Chapter 3
New Trends in Stem Cell Transplantation in Diabetes Mellitus Type I and Type II

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Abbreviations

ABMSCs	Autologous bone marrow-derived mesenchymal stem cells
ADSCs	Adipose-derived stem cells
CPC	Circulating precursor cells
DM	Diabetes mellitus
EPC	Endothelial progenitor cells
ESCs	Embryonic stem cells
PSCs	Pluripotent stem cells
SCs	Stem cells
T1DM	Type one diabetes mellitus
T2DM	Type two diabetes mellitus

3.1 Introduction

Diabetes mellitus (DM) is recognized as the most common metabolic disease, which affects more than 347 million people worldwide and is reported as major cause of morbidity and mortality in general population (Scully 2012). Currently, type 1 DM (T1DM) is reported as an autoimmune disease characterized by insulin secretion deficiency due to destruction of insulin-producing β-cells (Ashcroft and Rorsman 2012). It is well established that the type 2 DM (T2DM) associates predominantly with metabolically active obese, insulin resistance, and adipocytokine production imbalance leading secondary to dysfunction/apoptosis of pancreatic β-cell (Paneni et al. 2013). Despite contemporary treatment strategy, T1DM and T2DM are frequently coexisting with major microvascular and macrovascular complications leading to target organ damages, i.e., ischemic tissue injury, retinopathy,

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nephropathy, and diabetes-related cardiomyopathy (Ali and Dayan 2009). The ability of endogenous repair system to improve ischemic damage of the tissues and to restore of innate mechanisms of cell-to-cell cooperation to attenuate tissue perfusion and endothelial function is sufficiently worse (Cade 2008). As a consequence, intensified tissue remodeling and the extended ischemic injury lead to increased cardiovascular (CV) morbidity and mortality (Berezin 2016a). Finally, DM-related mortality may approximately twofold increase when compared with death rate in DM-free patient population (Nwaneri et al. 2013). Nevertheless, not all complications of DM are considered consequence of ischemic tissue injury, and they may closely relate to metabolic memory phenomenon (Berezin 2016b). Various factors contributed to increased CV risk in DM are determined, i.e., hyperglycemia, lipotoxicity, age-related and diabetes-related comorbidity, and known CV diseases. In fact, they all may lead to malignant evolution of the diabetes associated with poor outcomes and may reflect a shortcoming of current therapies. Currently established therapies molecular targets in diabetic patients affect not only insulin secretion, glucose regulator peptides, hormones, enzymes, and transporters. However, they should also mediate improving hypoglycemia, suppression of oxidative stress and endoplasmic reticulum stress, prevention of atherosclerosis, attenuation of dyslipidemia and endothelial function, modification of coexisting CV risk factors, and adequate control in comorbidities (Howangyin and Silvestre 2014).

Although there is an understanding of the several mechanisms and different phases in pathogenesis of DM, it is unclear whether alternative translational approaches regarding tissue reparation and restoration of failing β-cell function based on attenuation of metabolic processes via stem cell transplantation are effective (Holditch et al. 2014). Indeed, clinical use of pluripotent stem cells (PSCs), as well as embryonic stem cells (ESCs) and induced PCSs (iPCSs), appears to be promising and safe in a long-term prospective (Liew 2010; Abdelalim et al. 2014). As it is expecting, various types of ESCs and iPSCs lines having a great differential potential may translate into all cell types, and they have a high potency to differentiate into insulin-secreting β-like cells without or very low risk of immune rejection (Abdelalim et al. 2014). However, the results of the recently performed studies regarding regenerative care in DM are controversial and require to be explained in detail (Chidgey et al. 2008). In this context, there are discrepancies between results received in the animal studies and data that have been obtained in the clinical investigations. The first controversy relates to some inconsistencies, which might accompany the fact that several types of stem cells were tested as prospective for regenerative strategy, and not all of stem cells were available in routine clinical practice. The second controversy attached to the patients with different types of DM at several stages of evolution of the disease failed to uniform considered candidates for stem cells transplantation, and they would probably require further investigations (Aguayo-Mazzucato and Bonner-Weir 2010; Anastasia et al. 2010). Given the conflicting evidence concerning stem cell replacement in T2DM and T1DM, the aim of the chapter was to seek, analyzes, and summarize the data to clarify actual knowledge and identify the future perspectives for regenerative therapy in diabetics.

