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A review on StemCell Therapy for Diabetes Type 1 and Risk Factors

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ABSTRACT
Type 1 diabetes mellitus is one of several disorders that stem cell research in regenerative medicine has great potential for curing (T1DM). Replacement of -cells and management of the autoimmune response to insulin-producing cells should both be a part of any possible stem cell-based treatment for T1DM.Pluripotent cells from a variety of sources, as well as facultative progenitor cells from the pancreas and the liver, have been employed in ex vivo production of cells appropriate for transplantation to recreate a functional -cell mass. The most successful protocols to date have generated cells that express insulin and that closely resemble real insulin-secreting cells molecularly; nevertheless, these cells are frequently insensitive to glucose, a trait that needs to be addressed in future protocols.Clinical investigations for the modulation of the immune response using mesenchymal stromal cells or umbilical cord blood have already been conducted; however, conclusive results are yet awaited. This Review focuses on current methods for obtaining insulin-producing cells from various progenitor sources, highlights the key pathways and genes involved, and discusses several methods for modulating the immune response in T1DM patients.

Keywords
Pluripotent stem cell, embryonic stem cell, autoimmunedemolition, ectopicgrafting, progenitor cell,protooncogene protein

I. INTRODUCTION

Patientswith (t1Dm), distinguished by autoimmune demolition of the pancreatic cells that produce insulin,must use exogenous insulin to regulate their blood sugar levels. Even though the development of insulin has altered the situation considering the persistence of this set of people for nearly a century[1]. Patients with type 1 diabetes are nonetheless subject to difficulties related to diabetes from developing diabetic complications [2][3]. These problems are believed to be caused in part by a shortage ofmore significant physiological variations in insulin secretion glucose levels are higher than usual, therefore the hunt for efficient approaches to help patients regain a functioning -cell mass essential with t1Dm[4][5]. Human organ transplantation cadaveric human islets or the pancreas has permittedpeople with type 1 diabetes to develop insulin dependence and permanent treatment for type 1 diabetes must the cell deficiency and the autoimmune reaction to insulin-producing cells,as amply demonstrated by the transplanting in identical twins' segmental pancreatic transplants,the autoimmune response remains many years after disease onset.As a result, any -cell replacement therapy has some defence mechanism modification, whether by either medicine based on cell strategies.This evaluation mainly highlights the various approaches. Can generate insulin making, functional from cells a variety of progenitor cell kinds.The research aims to differentiate human stem cells into functional cells directly.However, some of these animal trials are shown here. Here, examples of human being stem cells being directly differentiated into functional cells are described.

From stem cells to β cells, there are many paths to take.

Efforts have been made to create effective techniques for convertingadult orembryonic stem cells into functional insulin-secreting cells. Many of these findings must be qualified becausespecificdeveloping pathways produce insulin-secreting cells that mature into real cells, such as cells in the foetal liver, brain and yolk sac[6]. A βcell's haveability to retain vastquantities of secreted insulin in a controlled response to a requirement in a certain way, such as stimulating glucose production, should be the defining characteristic of the cell.

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Human embryonic stem cells

Understanding the beginning stages of endoderm synthesis in human embryonic stem cells(HESCS)manufacturing has been based on the principles of normal embryonic development The first step in distinguishing of human embryonic stem cells(hesCs) into cells is the creation of particular endoderm[7]. visceral endoderm, which expresses the same indicators but produces different tissues[8]. Forkhead box protein A2 [FoXa2] and sex-defining region Y box [SOX](12) are two of these indicators. The transforming growth factor (TGF) and wntsignaling pathways, which are both developmentally active, must be replicated [9][10]. It is necessary to use the most recent methods for hesC cell differentiation. HesCs have been utilized to induce the differentiation of cells that express the transcription factor via activin A, fibroblast growth factor (FGF), and retinoic acid. PDX The following proteins are also used to identify definitive endoderm: SoX17, brachyury protein, FoXa2, CXC-chemokine receptor (CXCr), and Cerberus. Controlling hesC differentiation has been the subject of research into microscopic substances that can modify signal transduction pathways, gene expression, or metabolism. Both mouse and human esCs have successfully been used to stimulate the development of definitive endoderm.[11]. Large concentrations of these tiny compoundsendoderm expressing numerous endodermal markers were produced. Inducers with small molecules would be less expensive. Easier to manipulate and extra efficient than growingagents for directing differentiation. The afterwardsphase is to replicate the creation of the pancreas dorsal anlage in vitro, which relies on simultaneous retinoic acid signalling and Hedgehog signalling suppression, both of which have been successfully replicated[12]. In response to FGF10, retinoic acid and inhibitors of Hedgehog signalling endoderm cells generated by IDE2 and IDE1could grow into pancreatic progenitors in vitro. Furthermore, the little chemical indolactam v was applied to endodermal cells and caused pancreatic progenitor cells to express PDX1 at a rate of >45%. Protein kinase C signalling is induced by indolactam v, the same pathway that is activated following treatment withWnt3a

Induced pluripotent stem cells

induced pluripotent stem cells (iPS) have emerged as a thrilling possible unconventional to human embryonic stem cell(hesCs),[13]whose usage in research and clinical settings is still restricted in many countries. Clinical settings Through the use of specified parameters, it has been made possible. Pluripotent stem cells can be generated from somatic human cells. Giving human somatic cells the Pou domain class 5 allowed the creation of induced pluripotent stem cells from human and mouse cells. Also known as an octamer-binding transcription factor, transcription factor 1, Kruppel-like factor 4 (KLF4), mYC protein protooncogene (c-mYC), NANOG, and soX2 with combinations of Kruppel-like factor 4 (KLF4), nanoG, and lin-28 homolog A (LIN28). Oncogenes c-mYC and KlF4 are increased. Concern has been raised about the ability of induced pluripotent stem cells to cause tumors. The introduction of valproic acid, a histone deacetylase inhibitor, which enables reprogramming of primary human fibroblasts with only two factors, has solved this difficulty, oCt4 and soX2, thus making therapeutic use of reprogrammed cells potentially safer and more practical[14]. When the transcription factor genes were first delivered by retroviruses or lentiviruses, there were worries that viral integration into the host genome would increase the risk of tumorigenicity. New procedures were used to repeatedly transfect expression plasmids, resulting in iPs cells that showed no signs of plasmid integration[15].The question of whether iPs cells are actually similar to hesCs in terms of pluripotency has not yet been fully clarified, Despite the fact that the protocols for this reprogramming are rapidly evolving and no longer need the use of viral vectors and oncogenes. Additionally, the reprogramming factors oCt4, soX2, nanoG, and LIN28 have been overexpressed by lentiviral vectors to produce iPs cells from umbilical cord blood[16]. The efficiency of reprogramming was on par with that of keratinocytes and fibroblasts. Considering that umbilical cord blood is a source of juvenescent cells, using it allays concerns about employing adult somatic cells, which could undergo mutations over the course of an organism's existence.

