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Review

The use of patient-specific stem cells in different autoimmune diseases

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ABSTRACT

Autoimmune diseases are developed when the immune system mistakenly attacks the body's cells. These inflammatory disorders can be inherited or triggered by external forces, such as type 1 diabetes, which is caused by the immune system's destruction of pancreatic beta cells. So far, stem cells such as hESC and iPSC have been used to treat autoimmune disorders such as type 1 diabetes, rheumatoid arthritis (RA), multiple sclerosis (MS), and systemic lupus erythematosus (SLE), although these procedures have certain ethical concerns. On the other hand, bone marrow-derived mesenchymal stem cells (BM-MSC) are thought to be the best source of stem cells. Later, it was shown that mesenchymal stem cells produced from autologous adipose tissues have a great potential for producing huge volumes of stem cells. In-vitro and in-vivo investigations using autologous hematopoietic stem cells and autologous mesenchymal stem cells have been carried out on various rodent and human models, while clinical trials for inflammatory diseases such as multiple sclerosis and diabetes mellitus have yielded promising results. We attempted to summarise the usage of diverse stem cells in the therapy of various autoimmune disorders in this review. Shortly, we expect that the use of autologous stem cells will provide a new perspective on the treatment of autoimmune disorders.

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1. Introduction

Autoimmune diseases (AID) are mostly provoked due to the dysregulation of the balance of the immune system which can be triggered through activation of autoantibodies and autoreactive T lymphocytes. Around 80 different types of autoimmune diseases, but some of them occur most frequently which includes, Rheumatoid Arthritis (RA), Multiple Sclerosis (MS), Juvenile Idiopathic Arthritis (JIA), Systemic Sclerosis (SS), Diabetes Mellitus type I, Systemic Lupus Erythematosus (SLE), Inflammatory bowel and Addison disease etc. The classical AID therapies were found effective in most of the patients, but some patients show response only at the availability of high doses of toxic immunosuppressant drugs. Therefore, researchers are trying to use stem cell technique as an alternative source for the curing of autoimmune diseases. One of the examples of stem cell-based therapies is the use of hematopoietic stem cells which is found most effective and workable. In these procedures, growth factors are administrated to the patient, which normally activates the stem cells form in bone marrow (BM), after the collection of patient blood mature cells removed through different laboratory processes. Then blood is transferred to the patient through transfection after the treatment of radioactive therapy which removes dividing cells even of the immune system (Rosa et al., 2007). In this review, we are going to explain categorically the different and most common AIDs, their molecular

mechanisms and possible stem cell-based therapies which have been conducted in vitro, in vivo in addition to some clinical trials.

1.1. Autoimmune diseases

1.1.1. Diabetes mellitus

Autoimmune diseases are further classified into two types; organ-specific AIDs and systematic AIDs. Type 1 diabetes mellitus (T1DM) is an organ-specific disease characterized by insulin insufficiency. In individuals due to defective insulin-producing pancreatic β cells and only 10–20% of cells remain functional (Knip, 1997). Epidemiological studies revealed that the frequency of occurrence of diabetes mellitus type1 varies in different populations such as people in Finland are more susceptible than Chinese and Japanese. The huge rise in cases was observed during winter, indicated that environmental factors also affect the onset of disease and can be used as a target for cure (Echeverri and Tobón, 2013). About 90% of T1DM is caused due to stimulation of autoantibody against insulin-producing pancreatic islets such as GAD antibodies (GADA), named as glutamic acid decarboxylase 65 and 67 (Hagopian et al.,1995).

The best model for the cure of diabetes mellitus considered the generation of pancreatic cells through embryonic stem cells (ESCs) in which different factors such as NKX6.1 and PDX-1 transgenically expression leads to the generation of insulin, glucagon and