3.2 The Regenerative Care Paradigm

The paradigm of regenerative therapy bases on novel knowledge of pathogenesis and mechanisms of endogenous reparation mechanisms (Terzic and Behfar 2014). It has been postulated that regenerative therapy based on cell care might attenuate or reverse disease progression. In this context, stem cell therapies are applied essentially as adjuvants to standard of care with the goal of furthering an otherwise limited self-renewal capacity of the disease (Qi et al. 2012).

3.3 Expected Effects of Cell Therapy

The possible effects of cell therapy have many phases, and they affect several sides of pathophysiological mechanisms of DM evolution (Berezin 2014). The possible therapeutic approaches of cell care in diabetics are presented in Fig. 3.1.

The possible approaches are:

- Restoring and renewing of pool of the functional β-cells from human stem cells
- Stimulation of the endogenous reparation processes
- A main result of stem cell transplantation is regulation of metabolic processes through production of both cytokines and growth factors

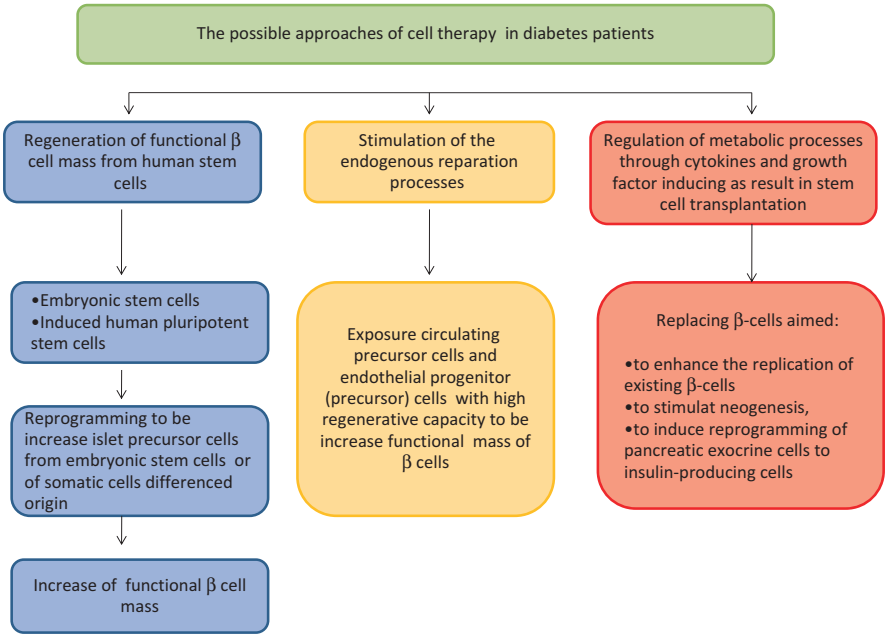

Fig. 3.1 The approaches toward improved clinical results in the diabetics enrolled for cell replacement therapy

3.3.1 Regeneration of Functional β-Cell Mass

Development of DM is characterized by the loss of functional pool of the pancreatic β-cells due to necrosis/apoptosis and negative autocrine/paracrine regulation that lead to progressive insufficiency in the insulin secretion (Holditch et al. 2014). The attempt to generate surrogate β-cells is widely used technology aim of which was to compensate the short supply of islets for transplantation to diabetics requiring daily short-acting insulin (Bhonde et al. 2014). Unfortunately, the poor availability of donor islets and high risk of rejection even within chronic immune suppression has severely restricted the broad routine clinical use of pancreas islet cell transplantation (Calafiore et al. 2014). Consequently, there is increased interest in islet cell that might obtain through neogenesis from stem cells' lines originated from embryonic or mesenchymal cells and then used as a translator for favorable responses in diabetics (Burt et al. 2002; Chen et al. 2014; Kojima 2014). The progress in our knowledge ragarding surrogate β-cells and β-cell like cells produced insulin has been mediating a use of ESCs, iPSCs, human perinatal tissues including peripheral blood mononuclears, cord blood, amnion, placenta, umbilical cord, bone marrow, pancreas, and postnatal tissues involving adipose tissue (Bhonde et al. 2014; Rabelink and Little 2013; Bhansali et al. 2009; Abraham et al. 2008; Burt et al. 2002; Lampeter et al. 1998). Although these progresses in derivation of β-cell-like cells from ESCs using reprogramming technology have taken a greater leap, the clinical implementation is limited due to controversies affecting human ESC rejection (Bhonde et al. 2014; Voltarelli et al. 2011).