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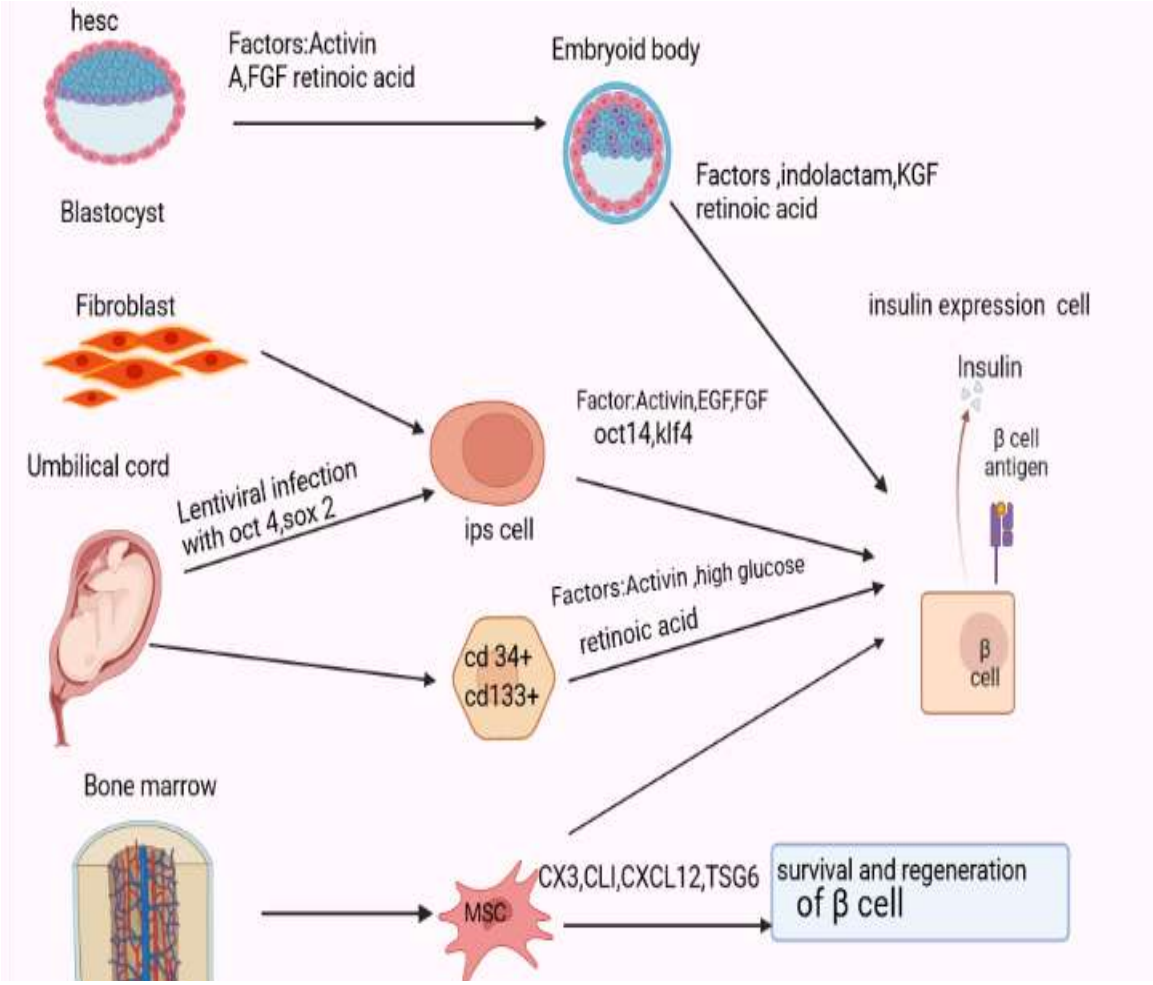

Figure 1.generating insulin-producing cells from pluripotent stem cells.

Different differentiation techniques recreate the cell development that occurs during embryogenesis. Despite the fact that robust insulin secretion in response to glucose has only been shown in hESC-derived insulin-positive cells, reprogramming fibroblasts and umbilical cord cells into iPS cells may represent a method to obtain a renewable and easily accessible source of undifferentiated cells that can provide accurate disease models in vitro and may eventually lead to a cell-derived therapy for T1DM. Although the ability of MSCs produced from bone marrow to produce insulin-expressing cells is unknown, they can aid in cell survival and regeneration. c-MYC stands for the Myc proto-oncogene protein; CX3CL1 for CX3C-chemokine ligand 1; CXCL12 for CXC-chemokine ligand 12; EGF for fibroblast growth factor; hESC for human embryonic stem cells; IDE for induce definitive endoderm; iPS for induced pluripotent stem cells; LIN28 for lin-28 homologA; and MSC for TSG6, tumour necrosis factor; SOX2, transcription factor sex determining region Y box; T1DM, type 1 diabetes mellitus; MSC, mesenchymal stromal cell.