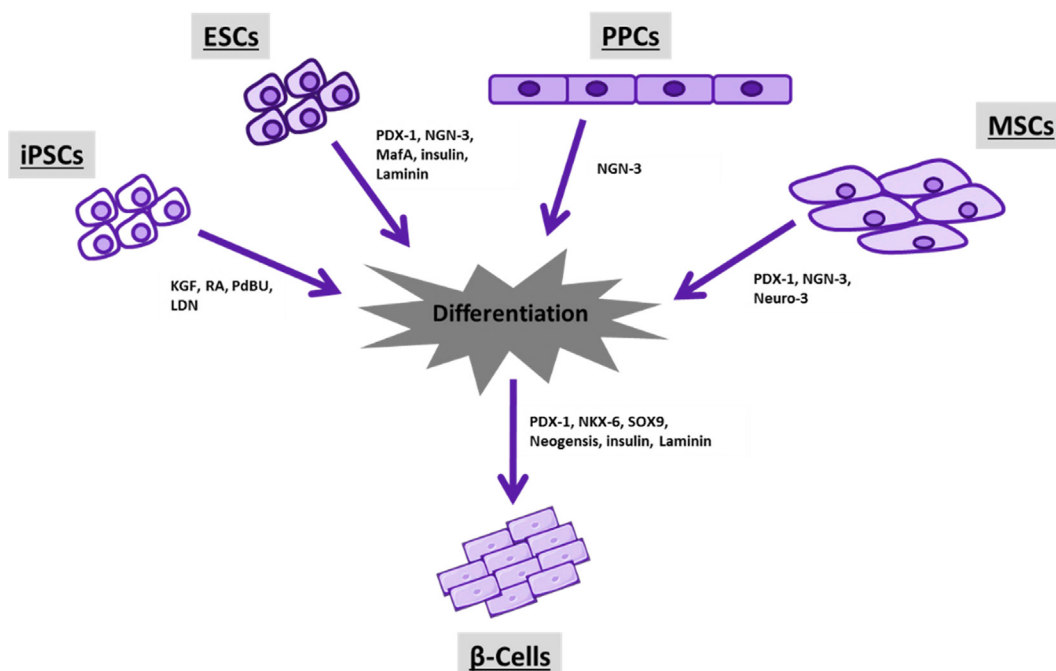


Fig. 1. Differentiation potential of Stem cells into pancreatic beta cells via various endogenic stimuli.

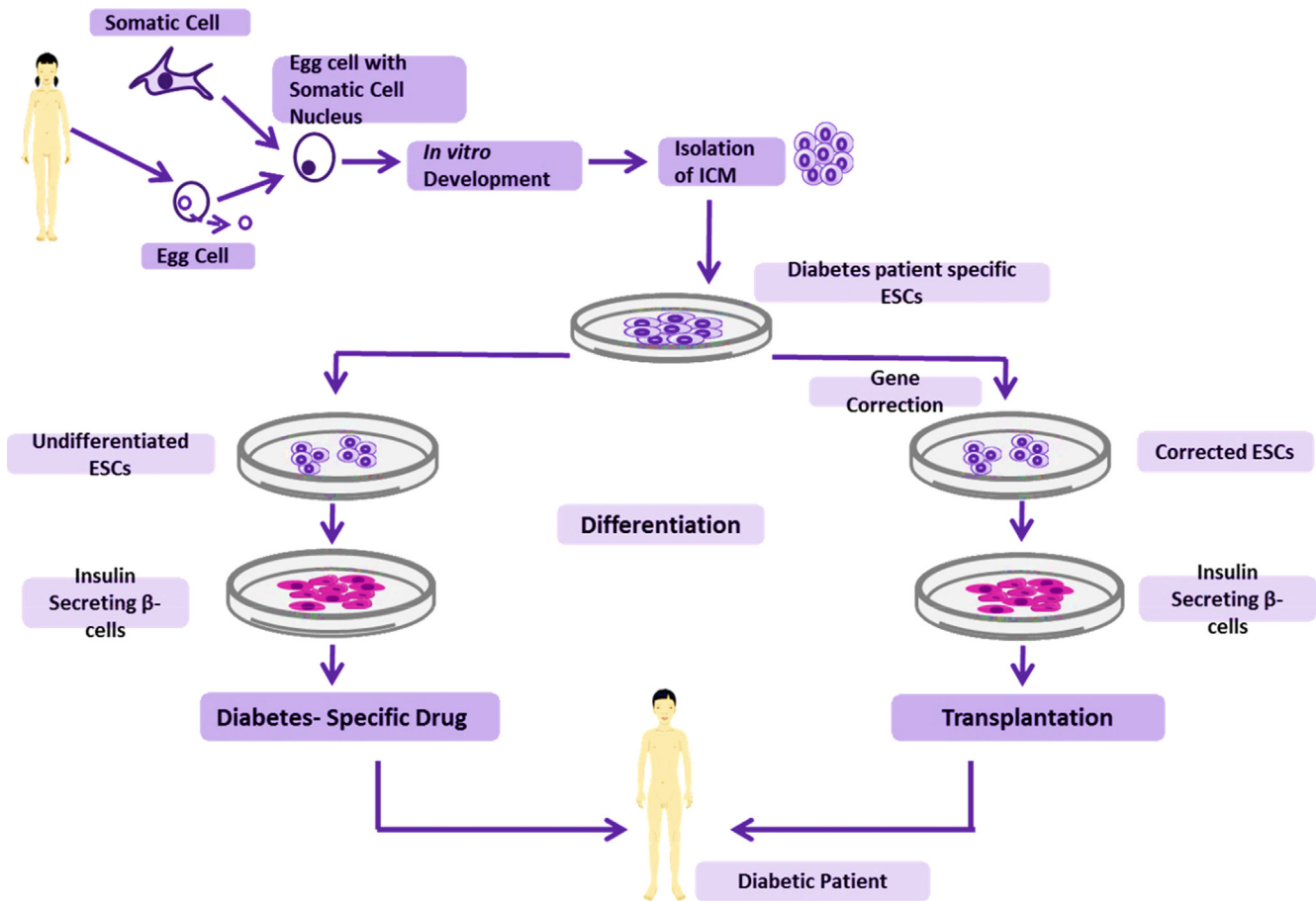


Fig. 2. Schematic representation of SCNT based ESCs isolation and its use in DM.

