was reported [29]. Finally, in the most recent years the field moved in the direction of finding new biologics with a lower islet cell and organ toxicity profiles: Drugs that target co-stimulation pathways in immune cells and/or adhesion molecules such as LFA-1, CTLA4-Ig, PD-1/PD-L1 and CD40 [30–32] or chemokine receptors (CXCR1/2) [33] have been tested in preclinical models and clinical trials. Remarkably, the increasing success in the clinical outcome underlines that improvements made in the last decades allowed to reach results closed to that obtained with whole pancreas transplantation [34]. At present, however, the lack of pancreas from heart-beating brain-dead donors, the only suitable source of human islets for clinical use until now, strongly limits the broad application of islet transplantation as a standard procedure. Many approaches aimed to find alternative sources of β cells are currently intensively investigated, in particular xenogeneic islets, immortalized β cell lines and stem cells able to differentiate into insulin-producing β cells.

β Cell replacement with xenogeneic pancreatic islets

Using pancreatic islets derived from other species seems an obvious way of providing the large amount of islets required for transplantation therapy. Most effort in this area has been directed toward the use of pig islets for many reasons: (1) Pig insulin can efficiently substitute human insulin because they differ by only one amino acid; (2) porcine islets regulate glucose levels in the same physiologic range as humans; (3) high yields of islets can be obtained with techniques established for human islet isolation and (4) pigs can be genetically modified for making their islets more suitable for the transplantation in humans [35]. One of the first clinical attempts made in 1994 by Groth et al. [36] who transplanted fetal pig islet-like cell clusters in T1D patients proved that porcine pancreatic endocrine tissue can survive in humans although the clinical benefit in these patients was barely detected. However, two main problems have limited the use of pig islets in humans: (1) the risk of an hyperacute immunologic rejection, because humans have natural preformed antibodies reacting to galactose-α1,3-galactose (Gal), a saccharide expressed on cells of lower mammals but not on cells of humans or monkeys [37] and (2) the risk of zoonosis, because porcine endogenous retroviral (PERV) sequences can infect several human cells in vitro and may be activated after the xenotransplant [38]. Promising findings coming from the transplantation of pig islet transplantation in the NHP (non-human primate) model provided the rationale for continued development of islet xenotransplant as a potential treatment option for T1D. Indeed, fundamental studies in NHP reported the long-term survival of neonatal [39] or adult [40] porcine islets in the presence of immunosuppression therapy. Besides, a recent study provided evidences that islets isolated from miniature pigs infused in diabetic NHP engrafted and maintained normoglycemia for more than 6 months in 4 out of 5 recipients with low-dose immunosuppressive therapy and adoptive transfer of expanded autologous regulatory T cells [41]. Moreover, in order to overcome the issue of the immunogenicity, genetically engineered pigs have been developed and some groups have reported variable survival gains using multiple genetically engineered pig islets transplanted in NHP [42, 43]. Another strategy currently studied to avoid immunosuppression consists in islet microencapsulation: Islets can be enveloped within a biocompatible membrane and isolated from the host immune system [44]. The promising results in the preclinical studies using the stringent pig-to-NHP model [45] and the case report of long-term function of encapsulated neonatal pig islets transplanted in a diabetic patient without immunosuppression [46] paved the way for pursuing the potentiality of islet xenotransplantation in extensive clinical studies. The first clinical trial was performed in Mexico co-transplanting neonatal pig islets with Sertoli cells in subcutaneous collagen-covered device in 12 patients with T1D in the absence of immunosuppression, but showed disappointing results [47]. In China, transplantation of neonatal pig islets in 22 T1D subjects treated with a multiple drug immunosuppressive regimen resulted in negligible clinical benefit [48]. Other clinical trials have been currently undertaken by Living Cell Technologies™ in New Zealand: They performed phase 1/2 clinical trials in Russia, Argentina and New Zealand (clinicaltrial.gov: NCT01739829, NCT01736228, NCT00940173). Neonatal pig islets encapsulated in alginate microcapsules (DIABECELL®) were transplanted in T1D patients, and their findings are expected to be published imminently. To date no subject, to our knowledge, has been rendered insulin independent with such approaches. In summary, encouraging results in prolonged graft survival and data concerning the safety of transplanted pig islets have recently been obtained and, although several concerns are still waiting for being addressed, this strategy may represents a therapeutic alternative in the near future.