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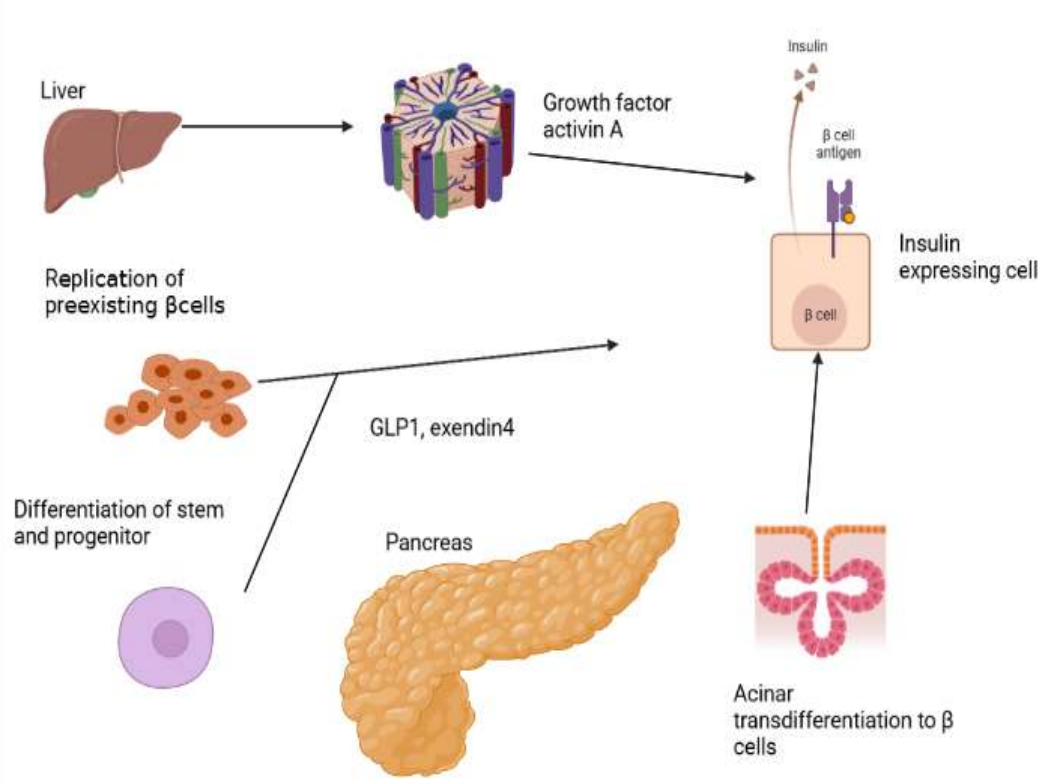

Figure 2. Methods for obtaining β cells from progenitor or stem cells that are unique to an organ.

New insulin-expressing cells can be produced by the pancreas itself through repetitionof pre- existing cells and acinar tissue's transdifferentiation inside cell, the progenitor or stem of the pancreas differentiation within the ductal pancreatic endothelium stem or progenitor differentiation within the ductal epithelium cell development. a different resource for embryological similar material that has undergone transdifferentiation into insulin-expressing cells is the liver.EGF, short for epidermal evolution agent; GLP1, short for glucagon-like peptide 1 HGF, short for hepatocyte growth factor; hESC, short for cell lines from human embryos; iPS, short for made programmable stem cells; LIF, short for leukaemia restrainedagent; NEUROD1, short for brain-derived differentiation factor ; NGN3, short for neurogenin3

Umbilical cord blood

Umbilical cords can be a prospective and easily accessible source of blood stem cells in addition to being used to make iPS cells., also known as stromal mesenchymal cells (msCs),which have been studied for their potential to modulate immune responses in t1Dm patients as well as their capacity to produce cells that express insulinIn vitro, islet-like masses created from mesenchymal stromal cells (MSCS) discovered in the human umbilical cord only moderately produced insulin[17]. According to the more focused method of flow cytometry,navel string blood cellsthat display CD133 and CD34, However, insulin secretion and content were not examined using immunohistochemistry[18]. When analyzing these studies, keep in mind our prior warning concerning what constitutes a "cell

Bone marrow-derived mesenchymal stromal cells

Since bone marrow-derived cells, such as msCs, have been shown to differentiate into a variability of lineages and are readily obtainable, they represent an appealing source for regenerative cell-replacement procedures with relation to t1DM. By raising serum insulin levels and decreasing hyperglycemic patients' blood glucose readings, bone marrow-derived cell transplantation improved the metabolic condition and longevity of recipients[19]. rats with streptozotocin-induced pancreatic tissue destruction.A detailed histological analysis of the pancreas of these animals revealed that cells transplanted from the bone marrow homing to the site of pancreatic injury and

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encouraging the development of insulin-optimistic recipient-derived cells, perhaps via secreting endothelial precursor cell products. On the other hand, a number of articles assert that cells originating from bone marrow can self-differentiate into insulin-positive cells[20],But there's still debate concerning this change in cell lineage. after streptozotocin treatment in cavy, pancreatic islets. In the last model, up to 3% of the human msCs, that were injected could be transplanted into the pancreas and up to 11% of the infused cells could be transplanted into the kidney. This finding implies that even though no cells were discovered in the spleen, liver, or lung. In the double wounded organs in the diabetic mouse model, the highest levels of engraftment were seen. The release of chemicals from pancreatic islets, which accelerate msC migration through a process mediated by CX3 C- chemokine ligand 1 and CXC chemokine ligand 12[21], may help to explain this preference of bone marrow-derived msCs for injured regions. A tissue milieu that promotes -cell activation and survival is thus hypothesized to be created by the cytokines released by msCs. According to preliminary findings, treating t2DM may also benefit from this strategy., after getting a bone marrow stem cell injection of autologous blood, patients with t2Dm had improved metabolic control and decreased insulin needs after a year. Although this study shows that msCs can theoretically enhance glycemic control, its use as a regular t2Dm treatmen is improbable given the price and dangers associated with this operation. Intravenous administration of msCs to mice reduced myocardial infarction even in the presence of lung cell emboli, according to an interesting study. suggesting that engraftment may not be required for human msCs to increase tissue healing.TNF-inducible, an anti-inflammatory protein, was released by the activated embolized cells.