somatostatin positive endocrine cells while other factors i.e. insulin, laminin and nicotinamide transfections produce pancreatic beta-like cell clusters that release insulin upon glucose stimulation and express PAX4 transcription factor (Solis et al., 2019). Human-induced pluripotent cells (iPSCs) and mesenchymal stem cell (MSCs) has also been used to produce pancreatic β cell that shows responses to glucose. In another study, various supplementation and small molecules such as growth factor, transforming growth factor β ($TGF-\beta$) and glucose increased the Ca^{2+} influx that resulted in granular secretion of insulin (Pagliuca et al., 2014).

Both embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) have been thoroughly investigated. For their multi-lineage differentiation capacity, and both show a high efficacy to differentiate into insulin-producing pancreatic cells. The creation of stem cells that are genetically identical to the patients is one of the most difficult challenges in future stem cell-based cellular treatments for AIDS. Efforts have been made for years to use somatic cell nuclear transfer (SCNT) to create patient-specific ESC lines for this purpose; nevertheless, there are ethical and practical difficulties that must be addressed. Filled this gap with the development of iPSC technology. Pancreatic cell differentiation from stem cells is a step forward in cellular treatment in the future (Fig. 1).

iPSC cell lines have been generated recently from different types of diabetic patients, and they have been successfully differentiated into insulin-secreting β cells. The Somatic cell nuclear transfer (SCNT) technique has been established where the nucleus of a somatic cell is transplanted into an enucleated egg cell. To do

the genetic reprogramming of the recipient cell. As a result, the newly generated pre-implantation embryos contain a similar genetic makeup to the parental somatic cells. Similarly, hESCs are isolated from the inner cell mass (ICM) of 5–7 days blastocyst which has been generated through SCNT. Such SCNT derived hESCs can be induced into multi-lineage cells including insulin-secreting β cells (Fig. 2).

1.1.2. Multiple sclerosis

Multiple sclerosis (MS) is an AID caused by inflammatory cells causing the breakdown or degradation of myelin in nerve tissue. Multiple sclerosis causes an increase in CD8 + T lymphocytes, which release several perforins and granules that directly destroy oligodendrocytes by demyelination (Wootla et al., 2012). Macrophages are also present, and they may play a key function in swallowing myelin debris. Demyelination causes axonal damage in neurons; this neuronal deficiency was recently treated with remyelination; however, this treatment was not particularly effective due to the development of irreversible damage. The detection of oligoclonal IgG bands in the cerebrospinal fluid (CSF), which has been proved to have a neuroprotective function, is one of the most essential investigative tests for MS (Watzlawik et al., 2010).

MSCs with multipotent qualities are regarded as a dependable source for treating MS in which autologous MSCs are injected and they exhibit neuroprotective and anti-inflammatory properties. Autologous MSCs were used to treat MS from 2011 to 2018 and were shown to have better quality control than the placebo group. In another in vivo study it was discovered that intravenous

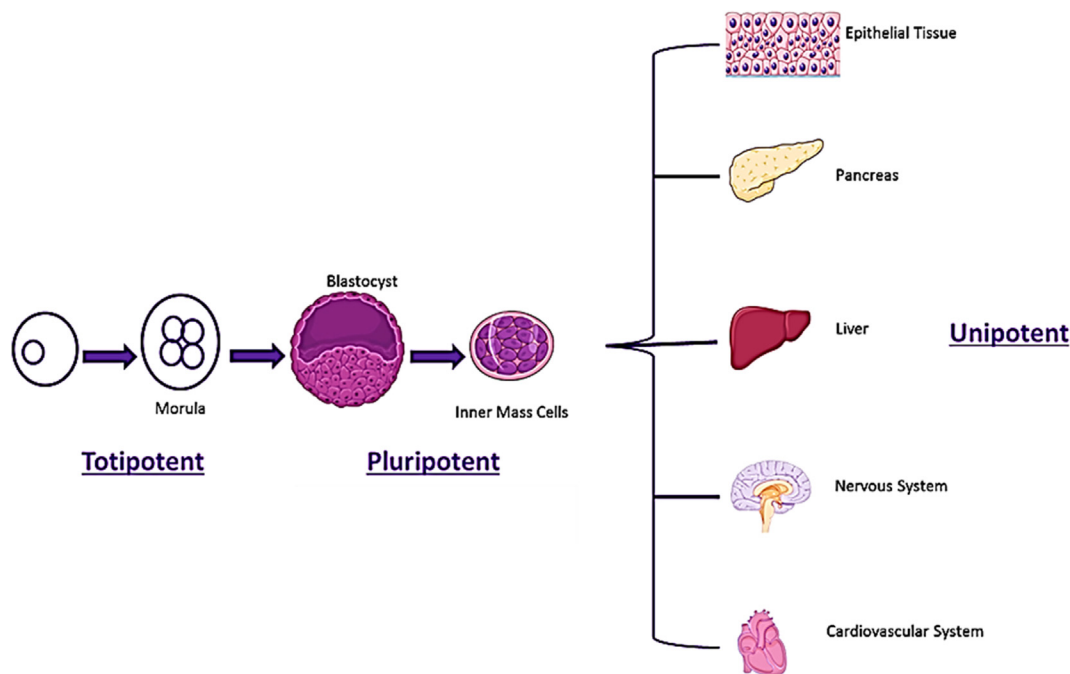


Fig. 3. Classification of Stem cells from different sources based on their potency.

