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REVIEW ARTICLE

Adult Stem Cell Therapy for Autoimmune Disease

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Many studies of autologous hematopoietic stem cell transplantation (HSCT) and allogeneic HSCT have been conducted for autoimmune disease in various animal models. Because of the substantial risk of morbidity and mortality associated with allogeneic bone marrow transplantation, autologous transplants justified trying this approach in patient with severe autoimmune disease who were refractory to current treatments. Remission was achieved in some of the patients and some of them relapsed. Recently, many *in vitro* studies have reported that mesenchymal stem cells (MSC) have immunomodulatory properties and immunosuppressive effects on MHC-mismatched lymphocytes proliferation by inhibiting naïve, memory and activated T cells, B cell, NK cells and dendritic cells. In addition, adipose tissue-derived MSC (AT-MSC) are becoming an alternative source of MSC for therapeutic applications because adipose tissues are abundant, easily accessible, easily obtainable with little patient discomfort and large amounts of AT-MSC can be easily obtained. A large body of *in vitro* research has shown that AT-MSC have same or similar immunomodulatory effects with bone marrow derived MSC. Drawing on this finding, the increasing numbers of researchers have turned on their attention to preclinical studies on AT-MSC. As this new path of research evolves with subsequent reports, MSC would make a significant contribution to stem cell therapy or combination therapy for ameliorating symptoms and curing autoimmune disease. By searching and studying the appropriate therapeutic gene, the therapeutic gene transfected stem cell therapy will be able to acquire the synergy effect and the combined advantage of gene therapy and stem cell therapy.

Keywords: Adult stem cell, Hematopoietic stem cell, Mesenchymal stem cell, Autoimmune disease, Stem cell therapy

Autoimmune disease

Autoimmune disease occurs when the body tissues are attacked by its own immune system as a result of an inappropriate immune response directed to self-antigens. Patients with autoimmune diseases frequently have unusual antibodies circulating in their blood that target their own body tissues. As a whole, over sixty autoimmune diseases affect about 6% of the population and are the third largest disease burden after heart disease and cancer (1). Autoimmune diseases can be broadly divided into organ-specific and systemic autoimmune diseases depending on the location of the target antigen and clinical features. Systemic autoimmune diseases include diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis, systemic sclerosis, and polymyositis. The feature of these diseases is that the targeted antigens are located throughout the body. Examples of organ-specific autoimmune diseases include Sjögren syndrome, Hashimoto thyroiditis, Graves disease, type 1 insulin-dependent diabetes, Addison disease, vitiligo, pernicious anemia, glomerulonephritis, myasthenia gravis and pulmonary fibrosis.

Prevalence of autoimmune disease

According to the analytical study on epidemiology and estimated population burden of autoimmune disease in the United States (2), the most prevalent autoimmune diseases are Graves' disease/hyperthyroidism (1.15%), rheumatoid arthritis (0.86%), thyroiditis/hypothyroidism (0.79%),

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vitiligo (0.4%), type 1 insulin-dependent diabetes (0.19%) and pernicious anemia (0.15%). The prevalence of other autoimmune diseases is as follow; primary glomerulonephritis (0.04%), multiple sclerosis (0.06%), SLE (0.02%) and Sjögren's (0.01%). Each of other disease (Addison's, chromic active hepatitis, myasthenia gravis, polymyositis, primary biliary cirrhosis, scleroderma and uveitis and so on) has prevalence rates of less than 0.005%. Women were at 2.7 times greater risk than men to acquire an autoimmune disease. A lot of eligible prevalence studies were conducted on multiple sclerosis, rheumatoid arthritis and SLE (2). SLE is the prototype multisystem autoimmune disease. The etiology of SLE remains unknown. Antigen-antibody complexes are produced and subsequently lodge in small vessels and the basement membrane zone of the skin and in various organ systems. A genetic predisposition, T cell defects, B-cell hyperactivity, hormonal alterations and environmental trigger likely result in the disordered immune response that typifies the disease (3). The prevalence of SLE in adults age over than 17 based on self-reported physician diagnosis was about 241 per 100,000 in the United states (4). African Americans are affected three times as often as Caucasians, and the rates of SLE among Asian and Hispanics may be higher. Women are affected nine times as often as men, and the onset of SLE in women most often occurs between menarche and menopause.

Current therapy and new prospects for treatment of autoimmune disease

The major immunosuppressive drugs of the last three decades in treatment of autoimmune disease have been corticosteroids, cyclophosphamide, azathioprine and methotrexate. In fact, these agents may be effective in autoimmune disease. Nonetheless, these agents are not uniformly effective and are associated with substantial toxicities. Through further understanding of immunopathogenesis of autoimmune disease and increasing knowledge of the immune system, many researchers are seeking to identify and trial novel immunotherapeutic strategies. These have included recombinant protein or gene therapies aimed at influencing particular immune cells (5) and molecules such as costimulatory molecules (6-8), cytokines (9) and chemokines (10).

Preclinical hematopoietic stem cell therapy in autoimmune disease model

The animal models of autoimmune disease are of two types; the spontaneous forms and the induced forms. In animal models, the best results have been obtained with the strongest lymphoablative/myeloablative regimens to achieve complete allogeneic chimerism is also highly effective in reducing the burden of autoreactive lymphocytes. This concept is to cure animals with overt autoimmune disease by replacing their bone marrow with that from an allogeneic donor of a normal or a noninducible strain. But the substantial risk of morbidity and mortality associated with allogeneic bone marrow transplantation has so far prevented its application in the treatment of patients with severe autoimmune disease (11). In contrast, the lower risks of autologous transplants justified trying this approach in patient with severe autoimmune disease who were refractory to current treatments. Some examples of preclinical hematopoietic stem cell therapy in autoimmune disease model are listed in Table 1.