Organ-specific stem or progenitor cells

The benefit progenitor cells or stem cell that are specific to an organ is that they are assigned to a particular differencepassageway which theoretically, would require less in vitro processing than using less committed pluripotent stem cells to produce completelyuseful cells. From adult rodent pancreas, There have been discovered to be putative multipotent and clonogenic pancreatic stem cells. Although it has been demonstrated that cells produced from these precursor cells express low concentrations of insulin mRNA produced ex vivo[22], and their relevance to the bulk of cells has not yet been determined.There have been reports of cells in the pancreatic ducts that resemble the liver oval cells, but it is still unclear what these cells actually are or what they do.

Duct epithelial cells

It has been proposed that the primary source of stem cells fot the evolution and restoration the pancreas is pancreatic duct epithelial cells[23].Genetic lineage tracing studies have revealed that after birth and after damage[24], the population of cells is significantly influenced by cells that express carbonic anhydrase II inside the ductal constructions.In a different study it was discovered that limited duct ligation in grown mice activated nGn3-manifestation cells close to or inside the ducts, which helped create additional cells. These results suggest that in living animals, cells inside the ducts, whether all epithelial cells or simply a subset, have the capacity to function as pancreatic progenitors.. To create insulin-expressing cells, rodent duct cells were modified in vitro. For a week, monolayers of 1–3% of the pancreatic cell aggregates from transgenic mice that release GFP when the mouse insulin promoter is activated were cultured. The cultures had 1.9 percent of the insulin mRNA seen in pure GFP-positive cells[25]. after differentiation.GLP1 and exendin-4[26][27], activin A, hepatocyte evolutionagent, or betacellulin, as well as tissue accumulation in pancreatic duct cell lines are all examples have all been found to induce the induction of insulin expression. After islet isolation, human pancreatic tissue that was left over was grown with FGF7, which directed to the creation of islet-like structures and an increase in the 10 to 15fold levels of insulin and glucagon mRNAs.What's more, these brand-new insulin-positive cells had the typical islet cell ultrastructure and were responsive to glucose Other studies have also demonstrated how to manipulate these cells to produce cells using growth factors as GlP1, gastrin, and epidermal growth factor(EGF), which supports their capacity to develop into useful cells.These insulin-positive cells' ductal origin was established using human ductal cells that had been extracted utilizing the antibody to the carbohydrate antigen 19-9 and immunomagnetic beads that were grown and administered to animals with impaired immune systems.

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Acinar cells

Since they both derive from the same progenitorThe majority of the cells in the pancreas are acinar cells and endocrine cells[28]. It's possible that acinar cells can be used as an in vitro source for the dedifferentiation-induced differentiation of cells into insulin-expressing process that depends on notch signalling[29].Initial research revealed that human exocrine pancreas acinar cells had the capacity to transdifferentiate into duct cells that were mucin 1-positive, cytokeratin positive, and amylase-negative[30]. Rat exocrine cells treated with a mixture of EGF and leukaemia inhibitory factor after adjustments to the cell growth environment produced functioning cells.The normoglycemia of diabetic mice[31], might be recovered in vivo using these exocrine-derived cells. More research projects using genetically modified, cultured mouse acinar cells acinar cells ability to change into ductal-like pancreatic precursors was demonstrated similarly . however, these precursors did not develop into pancreatic ducts. Yet another tactic entails direct reprogramming or acinar cells undergo in vivo transdifferentiation to become cells. Delivered by adenoviral vectors that contain certain copy factors PDX1, nGn3, and maFa) to the murine pancreas parenchyma.like cells with insulin positivity increased in size and ultrastructural features after triple adenoviral transduction, yet these cells only remained 20% Neither did they create islets, nor did they merge with them. In spite of this, these cells raised the fasting glucose levels. Animals with hyperglycemia[32].Given the apparent direct transition from one differentiated phenotype to another, which was claimed not to need cell cycle activation or dedifferentiation, this method may have a reduced risk of tumour development than one that uses a self-renewable, pluripotent cell type. Non-viral carriers for the transport of molecules are a worthwhile alternative to viruses, which raises questions concerning insertional mutagenesis and tumour initiation.

Liver cells

Additionally, liver cells are thought to be a desirable source for into functional cells because they share the expression of many specialized genes with pancreatic cells,.Additionally they have a common embryological ancestor with pancreatic cells and the primitive foregut which allowed them to develop transcription factors, glucose transporter type 2 and glucokinase.Several investigations that have either in vivo or in vitro virally presented various pancreatic copy factors into the liver have demonstrated some introduction of the phenotyp of βcells[33]. Using a lentivirus vector containing PDX1. retrovirally immortalized human foetal liver progenitor cells were successfully differentiated into cells that express insulin when transplanted into diabetic mice[34], these cells had a phenotype that resembled beta cells responded to glucose and helped to bring about euglycemia.

Somatic stem cells

Multipotent somatic or adult stem cells are present in differentiated tissues (SSC). These cells' natural function is to replace missing cells[35], in aging or damaged tissue in order to preserve and regenerate it. These undifferentiated cells are, in general, present throughout the bodies of both juvenile and adult animals and humans. SSC can be divided into numerous groups according on their morphology, cell surface characteristics, tendency for differentiation, and/or tissue of origin. Instances include mesenchymal stem/stromal cells (MSC), endothelial progenitor cells, and hematopoietic stem cells (HSC)and endothelial progenitor cell (EPS). However cord blood and bone marrow are two sources that are widely used as sources of SSC for stem cell therapy despite the fact that SSC can theoretically be separated from a wide variety of tissues. Adipocytes which have recently seen increased use. From diverse regions of the adult brain and spinal cord, neural stem cells have been extracted The ability of somatic or adults stem cells to divide or self-renew indefinitely and to differentiate to produce all the specialized cell types of the tissue from which they created has attracted the attention of scientists.

Foetal stem cells

A relatively novel type of stem cell is included in the group of foetal stem cells (FSC)[36], which can originate from either the foetus or from other embryonic tissues of foetal origin. Foetal stem cells are not the source of teratomas. Different kinds of fetal stem cells have been found, depending on the tissues from which they arise (such as amniotic fluid, placenta, etc.)