injections of MSCs can circulate into brain lesions and promote brain cell survival (Bejargafshe et al., 2019). MSCs generated from adipose tissue have also been used to treat brain injuries

1.1.3. Rheumatoid arthritis

Rheumatoid arthritis (RA) is an autoimmune disease that results in irreparable joint damage and loss of mobility, as well as affecting life quality and span. The development of lesions is also triggered by humoral and cellular immune responses. Rheumatoid factor is an autoantibody that is unique to the human IgG Fc region and is found in about 80% of RA patients (Snowden et al., 2004). HSCs are mostly involved in inflammation reactions, which propose that this disease origin is actually from problems patient in stem cells; however, further evidence is needed to support this statement. Keeping in view this background, it is speculated that RA can be eliminated through stem cell transplantation especially, through allogenic one (Bingham and Moore, 2004).

Studies revealed that autologous HSCs are more effective but sometimes syngeneic or allogeneic bone marrow transplant (BMT) also provide satisfying results but more rarely (Burt et al., 2004). Instead of leukapheresis, researchers are employing granulocyte-colony stimulating factor (G-CSF) with or without immunosuppression to mobilise the cells. The goal of these operations is to keep mature autoreactive lymphocytes out of the body, preventing them from being reintroduced (Brebant et al., 1999).

1.1.4. Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a systemic AID that is caused by defective stem cells, which results in a decline in proliferative capability and a decrease in CD34 + cells. When compared to control conditions, patients with a low amount of CD34 + cells have a higher rate of apoptosis and a lower rate of colony formation (Jayne et al., 2004). SLE is caused by a genetic predisposition as well as an environmental trigger, both of which promote immune system dysfunctions, one of which is vitamin D deficiency (Schneider et al., 2014). MSCs were found to increase disease activity in Lupus patients by two mechanisms: first, a reduction in protein in the urine, known as proteinuria, and second,

hypocomplementemia (a measure of disease activity) (Liu et al., 2018).

1.2. Cell sources for the cure of autoimmune diseases

1.2.1. Stem cells

Stem cells are specialized cells that have the ability to differentiate into a range of cell types and proliferate indefinitely to generate a pool of identical cells. Stem cells can be found in both embryos and adults; however, they are known as early lineage cells, which are distinct from progenitor cells, which have a lower proliferation potential (Atala and Lanza, 2012). Self-renewal, in which they must maintain their undifferentiated form, and division potency via telomerase, which increases their cell division limit, are two fundamental aspects of stem cells (Cong et al., 2002). Based on their potency, stem cells are separated into many categories of cells, such as totipotent stem cells, which can divide into multiple types of cells and are formed through the division of a fertilized egg earlier; hence, totipotent cells can generate an entire creature (Mitalipov and Wolf, 2009). Pluripotent stem cells can develop into practically any cell type generated from the embryonic germ layers (Ulloa-Montoya et al., 2005). MSCs, or multipotent stem cells, can develop into a variety of cell types (Schöler, 2007). Furthermore, oligopotent stem cells can develop into a variety of cell lines, including myeloid and lymphoid stem cells (Schöler, 2007). Finally, unipotent stem cells are cells that can differentiate into a single type of cell and are used to create tissue, but they vary from normal cells since they do not have the ability to self-renew (Schöler, 2007) (Fig. 3).

1.2.2. Hematopoietic stem cells (HSCs)

Hematopoietic stem cells (HSCs) are multipotent stem cells that can self-renew and regenerate many types of blood cells (Hawley et al., 2006). Hematopoietic stem cells, like other stem cells, are essential because they can be used in current cell therapy. HSCs make up 1:10 000 cells in the human bone marrow. The endosteal niche, which contains osteoblasts and is near to bone, and the vascular niche, which is connected with the sinusoidal

Table 1
The use of MSCs in the treatment of different autoimmune diseases.

Disease Type	Patients	Mesenchymal stem cell source	Administration Route	Results
Acute GvHD	55	Allogenic BM	IVI	30 patients improved
AcuteGvHD	1	Allogenic BM	IVI	Improved skin, gut, and liver
Scleroderma	1	Allogenic BM	IVI	Improved condition
Multiple sclerosis	3	Allogous and autologous fat	Mixed IVI and intrathecal	Clinical findings improved; MRI unchanged
Crohn's fistulae	4	Autologous fat	Intrafistula	75L% closure
Lupus nephritis	16	Allogenic UC	IVI	SLEDAI renal function improved
Systematic lupus nephritis	2	Autologous BM	IVI	No change

endothelium, are the two main stem cell habitats (Lewis and Blutt 2019). The HSCs primarily multiply in the placenta and fetal liver, then settle in the bone marrow after pregnancy, where they remained and were maintained throughout life. HSCs develop in the bone marrow microenvironment, where they interact with adjacent cells, which is important for their differentiation, survival, and proliferation (Stik et al., 2017).