3.3.2 Allogenic Pancreatic Islet Transplantation

Currently allogenic pancreatic islet transplantation is considered the most efficient method of regenerative care in DM (Nostro and Keller 2012). Transcriptional signaling mechanisms that are in vivo involved in pancreas reparation and islet pancreatic development are well-structured and closely controlled processes. In this context, up-regulated pancreatic islet transcripts in differentiating β-cell populations are required the formation of β-like cells producing insulin. Several clinical approaches toward reprogramming and differentiation of islet precursor cells from ESC base on regulation of the relevant transcription factor expression (Pdx1, Ngn3, Isl-1, etc.), some extracellular factors (Voltarelli et al. 2011), or lentiviral vectors (Jimenez-Moreno et al. 2015). These approaches might initiate creation of bioartificial pancreas, although a significant translation of similar idea into clinical application for T1DM and T2DM is not evident (Ludwig and Ludwig 2015; Khosravi-Maharlooei et al. 2015). However, the advantages in islet transplantation have exhibited a dramatic improvement in the 5-year insulin independence rates for diabetics (Khosravi-Maharlooei et al. 2015).

It was noted that there is another source for transplantation of exogenous human and nonhuman pancreas/islets or even artificial islets. However, any translational strategies regarding enhancing proliferation and maturation of endogenous β-cells, loss prevention of β-cell and β-like cells, or any methods regarding renewal of β-like-cell populations from ESCs and non-β-cells appear to be promised (Weir et al. 2011). Although currently used methods of regeneration enhancement of functional pool of β-cells from human ESCs appear as the most promising clinical approach for T1DM regenerative therapy (Lindahl et al. 2014), the cell replacement care regarding generation of unlimited sources of β-cells have been met with some sufficient limitations (Calafiore et al. 2014). As one, the purification procedure of desire cell population is a critical step to obtain enough portions of islet precursors needed to further cell-lineage selection (Soria 2001). The prevention of islets' loss in long-term prospective might need an immunosuppressant use (Jafarian et al. 2014).

3.3.3 Human Pluripotent Stem Cells

There are various ESC sources, which are considered as an appropriate resource of creating functional β-like cell generations in a safe and efficient manner (Fu 2014; Weir et al. 2011; Pandian et al. 2014; Soria 2001):

1. ESCs derived from surplus blastocysts reprogrammed for fertilization procedures in vitro
2. iPSCs created resulting in the reprogramming method of various somatic cells

The practical value of ESCs has been widely investigated during the last decade. At least two large clinical trials have recently completed, but clinical value of obtained results has become controversial (Philonenko et al. 2011). Although ECSs or adult stem cells, which were derived from various cell lines, may differentiate into β-like cells and restore the insulin production, they have represented the immune effects on the β-cells leading to their direct autoimmune destruction and destroying. (Calafiore 2014).

3.3.4 Induced Pluripotent Stem Cells

In this context, human iPSCs are discussed the most promising source for transplantation, because contemporary cellular reprogramming technology did not associate with immune modulatory ability of iPSCs did not represented immune modulatory ability (Bar-Nur et al. 2011). First iPSCs have been successfully derived from human somatic cells, i.e., dermal fibroblasts and keratinocytes (Soejitno and Prayudi 2011). It is known that redifferentiation of iPSCs into functional maturated pancreatic islets may modify disease progression through an increase of failing islet survival (Kudva et al. 2012). Importantly, the contemporary technology of iPSC

derivation from adult somatic cells completely excludes the exposure of embryonic cells. Currently, iPSCs have been derived from diabetics using integrating retroviral vectors that incorporate directly in the host genome (Reiland et al. 2011; Ma et al. 2013). In fact, various reprogramming systems are different in their ability to biosafety, and integration-free reprogramming systems are more modern and hazardless (Kudva et al. 2012; Sommer et al. 2012).