Stem cells and autoimmunity

The challenges of successfully using stem cells to treat type 1 diabetes The is not merely in producing functioning cells but also in overcoming the immunological response, including autoimmune and tissue rejection. The development of safe and efficient cell-based immunomodulation

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therapy comprises procedures including dermal heat-shock protein, i.v rabbit polyclonal anti-t-cell globulin, or intravenous humanized antibodies against CD3 (a subunit of the t-cell receptor complex)[37]. Despite the fact that several of these studies demonstrated effective short-term cell function preservation, only a small percentage of patients no extendednecessary insulin treatment.The most secure and productive immunomodulatory therapy would most likely incorporate a variety of techniques. Due to their ability to treat autoimmune disorders including type 1 diabetes. It may be beneficial to use bone marrow-derived msCs, umbilical cord blood cells, and. that of the immunological system. 12 of the 20 individuals in this study who ceased using insulin after receiving treatment for an average of 31 months with Hba_{1c} levels below 7.0 percent. Given the success of the current insulin-based treatment, this study was uncontrolled and extremely aggressive due to the use of the immunosuppressive drugs cyclophosphamide and antithymocyte globulin, which increased the risk of acute drug toxicity, infections, and sterility and may have outweighed the benefits. This study was contentious despite the shocking outcomes. In a different cell-based therapy, autologous umbilical cord blood is employed as a source of immunomodulatory cells since it has a significant population of immature, highly functional regulatory lymphocyt that can reestablish normal immunological regulation. Through this infusion, the effector T cells involved in cell-mediated autoimmunity may be rendered inactive, which could help reduce the inflammatory cytokine response. Patients with t1Dm (average age 5 years) who had saved autologous cord blood were participating in an ongoing pilot trial on the safety and effectiveness of autologous umbilical cord blood infusions shortly after the onset of the disease. Before administering the umbilical cord blood infusion, the children received no chemotherapy or other conditioning treatments.. There have been 15 autologous infusions administered thus far without any negative side effects. The preliminary findings of the seven children may suggest the use of a kill gene method, such as thymidine kinase, to eliminate undifferentiated cells; however, this approach would require genetic modification of the entire cell population and extensive research to ascertain the efficacy of the elimination of undifferentiated cells. As an alternative, the cells that are produced could be placed in macro- or microcapsules. Such encapsulation could also be helpful to stop cells from interacting with the host resistance system.

Stem cells and tumorigenesis

the use of cell lines or stem cells raises significant safety concerns. Before being transplanted into the patient, these cells go through numerous rounds of replication that could result in the build-up of chromosomal aberrations that could be carcinogenic. The p53 pathway could be activated by cell reprogramming as a reaction to stress[38]. Inhibiting the p53 pathway is therefore necessary for effective reprogramming, but doing so could make the successfully reprogrammed cells more likely to develop cancers[39].Before stem cells may be employed in a clinical environment, methods to Prevent cancer must be developed, as evidenced by the discovery of a genetic link between reprogramming and tumours.Negative selection techniques or effective differentiation protocols should be used in these tactics to exclude undifferentiated cells from in vitro differentiated cultures because even a small percentage of undifferentiated cells in the differentiated cell population might induce teratomas.. Although undifferentiated cells can be removed by flow cytometry cell sorting in a research facility using cell surface markers, this approach is very unlikely to be successful. potentially involve the use of a "kill gene" technique, such as thymidine kinase, to eliminate undifferentiated cells; However, in order to assess the efficacy of genetically altering all cell groups, substantial research would be needed. An alternate approach would be to bundle the resultant cells in macro- or microcapsules. Such encapsulation may also be helpful to keep cells from coming into contact with the host immune system.

Risk factors

Numerous risk factors effect the hazards of stem cell treatment. A hazard is well-defined as the product of the likelihood that harm .will occur and the seriousness of that harm .A possible source of injury is what is meant by a risk factor or hazard .The kind of stem cells employed their history of collection and culture, the degree of adjustment, and insertion site are a few samples of hazard factors. The dangers connected with various stem cell-based medicines may vary greatly as a result of the set of hazard factors. For a proper benefit/risk analysis of a stem cell-based medical product, all important identified risks (dangers or adverse events documented in clinical experience) as well

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as potential/theoretical risks (e.g. non-clinical safety) must be taken into account. There are various risk factor categories that can be found. First, the extrinsic risk factors resulting from the acquisition, handling, culturing, or storage of the cells will be discussed, followed by the extrinsic risk factors resulting from the clinical characteristics of the cells (such as surgical procedures, immunosuppression, site and mode of administration). Co-morbidities,etc.). It's critical to realize that if numerous risk factors from these distinct categories are present, a patient's risk may rise. The risk of novel stem cell-based therapeutics might theoretically be assessed using knowledge of potential risks and hazards gained from utilizing other/current stem cell-based medications. We'll start out by talking about the potential for growing a tumor. Each of these distinct factors, which is described in a separate paragraph, will be studied in relation to the likelihood of getting a tumor. The likelihood of immunological reactions, particularly in the context of allogeneic stem cell transplantation, is the second area of worry. The third-ranked danger is the transmission of human diseases and unintentional agents. The risks associated with potential additional risk factors for patients are also unknown.

1. Tumour formation

Some characteristics of cancer cells, such as a long lifespan, a low rate of apoptosis, and a propensity to metastasize, are shared by stem cells.As a result stem cells may be thought of as prospective candidates for cancerous transformation. Furthermore, the maintenance [40],of stem cells and cancer share comparable growth regulators and regulatory mechanisms . This may be the reason why the growth of tumors is commonly considered a major impediment to the safe application of stem-cell-based medications.Pluri or multipotent stem cell potency is a crucial element influencing the risk of tumour development . The tumorigenic potential of stem cell-based therapeutic products, however, also depends on these internal and extrinsic risk factors, including the site of delivery (i.e., the recipient's local environment for the stem cell) and the necessity for in vitro cultivation. the cellular reprogramming A donor-derived multifocal brain tumor was recently discovered in a 13-year-old boy patient with ataxia telangiectasia four years after the patient underwent a neural stem cell transplant. The sort of tumor that underwent biopsy was determined to be a glioneuronal neoplasm. The tumor was not of the host's origin, according to analysis, proving that the neural stem cells that had been implanted were its source. The tumor came from at least two donors[41], according to microsatellite and HLA studies..The periventricular tissue from babies aborted between weeks 8 and 12 provided the neural stem cells that were employed. After three to four passages, the cell population was employed, and the entire culture process took 12 to 16 days. In each treatment, 2-3 cc of 50-100 106 cells from 1-2 foetuses were administered, either directly injected into the cerebral white matter.