Currently, multipotent HSCs transplantation is considered operative therapy for many blood diseases where the culprit cells originate from either peripheral blood, bone marrow or umbilical cord blood. The HSCs transplantation is either in the form of autologous, allogenic or syngenic cells. In future, while performing HSCs transplantation it should be assured that it is the reversible procedure for most life-threatening diseases patients. Previously it has been established that the use of patient-specific somatic cells (stem cells) offers the greatest immunological compatibility and ominously increases the procedure success. Based on the published literature we can confidently posit that the use of autologous HSCs is the future for the treatment of various autoimmune diseases.

1.2.3. Adult adipose tissue stem cells

Adult tissues include periosteum, adipose tissue, dental, muscle, lymphoid tissues, and practically every other tissue have MSCs in varying amounts, although MSCs are mostly derived from bone marrow (Montesinos et al., 2009). Neonatal annexes, such as the amniotic membrane, placenta, Wharton jelly, and umbilical cord blood, are also potential sources (UCB). Although it is evident that bone marrow is the primary source of MSCs, several issues remain unresolved, such as the fact that bone marrow isolation is a difficult and intrusive method with a low number of progenitor cells due to the uncommon occurrence of MSC (1/100,000) (Da Silva et al., 2006). MSCs generated from adipose tissue have a higher proliferative rate and a stronger inhibitory effect on T-cell proliferation, making them more effective than BM-MSCs (Strioga et al., 2012). Practically, lipectomy or simple lipoaspiration are used for the removal of adipose tissues with low morbidity and high accessibility of tissue. The isolated tissue is treated with the collagenase enzymes for digestion and then stromal vascular fraction (SVF) is separated through ultra-centrifugation. After injecting ASC into the patient, they are an increase of 10,000-fold in the yield as compared to BM-MSC isolation (Pikula et al., 2013). Adipose-derived MSCs also have the following advantages over BM,

- Easy to isolate.
- Produces a high volume of cells per unit area.
- Low extraction costs.

Naive ASC expresses CD34 which doesn't support the ISCT criteria for MSC while in ex-vivo culture, proliferating cells lost the expression of respective marker (Gimble et al., 2010). Studies also revealed that ASC shows stronger immunosuppressor activity as compared to MSC from other sources while it also prevents the activation of β cells and ultimately affects the maturation and differentiation of monocyte (Bochev et al., 2008).

2. In-vitro experiments

Stem cells have been found to be effective in treating a range of autoimmune illnesses in both in vitro and in vivo investigations. In this section, we will try to provide a comprehensive summary of the numerous in vitro investigations based on the use of various stem cells (Table 1).

2.1. In vitro treatment of autoimmune diseases by patient-specific stem cells

Pluripotent stem cells have the ability to transform into a range of different types of cells. The patient has cells that can be returned to a more primitive, embryonic stem cell-like form. For instance, patient mesenchymal stem cells are multipotent and capable of developing into mesenchymal lineages. T cell proliferation is inhibited in the presence of MSCs when activated with particular antigens or polyclonal mitogens, according to in vitro studies. This study, along with many others, suggests that patient-specific MSCs could be exploited as an immunomodulatory source for the therapy of a variety of autoimmune disorders.

MSCs were first used as grafting agents in patients having abnormalities during hematopoietic stem cells transplant (Tyndall and Houssiau, 2010). Almost 90 clinical trials have been reported in which patients have received mesenchymal stem cells therapeutically however the efficacy of using mesenchymal stem cells as an immunomodulatory technique is lacking. As in the case of graft versus host disease cases with both favourable and poor outcomes have been described (GvHD). GvHD disease involves various organs and requires complex treatment therapies. Sun et al. (2010) reported that in the case of systematic lupus erythematosus, 14 out of 15 patients which do not recover with conventional treatment when treated with intravenous cyclophosphamide for 6–36 months and received BM-derived MSCs showed quick improvements with minimum toxicity. MSCs have been exploited as an immunomodulatory source in the treatment of autoimmune disorders in the clinic (Tyndall and Houssiau, 2010).

Various haematological disorders are caused by metabolic dysfunction, genetic abnormalities, or malignant changes in the normal cells. Specific stem cell therapy is being used to treat haematological disorders and many experiments are under process (Storb et al., 2003). In vitro expanded bone marrow, cord blood, and peripheral mobilized cells were used in the clinical trials. In vitro techniques are used to reduce the contamination during the removal of bone marrow from tumour cells, low cell dosage and reduced engraftment life (Mehta et al., 1996).