The discovery of novel technologies suggests seeking of possible approaches regarding generation of patient-specific iPSCs. Various reprogramming factors have been now identified as functionally acting molecules – the main role of which was to significantly improve the results of iPSC reprogramming procedure. However, prior to a clinical implementation of the iPSCs, a strong concerns about their specificity, kinetics, and safety is required. (Bai et al. 2013).

3.3.5 Trans-differentiation Procedure

Yet one of the attractive strategies for regenerative care is the trans-differentiation procedure based on the direct conversion of the single somatic cell to another type of cell (Ma et al. 2013). Recent studies have shown a new paradigm of trans-differentiation, i.e., using specific transcriptional factors to induce novel PSC generation through trans-differentiation or induce PSC trans-differentiation through transcription factors. The trans-differentiation procedure allows generating plastic intermediates synthesis, which may attenuate iPSC reprogramming and a wide range of tissue-specific precursor cells (Ma et al. 2013; Bai et al. 2013). Clinically based evidences are required to be disseminating knowledge about novel methods of iPSC trans-differentiation on routine clinical practice.

The results of the investigations regarding an ability of surrogate cells derived from ESCs to produce insulin in vivo have appeared to be controversial. It particularly relates to absence of the commonly used pretty accurate standard protocol. The currently implemented protocol represents the requirement regarding methods of derivation of the pancreatic progenitors from PSCs (Bar-Nur et al. 2011). Moreover, there are no commonly used essential criteria in helping determine number of in vitro generated β-like cells enough to further transplantation (Naujok et al. 2011; Naujok and Lenzen 2012). Therefore, human-derived bone marrow-originated mesenchymal stem cells (hBM-MSCs) may be considered as a source for reprogramming procedure of insulin-producing β-like cells. A specific protocol regarding the generation of insulin-producing islet-like clusters derived from hBM-MSCs has now been produced. (Jafarian et al. 2014). On this way, the platelet-rich plasma might attenuate the environment for further BMSC development and differentiation (Lian et al. 2014). It has been postulated that hBM-MSCs may be considered an optimal source for an appropriate transplantation procedure compared with iPSC, while large clinical investigations are required to obtain strong evidence regarding this item.

3.3.6 The Endogenous Reparation Process Stimulation

Recent studies have shown that the development of DM-related complications, i.e., critical limb ischemia, vasculopathy, peripheral neuropathy, accelerating atherosclerosis, and neuropathic diabetic foot, closely associated with dramatic decline of number of PSCs, circulating precursor cells (CPCs), and endothelial progenitor cells (PCs) (Russ et al. 2015; Berezin 2016c). Stem cells (SCs) play a central role in the precise regulation and an appropriate provision of the organism development at the embryonic stage. Therefore, SCs represent their direct potency in tissue regeneration and an ability to regulate innate mechanisms of endogenous reparation in adult life period (Sener and Albeniz 2015). Indeed, SCs have exhibited a high potency to differentiate into a wide spectrum of the cells and also to provide several soluble circulating transcriptional factors, which are required for tissue regeneration and maintenance of repair systems (Sener and Albeniz 2015). In fact, there are evidence that the SCs exposure might be effective through modulating inflammatory changes, tissue remodeling, extracellular matrix renewal, attenuation of cell migration, and maintenance of angiogenesis/neogenesis. It is reported that EPCs with immune phenotypes CD34+KDR+(VEGFR1) and CD31+133+ might have high therapeutic value in the healing process of neuropathic and ischemic lesions in DM (Sambataro et al. 2014; Shi and VandeBerg 2015). As it is expected, direct derivation of embryonic SCs to CD34+ cells might give a source for regenerative care in the future (Shi and VandeBerg 2015). The favorable effects of EPCs on target cells may associate with stimulation of the endogenous repair systems especially affecting the endothelium. The restoring of the endothelium structure and function may be deemed as a basis to improve natural evolution of DM and clinical outcomes in DM-related diseases, such as peripheral neuropathy, atherosclerosis, and critical limb ischemia (Berezin 2016d). In this context, the modulation of EPC-related signaling pathways may be useful for supporting trans-differentiation of the endogenous human SCs into functional β-like cells and mature endothelial cells (Mayhew and Wells 2010).