2. ex vivo stem cell culture

Since ESC and iPSC are naturally tumorigenic while they are in their pluripotent stage, in vitro differentiation is necessary for these cells before they can be used in therapeutic settings.in vitro proliferation and/or distinction of stem cells for SSC before administering to a patient may be preferable in some situations. Due to stimuli from both inside and outside the cell, stem cell proliferation and culture in vitro can alter the stem cell's properties. Each cell partition has a minor possibility of introducing harmful mutations, and during in vitro culture, mechanisms to fix these modifications might not work at all (such as immune detection) or just partially (such as cell cycle arrest, DNA repair).Reproduction number alterations and loss of heterozygosity brought on by cell culture have been reported for Following prolonged in vitro culture, spontaneous mouse cancerous morphogenesisMSC has been documented .Also described is the unplannedalteration of mouse brain precursor/stem cells .These altered cells generated tumours in vivo after being injected into animal brains, and their presence was discovered after about 10 cell culture passages. Investigations have also been made towards human MSC transformation. Even after thorough genetic characterization[42]. no supportiveindication for the transformation of human MSC has been discovered autonomously by multiple investigators .Human MSCs have been observed to spontaneously convert in some publications . On the other hand, According to a number of these authors, the presence of changed cells in their human MSC[43]. culture was done so as to avoid the original cell culture from being contaminated with tumorcells..Therefore, it is still debatable if human MSC can develop into a cancerous cell type following in vitro cultivation, much like they can in mice. Chromosomal

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modifications have been noted in MSC cultures, including clinical grade cells .The aneuploidy of genetic material 5 in specific, and to a lesser extent of chromosomes 8 and 20, appears to be the focus of these karyotypic abnormalities frequently .It was proposed that the occurrence of aneuploidy might depend on the donor Fascinatingly, extended culture did not necessarily result in the persistence of the aberrant karyotype . Because karyotype analysis took longer than expected, MSC with karyotypic changes have occasionally been transplanted into human patients without causing cancer growth. Therefore It is possible to draw the conclusion that even if chromosomal aberrations were discovered during the in vitro cultivation of MSC, the potential of spontaneous in vitro malignant transformation is still up for debate. Although further research is urgently needed, it appears that human MSC are currently less prone to malignant transformation during in vitro development than murine MSC.

3. Genetic modification

Before being used in therapeutic settings, some stem cells (like iPSC) may need to undergo laborious manufacturing processes, such as genetic alteration or reprogramming. It is crucial to take into account the various iPSC generation techniques since, depends on the methods used particularhazard factors may be pertinent.iPSCs from mice or humans have been produced using retroviruses and lentiviruses.These viruses' genetic makeup has been changed to encode the genes needed for iPSC alteration. The employed viruses can incorporate into the cell genome by using this genetic reprogramming. As a result the cells' genomes may have several viral integration sites. In patients getting gene treatment for X-linked severe combined immunodeficiency, the use of retroviruses and lentiviruses creates safety concerns comparable to those that have been seen in those patients. About half of the chimeric mice produced with iPSCs [44].It has been shown that by integrating the reprogramming components deleted from the genetic material by elimination or transposase action, iPSCs can be produced utilizing a mediated approach. In turn this prevents the adverse effect associated with the integration of the reprogramming components .Theusage ofproto oncogenes and viral integration is not the merelyhazard factors that could cause cancer development after iPSC production. The epigenetic status of the chromatin [45],is also significantly and gradually altered by iPSC induction .It has been proposed that epigenetic modifications such as changes in the manifestation of oncogenes or cancer suppressor genes, can alter the tumorigenic potential of cells. However at the moment there is two additional methods are created to yield iPSCs with a lesserhazard of cancer development while avoiding viral incorporation.Firstly production of iPSCs has also been performed without viral integration using adenoviral vectors or plasmids that encode the required reprogramming components.. Second the production of iPSCs has been effectively accomplished using chemicals and tiny compounds. These methods rely on reprogramming factors that are endogenously activated, as was discovered for the reactivation of the Oct3/4 gene. Despite this, it should be highlighted that even in the absence of transgenes, minute plasmid fragments or chemically induced mutations may still arise.

4. Bystander tumour formation

Stem cells can both generate tumours and have an impact on how existing tumour cells[46]. develop and proliferate .One and only MSC has researched this. Studies conducted in vitro and in vivo have found that administering MSC to tumours inhibits it, speeds it up, or has no effect on it at all .The effect that is likely to be seen is dependent on the type of cancer cells, theproperties of the MSCs employed, the immune system's health, the time, and the location of the injection. It has been suggested that MSC may either offer supportive stroma fostering a conducive environment for tumour growth (see the section on immune regulation below) or MSC may lessen immunological rejection of the tumour cells, promoting ongoing tumour growth. There is no proposed cause for the sporadically reported reduced tumour development. The applicability of these findings for clinical application in humans is unclear because all of these studies were conducted in vitro or using animal models. Notably a difference in tumour growth between an in vivo and in vitro environment has also been found and has however, it is challenging to determine how likely this risk is.There are several ways to reduce the risk of tumorigenicity, distinguishing tumorigenic stem cells from non-tumorigenic stem cells (for example, by cell sorting on specific "tumorigenic" surface antigens) or promoting differentiation to lower the quantity of pluripotent or multipotent stem cells in the cell preparation.It should be highlighted that it may be difficult to locate truly precise antigens in practise to select the target cell population. Another strategy would be to

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deliberately destroy undesirable stem cells, for as by introducing a suicide gene creating killer antibodies that target stem cell surface antigens or using chemotherapy (hESC and iPSC are rapidly proliferating cells).