In vitro development of blood progenitor cells can be utilised to support hematopoietic stem cell therapy and minimise post-chemotherapy neutropenia, according to a study. CD-34 cells activated breast cancer patients' peripheral blood progenitor cells and cultivated them for 10 days.

On day 1, patients received the unexpanded peripheral blood progenitor product and engrafted neutrophils in 6 days while on day 2 the patients received expanded peripheral blood progenitor

Table 2
Technologies used in HSCs transplantation.

	Total	Multiple Sclerosis	Systemic Sclerosis	Rheumatoid arthritis	Juvenile idiopathic arthritis	Systemic Lupus Erythematosus	Immune Thrombocytopenia	P-value
Source of stem cell								0.0001
BM	54	12	2	1	23	11	2	
BM ± PB	419	138	69	69	28	51	8	
Mobilization of peripheral blood								0.0001
GF	89	15	7	41	9	2	4	
Cy ± GF	289	112	59	28	13	43	2	
Others	42	11	4	0	6	6	2	
Conditioning								0.0001
Cy	117	2	38	63	0	1	3	
Cy + ATG + drugs	127	22	23	3	21	34	3	
Cy + radiation	48	13	2	0	19	12	0	
Bu + Cy	24	16	0	2	1	1	1	
BEAM + ATG	92	82	1	0	0	4	1	
Other	23	3	1	1	4	3	2	
Intensity								0.0001
High	72	29	2	2	20	13	1	
Intermediate	225	105	25	3	23	40	4	
Low	134	4	38	64	2	2	5	
In vitro purging								0.0001
CD 34 selection	213	60	46	38	21	24	4	
CD selection ± T B depletion	36	12	9	2	5	2	1	
T/B depletion	17	4	1	0	11	0	1	
Chemotherapy	19	3	0	1	5	1	1	

ATG: anti-thymocyte globulin. Cy: cyclophosphamide. Bu: busulfan. BEAM: polychemotherapy. T/B: T/B cell depletion.

cells and they engrafted neutrophils in 8 days. The reported mean time for neutrophil engraftment was reported to be 9 days (McNiece et al., 2000).

Multiple sclerosis patients have benefited from HSC transplantation. HSC treatment after body exposure to radiation and cyclophosphamide treatment prevents relapses in organisms suffering from autoimmune encephalitis (Atkins and Freedman, 2013). It was reported that autoimmune disease could be transferred by hematopoietic stem cells transfer, but it is possible to transfer immunity against autoimmune diseases like systemic lupus encephalomyelitis, adjuvant arthritis, diabetes mellitus and antiphospholipid syndrome. Hematopoietic stem cells from disease-resistant animals can prevent autoimmune disease development in recipients (Sykes and Nikolic, 2005). Various HSCT techniques, treatment of autoimmune diseases via HSCT under different conditions in both in vivo and in vitro have been discussed in Table 2.1 and Table 2.2. The study reported that the female's proportion was higher in all the autoimmune diseases as compared to the male except in the case of thrombocytopenia (Table 2).

3. In-vivo experiment

We attempted to present a comprehensive overview of the many in vivo studies on the use of different stem cells to treat autoimmune disorders that have been conducted to date.

3.1. Autologous stem cells

Autologous stem cells are regarded a possible stem cell site because of their ability to create virtually any type of cell. MSCs, or stromal stem cells, are derived from bone marrow and can differentiate into a variety of adult tissues. MSCs, or multipotent and non-hematopoietic progenitor cells, are thought to be a viable technique to regenerate tissue (Bai et al., 2009). They are a therapeutic tool for the treatment of severe stubborn autoimmune diseases due to their immunomodulatory properties, limited immunogenic potential, and effect on immune response

(Passweg and Tyndall, 2007). MSCs can develop into cells from three germ layers, including neuroectodermal cells, and can proliferate in vitro.

3.1.1. Immunomodulatory property of MSCs

MSCs have immunoregulatory activity and can influence both innate and adaptive immunity. Evidence shows that T cell proliferation is inhibited when they are stimulated by polyclonal mitogens or particular antigens and that this suppression may be reversed using MSCs. The lymphocytes are arrested in the G0/G1 phase of the cell cycle which causes the inhibition (Nauta and Fibbe, 2007). Furthermore MSCs have been shown to affect the cytokine secretion profile of T-cell subsets with a decrease in the production of interleukin (IL)-6 tumour necrosis factor (TNF)-interferon (IFN)- and IL-17 and an increase in anti-interleukin-10 and interleukin-4 in the presence of MSCs (Pramanik, 2012). The literature also indicates MSC-mediated alternation in the ratio of T-helper1/T-helper2. Moreover several types of research revealed that MSCs inhibits the in vitro induction of Cytotoxic T Lymphocytes (CTL). MSCs modulates the different cells immunological activity as inhibitory effect on dendritic cell (DC) differentiation and T cell proliferation which is one of the prime factors involved in activating autoimmune disorders MSCs significantly limit CD8, CD4 memory and naive T-cell growth. The procedure begins with the initial cell-to-cell contact phase, during which MSCs secrete a variety of specific mediators, including prostaglandin E2 (PGE2), TGF and the indoleamine 2, 3-deoxygenase (IDO) enzyme, which converts tryptophan to kynurenine and inhibits T cell responses are both stimulated by IFN. MSCs also influence immunological responses by promoting the generation of regulatory T cells (CD8 + Tregs), which suppress lymphocyte proliferation (Nauta and Fibbe, 2007). The summary of Immunomodulatory properties of MSCs is illustrated below in Figure