3.3.7 Regulation of Metabolic Processes via SCs

Replacing β-cells is frequently considered a simple way to enhance the population of pre-existing β-cells, stimulate angiogenesis, and reprogram pancreatic exocrine cells to β-like cells with ability to produce insulin (Berezin 2014). Cellular approaches based on SCs transplantation may also be useful for restoring the immune system response in T1DM or to attenuate insulin resistance and adipocytokines' abnormalities in T2DM. It has been predisposed that identification of novel transcription factors and development of strategies for their modulation could lead to effective regeneration of functioning pool of pancreatic β-cells (Soria 2001; Pandian et al. 2014; Weir et al. 2011). Other promising soluble circulating factors, which could translate the effects on SCs, are cytokines and growth factors, but their clinical significance in diabetics is not yet clear and requires more investigations.

3.4 Results of Preclinical Studies of Stem Cell-Based Therapy

The first experience in the treatment of DM with using cell technologies was based on employment of the native SCs, as well as unfractionated or enriched in subpopulation PCs, while the next generations of cell delivery, i.e., directly reprogramming SCs, human bone marrow-derived mononuclear cells; lineage-specified PCs, are discussed as a more prospective cell resource, which appears to be much more promised for cell therapy.

3.4.1 Reprogramming Stem Cells

Therapeutic cloning of cells has now entered a new era in cell recruiting and reprogramming procedures in clinical settings. The novel approach has become affordable and assessable in the treatment of DM (Kang et al. 2010). By now commonly used essential requirements and regulatory approvals regarding clear design of SC use and recruitment of SCs for further reprogramming have been created (Zhou and Ding 2010). Apart from SCs suitable for reprogramming, it discussed ESCs and multipotent adult SCs/PCs derived from various tissues, i.e., pancreas, peripheral blood, intestine, liver, bone marrow, brain, etc. (Nsair and MacLellan 2011).

There is a large body of evidence regarding clinical exposure of some recombinant proteins and/or several pharmacological-active drugs that might initiate and then support the reprogramming process in the target cell population (Burns et al. 2006; Tancos et al. 2012). Various approaches including nonintegrating, nonviral, and nongenetic methods have been developed for generating clinically compatible iPSCs (Tancos et al. 2012). The are some conditions that have now been determined in vitro in which cell pluripotency is maintained, and even an ability to differentiate to specific somatic cells is desired (Lu and Zhao 2013). Hindley and Philpott (2013), summarizing our knowledge of the possible links between the core cell cycle machinery and the maintenance of iPSCs pluripotency, have emphasized that some advantages of therapeutic non-β-cell cloning includes low rate of the autoimmune reaction after transplantation (Teng et al. 2013). Although a strict similarity of iPSCs with ESCs is determined, the efficacy of reprogramming procedure is now low. Recent study performed by Soejitno and Prayudi (2011) has revealed that a typical reprogramming event may count only 0.01–0.1% of the entire cultured cell population. In fact, the establishment and design of SCs bank is discussed widely (Taylor et al. 2011). However, human iPSCs have demonstrated enormous clinical potency, which may affect their unique capability to self-renew and their innate ability to self-differentiate into all cell types when compared with human ESCs

(Yeo amd Ng 2011). However, whether or not reprogrammed iPSCs have remained fully pluripotent at long time, it is not yet clear (Kang et al. 2010).

Little is known about the importance of the abovementioned advances of iPSCs for developing a new treatment strategy in DM (Fu and Xu 2012; Jiang et al. 2014). It has been postulated that the nature of the pluripotency is under a tight mutual counter-regulated control of genetic and epigenetic mechanisms. It is unclear whether the pluripotency is essential for an increase in the efficacy of cell transplantation or there is no usefulness in pluripotency in safety at long time (Kao et al. 2008). All these unresolved issues should be addressed to further large investigations.