5. Adventitious agents

Terminal sterilization, purification, virus elimination and inactivation are inevitably excluded from the manufacturing of cell-based pharmaceutical productsthe usage of stem cells that are not autologous and/or have been cultured, has a significant hazard due to the use of stem cells that are not autologous and/or have been cultured virus and microbial safety. These dangers are present in all cell-based medicines and are not specific to stem cells. For stem cell lines that were primarilyproposed for study objectives rather than to be employed in therapeutic applications, donor history is very crucial. Reactions that are life-threatening or even deadly can result from the risk of bacterial, viral, fungal, or prion infections being transmitted from donor to receiver. There has been disease transmission reported following allograft surgery[47]. Other than the frequently used HCS, very little is known about how adult somatic stem cells might transmit disease. It has been shown through in vitro testing that MSC are susceptible to CMV and HSV-1 infection. Ex vivo expanded MSC derived from CMV positive individuals in good health, however, could not have any CMV DNA found using sensitive PCR techniques .There is no information in the scientific literature about pluripotent stem cells' vulnerability to accidental chemicals. Although tissue culture methods have improved, Still occasionally required are feeder layers and serum for the in vitro isolation and development of (pluripotent and somatic) stem cells. It is possible to increase the danger of disease transmission (such prion) and host immune system activation by biomolecules by using non-human feeder cells or animal products in tissue culture, such as foetal bovine serum (FBS) (such as non-human sialic acid).There is a chance that stem cell expansion in medium with added FBS could spread prion and viral infections and result in immunological rejection. An alternative that may be safer is autologous or donor-derived plasma. For FBS and might still permit appropriate cell differentiation and proliferation. In fact, it has been reported that switching from FBS to human platelet lysate causes accelerated/enhanced proliferation without genetic problems .However, because serum from elderly people has reportedly been shown to interfere with MSC function, using autologous patient serum may not be as advantageous. ability to differentiate and proliferate .When feasible The employment of a membrane between feeder cell and stem cell cultures or the isolation and cultivation of cells without the use of feeder cells, will increase the viral safety of the stem cell-based therapeutic product. With regard to their potential for application in humans, the majority of ESC lines still in use today were developed largely for basic research. These cell lines cannot have been isolated without feeder cells and FBS. Some of these ESC lines may soon be used in clinical settings, making the possibility of adventitious agent contamination a serious safety concern. It is not always simple to regenerate an ESC line in a safer environment for culture. though, as everysingle ESC line might be thought of as unique. As unintentional agents are tested for, the safety of stem cell-based medications will increase. Products with an unlimited capacity for cell division, such ESC or iPSC cell lines may be able to achieve this. While treating the patient and checking for the existence of adventitious agents simultaneously may not be possible with independently manufactured cell groups or SSC preparations (s). Because many stem cell therapies need immune suppression, the patient's vulnerability to contracting or reactivating (latent) viruses is another consideration in viral integrity. Immune suppressive medications could be necessary when employing allogenic stem cells, which can substantially weaken the host immune system. Herpes virus stimulation is critical because it makes allogeneic stem cell implantation more challenging in HSC transplants.

Other risk factors

Before using (stem) cells clinically, there are a number of additional risk considerations that should be taken into account. Only scant scientific data is available for the majority of these issues.

1. Biodistribution/Ectopic grafting

The (bio) scattering of the supplied stem cells is a significant risk factor. MSC have a history of homing to certain tissues, including the bone marrow, muscle, and spleen, particularly in pathological situations like ischemia or malignancy[48]. What causes MSC migration is still unknown. According to data, adhesion molecules, chemokines, and their receptors are all implicated. However, it has been observed that when utilized to treat myocardial infarction, only a

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small number of cells homing to the site of injury following intravenous injection (Injection into the myocardium or the coronary artery) .The fate of the non-engrafted (stem) cell and even when administered near the damage site, the engraftment level seems to be extremely less. and the dangers of their distribution to undesirable organs are also unknown. The engraftment of the stem cells at these off-target or remote places is one potential. As previously mentioned, the recipient's local environment may have an impact on the stem cells biological characteristics, although it is unclear whether or not these impacts could be dangerous. Given the scant information, the risk of such ectopic engraftment and its consequences should be considered.

2. Mode and site of administration

The potential high cell count required for the favourable effect of stem cell usage may be another danger concern. It is largely unknownnumber cells are required, but given the (very) less retention level and potential less cell survival, a significant number of cells may be necessary to get the greatest clinical benefit. Concentrated cell injections into tissue could have negative effects. Cells can group together, especially if they are passed through tiny needles and sheared .Following injection, these aggregates may result in pulmonary emboli or infarctions. The portal vein can be injected into, although this needs specialized (surgical) treatments that may come with additional hazards. Serious negative consequences resulting from difficulties with the procedure combined with Clinical experiences with HSC transplantation[49], have revealed the presence of illness states, such as veno-oclusive disease The application of the cells at particular sites (such as the site of injury) may also be useful, such as intracardially, however it may also require specialized techniques and/or surgery, both of which include risks, at the location of brain lesion or spinal cord injury.

3.undesirable (de)differentiation

As previously stated, it is doubtful that undistinguishableESC or IPSC will be employed in the clinic and that ex vivodistinction into a desirable phenotype will be required prior to injection. Dedifferentiation of stem cells may take place in vivo or in vitro , however this is not known. Although differentiation of somatic cells or differentiations into a different cell type have both been shown it is unknown whether these processes have negative clinical repercussions. Additionally, MSC There is evidence that certain mesenchymal cell types can differentiate into undesired ones like osteocytes and adipocytes. Animals given BM derived MSC for (induced) myocardial infarction[50]. have shown encapsulated formations in the heart that contain calcification and/or ossification. It follows that unwelcome differentiation is not merely a theoretical concern; yet, the causes of this risk are not identified. Distinctness or In principle, the culture of stem cells may also result in cellular changes including changed secretionmethod or cell surface chemicals maythat affect the ex vitro characteristics of the supplied cells. This could have unanticipated negative or harmful effect.