3.1.2. MSCs based therapy in multiple sclerosis

A study found that systemic injection of MSCs reduces disease severity both at the outset and at the peak of the disease in the

autoimmune encephalomyelitis (EAE) disease model (Bai et al., 2009). Clinical trials, on the other hand, demonstrated that MSC treatment causes demyelination in the brain and spinal cord, as well as a reduction in T cell and macrophage penetration in the central nervous system parenchyma (Bowles et al., 2014). Moreover, the pathogenic proteolipid protein-specific antibodies were also inhibited and significantly reverting disease symptoms were observed like fewer relapses, reduction in demyelination, axonal loss in the treated mice. The MSCs homing were detected in inflamed areas of CNS as well lymphoid organs even after some week of MSCs administration. Besides this, MSCs also show a neuroprotective effect via recruitment of local progenitors, the secretion of soluble neurotrophic factors, and the ability to generate neural cells.

A study accomplished by Zappia in 2013 showed that MSC could disturb the prototypical T cell-mediated response in autoimmune disease i.e. EAE. In the study, they have injected the MSC on days 3 and 8 and a reduction in disease severity was achieved which reaches statistical significance on day 17 as compared to control. Injecting unpurified marrow cells at the same time points lead to a remarkable difference from control. The clinical outcomes are linked with reduction of demyelination, a notable decrease in macrophages and T cells infiltrating towards CNS parenchyma and MSC administration was still effective after disease onset and used as EAE treatment. Thus, MSC on 24th day helps in disease stabilization and at the time give rise to a suitable time frame for transplantation of neural stem cells in EAE disease models. MSC administered on the 24th day did not show any irrefutable changes in disease and pathology scores. Therefore, the changes after disease onset (occurrence of first symptoms) and at the peak of disease (around day 15) along with the administration of MSC were evaluated. Both administrations were able to halt the disease progression with a significant reduction in cumulative disease score. MSC treated mice did not show any sign of associated diseases or cancer even after 3 months. Therefore, MSC is found an effective source before and after the disease and was not inducing a state of immunodeficiency.

3.1.3. MSCs based therapy in rheumatoid arthritis

Ameliorating effects in mouse models were also observed rheumatoid arthritis (RA) where the patient's derived MSCs were administrated and as the resulting improvement in clinical score, reduction in the expression chemokines and inflammatory cytokines with a rise in the expression of the anti-inflammatory cytokine which ultimately prevents the tissue from severe damage (Dirk et al., 1989). The experiments conducted on autoimmune myasthenia gravis mice and rat models also presented favourable results. The studies demonstrate the same features as reduced clinical symptoms, inhibition in the proliferation of AChR-specific lymphocytes and improvement in the overall body weight.

3.1.4. MSCs based therapy in type 1 diabetes mellitus (T1DM)

T1DM differs from T2DM in that it is characterised by the autoimmune destruction of pancreatic-cells by T lymphocytes. Insulin injection is currently considered a remedy for type 1 diabetes, but its long-term control is unknown because exogenous insulin does not promote insulin secretion (Vija et al., 2009). Currently, Islet transplantation is an option to make the patient insulin-independent; however, intrinsic complications and inadequacy of organ transplantation are yet to be solved. Along with these complications, stem cell therapy, generation of MSCs derived-insulin producing pancreatic beta cells signifies a striking opportunity for the cure of DM (Chamberlain et al., 2007). This therapeutic strategy has been used in numerous mouse models, and promising results were obtained which help in the recovery of hyperglycemia condition.

3.1.5. MSCs based therapy in systemic lupus erythematosus (SLE)

MSC based treatments are also able to ameliorate the disease condition in SLE disease murine models. It was observed autologous MSC infusion lead to reduced glomerular IgG a decrease in autoantibody decrease C3 depositions and proteinuria while improving bone formation and osteoblastic reconstruction. MSCs' immunomodulatory activity is a key component in the therapy of immune-mediated illnesses. This was discovered lately while working on MSC-based treatments in various autoimmune models (Table 2).