β Cell replacement with expanded β cells

Unlike blood, skin or intestine, that are tissues with a relatively rapid turnover of cells, β cells in the pancreatic

islets are a quiescent population with a proliferative ratio of 0.1–0.3 %/day in 1-year-old mice [49] and negligible proliferation, except for the first years after birth or during pregnancy, in humans [50]. During the past 30 years, many attempts have been made to generate human β cell lines from many pancreatic sources, but insulin production by these cells was extremely low or limited at few passages [51, 52]. In 2005, Narushima et al. [53] reported the successful establishment of a functional human β cell line, NAKT-15, that looked promising for cell therapy of diabetes, but no new reports on the utility of this cell line have been published since then. In 2011 another human β cell line was established transducing human fetal pancreas with a lentiviral vector that expressed SV40LT and human telomerase reverse transcriptase (hTERT). One of the cell lines generated with this strategy, the EndoC-βH1, was further characterized and resulted able to secrete insulin in response to glucose stimulation, was stable at least for 80 passages and expressed many specific β cell markers, without any substantial expression of markers of other pancreatic cell types [54]. In view of clinical use, a second generation of human β cell lines has been recently developed; the conditionally immortalized EndoC-βH2 cell line is based on Cre-mediated excision of the immortalizing transgenes, leading to an arrest of cell proliferation and pronounced enhancement of β cell-specific features such as insulin expression, content and secretion [55], but further studies are required to determine the actual safety of these cells.

β Cell replacement with stem cell-derived β cells

Currently, many opportunities for the cell therapy of single-cell disorders like T1D are offered by stem cell differentiation. Stem cells are, by definition, undifferentiated cells that hold both the potential to differentiate into a large variety of specialized cell types and the ability to go through numerous cycles of cell division while maintaining their undifferentiated state (self-renewal). The first attempts focused on adult stem cells because many tissues offered the possibility to derive progenitor cells able to differentiate into pancreatic β-like cells, but until now none of the sources analyzed has proved able to produce "true" β cells capable of secreting insulin in response to glucose and normalizing glycemia in diabetic animal models [56]. So far, the most promising source of cells for cell/organ replacement therapies is pluripotent stem cells.

Embryonic stem cells

Because of their self-renewal abilities and the capacity to differentiate into any cell of the body, embryonic stem cells (ESC) have always been considered the most auspicious source for cell replacement therapies. In fact, the development of ESC lines from the inner cell mass of early stage human embryos [57] offered the potential to generate any specialized cell type in large quantities, including insulin-producing cells. Novocell, a preclinical-stage stem cell engineering company focused on diabetes, that in 2010 changed its name into ViaCyte, developed a differentiation protocol of human ESC into β cells, designed along the lines of pancreatic organogenesis in vivo. This protocol brought ESC through subsequent stages on the desired path: from definitive endoderm to posterior foregut, then to pancreatic endoderm, progenitors of endocrine pancreas and, finally, to hormone-producing endocrine cells. With their five-step differentiation protocol, ViaCyte succeeded in obtaining about 7 % of cells that expressed high levels of proinsulin that was processed, albeit inefficiently, to insulin and C-peptide [58]. Two other groups, using different culture conditions, confirmed that ESC are able to differentiate in insulin-producing cells, albeit with a lower efficiency [59, 60]. Subsequently, Baetge and colleagues improved their results optimizing their differentiation protocol and transplanting ESC-derived pancreatic progenitor cells into mice such that after 3 months in vivo the implanted cells differentiate into mature endocrine cells that can regulate blood glucose levels after diabetes induction [61]. The same group recently developed a scalable and standardized system for the production of functional pancreatic progenitors from human ESC, further optimizing their differentiation protocol for the CyT49 ESC line [62]. Finally, on October 29, 2014, ViaCyte announced the beginning of a phase 1/2 clinical trial (clinicaltrial.gov: NCT02239354) and that the first patient of this study was successfully implanted with ESC-derived insulin-producing cells delivered under the skin in a proprietary device with a selectively porous cell-impermeable membrane, called the Encaptra® drug delivery system; this device is designed to protect the implanted cells from possible immune rejection, to permanently contain the cells and prevent their distribution away from the implantation site. This is the first time that an ESC-derived cell replacement therapy for diabetes is studied in human subjects, and it represents the culmination of a decade of effort by the ViaCyte team (http://viacyte.com). Meanwhile, modified or improved protocols have been established using combinations of cytokines and small molecules, such as fibroblast growth factors, sonic hedgehog pathway inhibitors (KAAD-cyclopamine or SANT-1), retinoic acid, nicotinamide, protein kinase C (PKC) activator (indolactam V) or TGF-β pathway inhibitors (Alk5 inhibitor, dorsomorphin or noggin) [63–65]. Noteworthy are in particular the directed differentiation strategies reported by the research units of Melton and Kieffer [66, 67]. These two groups reported an efficient approach to generate