3.4.2 Bone Marrow-Derived Mesenchymal Stem Cell Replacement

Since the first derivation of ESCs and iPSCs, the safety of clinical application of the cell therapy has been come under watchful gaze. Recent benefits in reprogramming regarding transgene-free iPSC have taken into consideration the potential of implementation of the PSC differentiated from different populations (Jung et al. 2012). Care with mesenchymal-originated PSCs is an extremely fast-growing method of regenerative medicine that has now proven their high safety and efficacy in the therapy of various states and diseases. Human bone marrow mesenchymal SCs (hBM-MSCs) are a self-renewing pool of the multipotent cells that is able to migrate to the sites of the pathological process and then mediate regenerative effect in situ. Animal model of T2DM showed that a 6-week period after successful hBM-MSC transplantation was associated with a sufficient decrease of the fasting blood glucose and lipid plasma levels. Additionally, the circulating C-peptide level was significantly increased (Pan et al. 2014). El-Tantawy and Haleem (2014) have reported that use of the autologous BM-MSCs has significantly prevented alterations of tissue and markedly attenuated alloxan-induced oxidative stress in albino rats with DM. Authors believed that BM-MSCs may be helpful in the prevention of diabetic complications associated with oxidative stress.

Tang et al. (2014) have studied the effect of autologous BM-MSCs in miniature pigs with established streptozotocin-induced DM. The obtained results have showed that BM-MSCs transplantation may prevent natural evolution of DM in animals that is associated with restoring blood glucose, serum insulin, and C-peptide levels, as well as attenuation of the oral glucose tolerance test and an increase in the islet numbers. These data suggested the implantation of autologous BM-MSCs for T1DM may partially improve a glucose homeostasis through restoration of the pool/function of β-cells and attenuation of the pancreatic microcirculation. Overall, the majority of the investigators believe that the BM-MSC transplantation is a safe and

an effective procedure with great long-term prospective regarding clinical evolution of DM (El-Tantawy and Haleem 2014; Tang et al. 2014).

3.5 Clinical Efficacy of Stem Cell-Based Regenerative Therapy

There are controversial results regarding clinical efficacy of SC therapy in T1DM and T2DM patients (Matveyenko and Vella 2015; Moore et al. 2015). In prospective, open-labeled, two-armed study in T1DM (n = 20), Thakkar et al. (2015) have infused allogenic and autologous adipose-derived insulin-secreting mesenchymal stromal cells (IS-AD-MSCs) in combination with bone marrow-derived hematopoietic stem cells (BM-HSCs). Authors have concluded that co-infusion with the use of autologous IS-AD-MSCs and BM-HSCs have appeared to be a better method for long-term control of hyperglycemia when compared with isolated allogenic SC therapy. Surprisingly, allogenic SCs infusion has exhibited very varied effects on fasting glucose level, while safety of the treatment was good. In similar small studies, it was shown that the implantation of mesenchymal stem cells may lower glucose levels via paracrine-mediated influences rather than through direct transdifferentiation of transplanted precursors into β-like insulin-producing cells (Katuchova et al. 2015; Dave 2014; Ezquer et al. 2008). As it is expected, BM-HSCs may represent pro-angiogenic and immunomodulatory effects that might be useful to improve metabolic control in DM, especially when there is coadministrated transplantation BM-HSCs with pancreatic islets (Trivedi et al. 2008). Probably similar approaches might have more efficacy and safety.