3.2. Treating autoimmune diseases via autologous HSCs

Two experimental models of autoimmune illness (Buffalo rats) were used in preclinical research. Systemic arthritis is the consequence of adjuvant arthritis, whereas experimental allergic encephalomyelitis causes persistent remitting relapsing illness. The hereditary/spontaneous AID and the induced AID animal models are divided into two categories (Alexander et al., 2016). The bulk of the time, sickness occurs with age in the former, although not in all vulnerable strains. T1MD, SLE-like syndromes, and a complex syndromic type of arthritis/ dermatitis/ colitis in HLA-B27 transgenic rats are disease models that fall under this group. The second type, on the other hand, does not emerge naturally; vaccination stimulates certain tissues, resulting in AID, for example. MS is studied using an EAE disease animal, while rheumatoid arthritis is studied using arthritis or bacterial antigens such as *Mycobacillus tuberculosis*. The pathogenesis of AIDS in humans is complex. Environmental or genetic factors are the most common causes. As a result, the inducible AID animal model is a better choice for pre-clinical research. The therapeutic potential of autologous bone marrow transplantation has already been established in a rat model of induced EAE and arthritis.

3.2.1. Autologous HSCs transplantation for MS

Experimental autoimmune encephalomyelitis (EAE) is a demyelinating CNS autoimmune disease caused by either adoptive transfer of primed T cells or in vivo myelin peptide vaccination. HSCs can be obtained either in the syngeneic form or from a syngeneic animal suffering from the same disease stage. All HSC sources may be allogeneic, autologous, or pseudo-autologous can induce remission and prevent the relapse during the acute phase of MS. On other hand, HSCT is considered a futile therapy for chronic or late-stage autoimmune encephalomyelitis.

The use of autologous HSC therapy to reset the immune system appears to be effective. The suppression of lymphopenia, which is a more durable "immune reset" due to the regeneration of antigen-based naive immune system from HSCs, leads to remission after autologous HSC transplantation.

Researchers discovered that a new and antigen-naive T-cell repertoire emerges from the HSC compartment via thymic regeneration in MS patients by analysing T-cell receptors using various methods such as FACS, PCR, and sequence-based clonotyping, as well as new thymic T cell emigrants using the T-cell receptor excision circle. This suggests that HSC transplantation with substantial immune suppression leads to an efficient long-term immunological reset, regardless of whether immune suppression-mediated lymphopenia persists (Mancardi et al., 2001).

4. Discussion

Autoimmune disease occurs when the immune system of the body attacks its tissue due to an inappropriate immune response considering the body cell as self-antigens. The body fluids of the patient have uncommon antibodies that target body tissues, along

with autoimmune diseases. About 6% of the human population is affected by sixty autoimmune diseases and consider as the third-largest global burden after cancer and heart disease.

Many experimental studies of HSC transplantation and allogeneic HSC transplantation have been conducted on autoimmune disease in numerous murine models. Because allogeneic BM transplantation carries a high risk of mortality and morbidity, autologous transplantation is regarded as a justifiable option in patients with severe autoimmune disease who have failed to respond to conventional therapy. Therefore, autologous stem cells derived from the same patient hold a safe option for this treatment without the risk of any immune rejection and allogeneic sensitization. After HSC transplantation in remission was attained in certain patients while others relapsed. As we previously mentioned and also some other reports identified that MSC has immunosuppressive effects as well as immunomodulatory properties on certain lymphocytes proliferation by different immune cells i.e. B cell, naïve memory and activated T cells, dendritic cells and NK cells. The various secreted molecule such as interleukins, TGF, IDO, NO and PGE2 together with many others pose immunosuppressive properties. The bottom line is that these kinds of properties or features make the stem cells an ultimate source for providing long-term and sustained protection from autoimmunity.

As this new research horizon evolved, patient-specific stem cells, particularly MSCs, will be the major shareholder in stem cell treatment or combination therapy for alleviating symptoms and curing autoimmune disease with minimal or no immunological rejection.

5. Conclusion

From the limited data available, it is concluded that autologous stem cells of patients are used as an effective therapeutic strategy. Although there are many cell sources of stem cells hESC, iPSC, they have ethical issues, so patient-specific MSCs and HSCs cells can be used for treating autoimmune diseases. Autologous stem cells are also considered as the best regimen for each disease, both in terms of tolerability and efficacy. In vitro treatment methods reduce the issues which could arise due to complications and contaminations during tumour removal, and these techniques also increase the engraftment life. It has been briefly demonstrated that many clinical trials are done on the usage of patient-specific stem cell therapy for altering or aborting many autoimmune diseases. Many of these trials went successful for treating AD-like type 1 and 2 diabetes and systemic lupus erythematosus while, many trials are still in progress for treating AD-like RA, osteoarthritis and many autoimmune-induced neurological disorders. Multiple sclerosis is also treated efficiently in vitro with iPSCs derived HSCs. Muscular dystrophy is also treated also with induced pluripotent, in vitro derived satellite cells. In conclusion, as this new research horizon evolved, patient-specific stem cells, particularly MSCs, will be the major shareholder in stem cell treatment or combination therapy for alleviating symptoms and curing autoimmune disease with minimal or no immunological rejection.

CRedit authorship contribution statement

Zuhair M. Mohammedsaleh: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Writing – original draft, Writing – review & editing, Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Visualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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