in vitro 20–50 % insulin (C-peptide)-positive cells from human ESC. Upon transplantation into immunocompromised mice, the graft (composed of endocrine and ductal cells) restored normoglycemia within 2 [66] or 6 weeks [67], a tremendous improvement compared with the 2- to 3-month period required after transplantation of ESC-derived pancreatic progenitors [61]. Nevertheless, the similarities and differences between β-like cells generated by all these groups remain to be elucidated by a direct comparison. Despite significant successes, three main problems still limit the use of ESC-derived insulin-producing cells. First, due to their pluripotency, undifferentiated cells give rise to teratoma formation in vivo and the transplantation of unselected differentiated cells would inevitably lead to tumorigenesis because of the presence of some residual undifferentiated cells [61]; several attempts have been made to identify surface markers able to select pancreatic progenitor cells [68, 69], but the safety of the selected cells requires further investigation. Another unsolved problem is related to the evidence that each ESC line has a different propensity to give rise to pancreatic cells [70]. Therefore, many cell lines have to be tested (and, accordingly, the differentiation protocol must be optimized) in order to identify a set of ESC lines that could facilitate genetic matching of donor cells to patients and therefore prevent graft rejection and lifelong immunosuppression. The last major problem, which greatly limits the use of ESC in many countries of the world, is the presence of ethical concerns regarding the destruction of human embryos for the production of these cell lines.

Induced pluripotent stem cells

To overcome these obstacles and still obtain pluripotent cells, the group of professor Yamanaka (winner of the Nobel Prize in 2012 for this discovery) succeeded in 2006 in reprogramming adult somatic murine cells into induced pluripotent stem cells (iPSC) through the forced expression of 4 genes (OCT4, SOX2, KLF4 and c-Myc) [71]. One year later, Yamanaka's and two other groups have successfully repeated the reprogramming process using human somatic cells [72, 73]. Mouse and human iPSC resulted highly comparable to ESC as these cells showed the same morphology, the same proliferative capacity, had similar telomerase activity, a normal karyotype, expressed surface markers and genes that characterize ESC and were also able to form teratomas in vivo and to differentiate into cells of all three germ layers in vitro [71, 73].