3.6 Limitation of the Regenerative Therapy

Because T1DM is considered a chronic metabolic disorder characterized by targeted autoimmune-mediated β-cell destruction, there are some limitations regarding successful transplantation of both pancreatic islets and SCs (Xiao et al. 2014). By now, the islet transplantation in T1DM has been determined as the curative therapy only. Yet, there are several technical limitations regarding donor shortages and cellular damage that may appear within the isolation process and critically limit the further exposure of cultured cells (Jun et al. 2014). However, there is a method created for successful islet transplantation and based on coculturing single primary islet cells with adipose-derived stem cells (ADSCs) in concave micro wells. It has suggested that ADSCs may protect islet cells from damage and increase their survival in the culture prior to transplantation. In animal model xenotransplantation of microfiber-encapsulated spheroids has shown that coculture-transplanted mice maintained their blood glucose levels better than monoculture-transplanted mice. Moreover, it needed sufficiently less islet mass to reverse DM. Jun et al. (2014) have reported that the method for culturing islet spheroids might became a novel step in

creating bioartificial pancreas. However, exaggerated immunogenic capacity and potent tumor-induced capability of transplanted cells have remained serious reasons for clinical implementation, while iPSCs, ADSCs, and BM-MSCs might be considered as a future of regenerative care (Schuetz and Markmann 2015).

3.7 Expectancies of Cell Replacement Care in Diabetics: From Bench to Bedside

It is well known that all forms of DM associate with the loss of pool of insulin-produced cells. In this context, the replacement of β-like cells, pancreatic islet, and iPSCs might be argued as a way to attenuate the natural evolution of the DM through improvement of metabolic control (Schroeder 2012). On the other hand, the metabolic abnormalities in DM do not limit a loss of insulin production. The results of the preclinical studies have supported an idea that the cell replacement might improve the entire regenerative potency including islet restoration and prevention of the metabolic memory phenomenon in target cells. Interestingly, the regenerative paradigm has been involved in various clinical settings appearing to be related to cultured SC platforms (Kojima 2014), while contemporary techniques for human ESC generation are known as genetically diverse, patient-specific, or disease-related SCs (Deng 2010). However, the efficacy of the several methods regarding standardization of cell isolation, the conversional nuclear transfer and delivery protocols have now assayed as very low, and the safety of the procedure has remained under discussion and evoked a serious concern even for iPSCs (Hao et al. 2009; Naujok and Lenzen 2012). Moreover, Soejitno and Prayudi (2011), thinking about SC application in several clinical setting, have determined limiting factors, which explain an increased risk of complications after cell therapy. Consequently, the use of retroviral or lentiviral vectors, coadministration of cMyc oncogene, may associate with low efficiency of reprogramming, allogeneic immune rejection, other autoimmune response, and tumor formation resulting in pre-existing epigenetic signature of the target cells (Fu 2014). The resolve of these issues might be mitigated by a breakthrough in the contemporary technology in iPSCs (Fu 2014; Li et al. 2010).

3.8 Future Perspectives of Regenerative Therapy

The shortcoming benefits of the cell therapy in DM relate to implement in routine clinical practice the own patient cells, which are directly differentiated into β-like cells under influence of the specifically created reprogramming technique (Chen et al. 2014). On this way, the correct choosing of the cell source (i.e., adult cells of intestine, pancreas, liver, bone morrow) is discussed as a limiting factor which contributed in successful transplantation of functional insulin-producing cells because no transplantable pancreatic islets were now found (Kojima 2014). The next expectation is creating appropriate techniques that could help to seek the personally

patient-specific transcriptional factors required for islet regeneration and trans-differentiation of the target cells into β-like cells suitable for adequate insulin production (Jang et al. 2012; Boland et al. 2012). Currently synthetic DNA-based small molecule, which do not directly affect genome manipulation and allow to regulate and trigger epigenetic mechanisms, i.e., epigenetic enzymes or signaling pathways, of trans-differentiation of own cells into β-like cells with desired phenotype, have been found and broadly investigated (Sohn et al. 2012; Zou et al. 2012; Dadheech et al. 2015). Finally, protection of transplanted cells or renewal β-cells/pancreatic islets from destruction by immune reaction via discover of potent pharmacological agents appears to be promised (Lysy et al. 2012; Kim 2014).

3.9 Conclusion

Cell replacement therapy is considered a promising approach in the combined therapy of DM at the different stages of its evolution. The implementation of the novel technologies regarding isolation, sorting, culture, reprogramming, and trans-differentiation of SCs open serious prospective for achieving adequate control under metabolic abnormalities in all types of the DM, while several coexisting ethical and practical concerns require resolving in large clinical trials in the future.

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