4. Purity and identity

Finding a untaintedgroup of the necessary stem cells is a crucial challenge that must be addressed.Unwanted outcomes could result from cell contamination[51], Alternatively, indistinguishable ESC from ESC-derived cells may be a cause of cancer formation Additionally, a number of papers that claimed MSC underwent spontaneous transition events have lately been retract due to the inability to replicate the stated observations. It was found that the original research used contaminated human fibrosarcoma cells HT1080 .These examples show that even relatively minor hazards should be taken into account. Of course, such inaccuracy should be avoidable by good industrial or good laboratory practises.

5. (Lack of) functional characteristics

Additionally, some stem cell therapies may come with dangers. For instance, myocardial infarction is treated with stem cells (MI).Arrhythmias are one of the major causes for safety concern [52].These were observed in some trials utilize stem cell-based therapy for the therapy of heart inability or myocardial infarction(MI), but not all of them .The type of cell that is employed and the method of delivery may affect the hazard of arrhythmias .These arrhythmias could be brought by insufficient differentiation or poor cell-cell interaction (seen ex vivo with MSC), a hyperactive state of the heterogeneous dispersion of action potentials, also known as MSC. Generally speaking, cardiac cell treatment projected to have many electrical effects, including Possibly destabilizing, while others are unmistakably advantageous.

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6. Donor and recipient clinical characteristics

That is a danger of stem cell-tissue refusal when allogenic stem cells are employed, although this risk may be (in part) mitigated by matching donors and patients, immunological using immune suppressants or sequestration each have their own disadvantages. There are many additional elements that could or might not increase the hazard associated with a clinical use of a stem cell-based medical invention. These may be either inherent properties of the stem cell-based medicinal product or more externalhazard agents connected to, for example, the product's industrialization process or kind of use. When stem cells are employed in an autologous environment, for instance, the underlying condition or treatment may have an effect on the quantity and performance of the stem cells which may result in an unintended side effect. Another illustration may be the secretion of (unknown or unknown) trophic agents and/or a diversity of progressagents by the stem cells[48].

II. CONCLUSIONS

One of the most treatable diseases with stem cells is type 1 diabetes. Replacing cells with new ones to attain independence from the necessity the for exogenous insulin therapy[53] has been demonstrated in principle byimplantation of complete pancreas or separatedisletsThe successful use of stem cell-derived cells in clinical practise is eagerly anticipated by patients and clinicians with t1Dm. Stem cell research continues to hold out promise for the creation of a sustainable reservoir of cells. The reprogrammable type of cell and the elements required to control the expression of a particular set of genetic factor that give the cell its distinct character are both taken into account by current differentiation techniques. There are still a lot of problems to be overcome before this strategy can be used as a treatment, even if there is a plentiful source of derived cells-stem cell with strong glucosreceptiveness. The maturation of insulin-positive cells in vitro is a significant problem that has to be addressed. The major function of cells, robust glucose-induced insulin production has only been detected in insulin-positive derived cells-hesc after several months of in vivotransplantation has. For usage in vitro, efficient functional maturation methods must be created As of right now, the amounts of C-peptide released by in vitro differentiated islet-like cells derived from iPs cells and hesCs are incredibly tiny when related to those of adult human cells. At current time, the use of iPs cell derived cells in -cell replacement treatment is not possible due to the use of viral vectors in their creation. Despite the determining of highly effective particles that drive this procedure in vitro, Problematic is the poor success rate of effective differentiation to functional cells . It is crucial to develop effective differentiation processes that boost the emergence of cellular sources of insulinand their capacity to respond to glucose. Despite the fact that there are still many obstacles to overcome, the rapid advancement of science and the ongoing developments in this field create the idea of an efficient stem-cell treatment for t1Dm a feasible objective for the near upcoming. Somatic stem cell therapy's early clinical results might be encouraging. However, there are still a lot of unanswered questions surrounding the potential hazards. The amount of information and understanding of the dangers related to stem cell therapy are growing. It is challenging to assume results from single study to another as well as from single stem cell-based pharmaceutical invention to another due to the wide variations between studies (e.g., study procedure, patient group, heterogeneity of the delivered cell number,location/timing of injection).At the moment, mesenchymal stem/stromal cells and hematopoietic stem cells have the most clinical experience. The endothelial progenitor cell clinical practice is more generally positive. As was already mentioned, iPSC have a larger perceived risk of developing tumours than ESC.Since the methods to produce these cells isstill and all rather novel and strategies to produce them furthersecurely are hastily improving.

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LIST OF ABBREVIATIONS

TIDM	Type I diabetes mellitus
HESCS	Human embryonic stem cell
TGF	Transformation growth factor
IDE	Induced definitive endoderm
IPS	Induced pluripotent stem sell
MSCS	Mesenchymal stem cells
FSC	Foetal stem cell
HSC	Hematopoietic stem cell
FBC	Foetal bovine serum
MI	Myocardial infraction
KLF4	Kruppel like factor 4
EGF	Epidermal growth factor
SSC	Somatic stem cell

Highlights Document

- Patients with type 1 diabetes are nonetheless subject to difficulties related to diabetes from developing diabetic complications
- A β cells have ability to retain vast quantities of secreted insulin in a controlled response to a requirement in a certain way, such as stimulating glucose production
- It's possible that acinar cells can be used as an in vitro source for the dedifferentiation-induced differentiation of cells into insulin-expressing process that depends on notch signalling
- Some stem cell therapies may come with dangers. For instance, myocardial infarction is treated with stem cells (MI)

Authors contributions

All authors agreed to submit to the current journal, provided final approval of the version to be published, made significant contributions to the conception and design, collection of data, analysis, and interpretation of data, participated in writing the article or critically revised it for important intellectual content, and agreed to be responsible for all aspects of the work.

Conflictof Interest

The authors have no known conflicts of interest.

EthicalAprovals

This study does not involve experiments on animals or human subjects.

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