Several strategies to differentiate iPSC into cells capable of producing insulin have been tested, with original protocols or borrowing the experience from ESC. The first paper that reported successful differentiation of human iPSC into insulin-secreting cells dates back to 2008, when the group of Zhang adapted the four-step differentiation protocol developed for ESC from Jiang et al. [60] and obtained for the first time β-like cells in vitro from reprogrammed human fibroblasts. Unfortunately, the efficiency of differentiation process was very low and the total C-peptide content was significantly lower compared to adult β cells [74]. Subsequent studies focused on the culture conditions in order to increase the efficiency of differentiation of the iPSC into insulin-secreting cells; for example, in 2010 the group led by Yupo Ma applied a protocol previously successful for murine ESC [75] to iPSC derived from adult mouse fibroblasts. With this differentiation protocol, they were able to obtain up to 50 % of cells capable of secreting insulin in response to glucose stimulus from murine iPSC and, if transplanted into diabetic mice, these cells were capable to restore normoglycemia [76]. It remains to be confirmed whether the same differentiation protocol could have the same efficiency in differentiating human iPSC. One year later, it was reported the differentiation of human iPSC into insulin-secreting cells responsive to glucose using a protocol that requires the addition, compared to ViaCyte one, of two molecules: indolactam V [63] and GLP-1. The differentiation efficiency was very low, as only 1.29 % of insulin positive cells were obtained, and their ability to secrete insulin in vivo has not been verified [77]. Encouraging results have been reported by other several in vitro studies that used protocols mimicking the mechanism of in vivo pancreas development to guide the differentiation of iPSC into β-like cells [78–82] but with a lower efficiency compared to ESC. Insulin-producing cells, although with low efficiency, were also generated with iPSC derived from the reprogramming of fibroblasts of two patients with diabetes [83], opening the way not only to autologous cell replacement therapy of T1D, but also to in vitro modeling of this disease. Last year two important groups described for the first time that pancreatic cells derived from the differentiation of pluripotent stem cells (both embryonic and induced) are capable to revert diabetes in mice [66, 67]. The Melton's group, in particular, described a 4- to 5-week in vitro differentiation protocol which involves a combination of sequential culture steps using factors that affect signaling in numerous pathways, including signaling by WNT, activin, hedgehog, TGF-β, retinoic acid and γ-secretase inhibitors, and leads to the generation of ∼50 % of C-peptide and Nkx6.1 double-positive cells from both ESC and iPSC [66]. These results brought to the foundation of a company, called Semma Therapeutics (http://www.semma-tx.com/), focused on the development of an ESC- or iPSC-based therapy for diabetes.

In conclusion, iPSC retain the same essential properties of ESC, included the ability to differentiate into β cells, but offer the advantage of allowing the generation of

autologous cells that might be useful for cell therapy. However, the main problem of iPSC, which currently still preclude their use in humans, is related to their intrinsic characteristic: As pluripotent cells, like ESC, also iPSC determine the formation of tumors when transplanted into immunodeficient animals. In addition, other problems are caused by the reprogramming process itself, as the use for transfection of integrating virus like retroviruses may cause insertional mutagenesis, interfere with gene transcription and induce tumors formation [73]. To overcome these obstacles, various strategies have been developed: The removal of the oncogene c-Myc from the set of genes required for reprogramming [84] or the use of new classes of vectors for reprogramming that do not integrate into the host genome [85], thereby drastically decreasing the tumorigenicity risk without altering the pluripotency. It is then clear that many efforts still need to be done in order to make both processes of reprogramming and differentiation safer and more efficient. It should also be considered that, although iPSC offer great hope for cell replacement therapy for diabetes, a potential translation in recipients with T1D will require strategies to avoid recurrence of autoimmunity, in the form of a selective immunosuppressive therapy or of an encapsulation device for their immunoprotection [86].

Conclusion

Insulin treatment is not a cure for patients with T1D and does not eliminate the long-term complications associated with the disease. Major advances have been achieved in the field of β Cell replacement through islet transplantation, mainly due to novel immunosuppression strategies. As limits of islet transplantation are addressed and overcome, cellular therapy will become the choice for a wider parterre of people with diabetes. In this scenario, more and more insulin-secreting cells will be needed and this necessity is strongly pushing the search for alternative sources. Xenogeneic islets hold a great potential, and recent studies have marked significant progresses in controlling immune rejection toward xenoantigens. New β cell lines have also been established, and their safety is currently under investigation. Currently, the most significant advances come from the stem cell field; in fact, it has been described that human ESC and iPSC are able to generate pancreatic progenitors and/or functional β cells in vitro that can treat diabetic mice, and a clinical trials with ESC-derived cells is ongoing in T1D patients. Moreover, the stem cell approach may synergize well with other developing innovations such as the generation of immune isolating and retrievable devices, fundamental to allow cell therapy without immunosuppression and to overcome the safety concerns about tumorigenic cells. It is likely that altogether these experiences will change the way we treat T1D and lead to new therapeutic options for patients with diabetes.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standard All works cited in this review have been published in journals that require approval by the Ethics Committees of the conducted experiments.

Human and animal rights This article does not contain any studies with human or animal subjects performed by any of the authors.

Informed consent All works cited in this review have been published in journals that require that informed consents of participants to reported clinical trials are collected.

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