Clinical trials of hematopoietic stem cell therapy in autoimmune disease

Autologous hematopoietic stem cell transplantation was initiated for treatment of severe autoimmune diseases beginning in the early 1990s (22). And then, immunoablation with autologous hematopoietic stem cell rescue has been used in over 1,300 autoimmune disease patients, around 150 with SLE (23). In SLE, some patients have experienced durable remissions with loss of autoantibodies, whereas others either did not respond or died as a result of the treatment (23). For examples, phase I study-treatment of severe SLE with high-dose chemotherapy and autologous hematopoietic stem cell transplantation (HSCT) was tried in seven patients who showed persistant SLE despite use of cyclophosphamide (24). Nine patients underwent stem-cell mobilization but two were excluded before transplantation because of infection. The remaining seven received high-dose chemotherapy and stem-cell infusion, and they remained free from active lupus at a median follow-up of 25 months and improved continuously after transplantation, with no immunosuppressive medication or small residual doses of prednisone. Burt et al. (22) reported a single-arm trial of 50 patients with SLE refractory to standard immunosuppressive therapies and either organ- or life-threatening visceral involvement. According to their report, two patients died after mobilization, one from disseminated mucormycosis and another from active lupus after postponing the transplantation for 4 months. A retrospective analysis of 53 SLE patients treated with HSCT in Europe was reported in 2004 (25). According to their report, remission was achieved in two

Table 1. Examples of hematopoietic stem cell therapy in animal model of autoimmune disease

Authors and reported year	Disease or Animal model	Species	Source or mechanisms	Effect
Burt et al., 1998 (12) Karussis et al, 1993 (13) van Gelder et al., 1993 (14)	Multiple sclerosis Acute EAE (experimental allergic encephalomyelitis)	Mice Guinea pig Buffalo rat	Myeloablation and Syngeneic bone marrow transplantation (BMT)	Cure, decreased relapse rates or decreased severity
Pestronk et al., 1983 (15)	Myasthenia gravis	Rat	Lethal dose cyclophosphamide, Syngeneic BMT	Eliminates ongoing immune responses and reconstitutes the immune system in its original state
Kamiya et al., 1993 (16)	Adjuvant and collagen induced arthritis	Mice	Irradiation, Syngeneic or Allogeneic BMT	Especially, allogeneic BMT blocked the induction of CIA, suppressed the progression of the arthritis
Van Bekkum, 2000 (11)	Adjuvant arthritis	Buffalo rat	CY+ low dose TBI Autologous BMT	Respond very well
Van Bekkum et al., 1989 (17)	Adjuvant arthritis	Rat	TBI+ syngeneic or allogeneic BMT	Treated effective
Beilhack et al., 2003 (18)	Type 1 DM	NOD mice (spontaneous model)	Syngeneic hematopoitic stem cells transplantation (HSCT) or Congenic grafts	Not cured
			Allogeneic HSCT	Block allo-and autoimmunity
Morton et al., 1979 (19)	NZB	NZB mice	Allogeneic BMT	Reversal of autoimmune syndrome
Ikehara, 2001 (20)	SLE	MRL/lpr mice	Bone marrow allograft BMT only	Only transient effects (3 months)
			BMT+bone grafts (to recruit donor stromal cells)	Prevent the recurrence of autoimmune disease
Smith-Berdan et al., 2007 (21)	SLE	NZB/W F1 female	Allogeneic HSCT with nonmyeloablative conditioning	Improved survival, decreased proteinuria, circulating immune complexes and autoantibodies to nuclear antigens

third of the SLE patients and one third of them relapsed after median 6 months. Twelve % showed treatment related mortality, and five years disease-free survival was about 50%. Voltarelli et al. determined the safety and metabolic effects of high-dose immunosuppression followed by autologous nonmyelablative HSCT in fifteen type 1 insulin-dependent diabetes patients. During mean 18.8 month follow-up, fourteen patients became insulin-free. There was no mortality. But, the only acute severe adverse effect was culture-negative bilateral pneumonia in one patient and late endocrine dysfunction in two others (26). Phase I/II trials for auto-HSCT in systemic sclerosis have been conducted by a number of groups. Trials using myeloablative conditioning regimens or lymphpablative conditioning regimens with the addition of CD34+ cell graft enrichment are ongoing. In the most recent European data from the EBMT/EULAR registry, 57 patients had undergone HSCT for systemic sclerosis. Ninety two% of patients had partial or complete responses, initial transplant mortality was 17%, and overall projected 5-year survival was 72% (27). The data of autologous HSCT for rheumatoid arthritis (RA) are available from more than 70 patients. Most centers report initial responses, but recurrence of disease is common (28). In 1998, the first conference was opened to establish guidelines regarding HSCT in multiple sclerosis. But, nearly 10 years later, the

debate regarding HSCT in multiple sclerosis continues, with some authors cautioning that ethical application of HSCT for multiple sclerosis is problematic in the face of clinical uncertainties in predicting future disease course in multiple sclerosis patient (29). Twelve patients, who had Crohn's disease refractory to conventional therapies, were enrolled in a phase I trial of lymphoablative-chemothrapy followed by autologous HSCT in a Chicago center (30). Median follow-up at the time of the report was 18.5 months in 11 evaluable patients. One patient died in an accident. Improvement on Crohn's disease Activity Index scores were remarkable shortly after transplant, all patients achieved a drug-and disease free transient interval. Fourteen patients with systemic vasculitis were followed-up after HSCT (31). After autologous HSCT, there were eight infections among patients. However 50% of patients experienced at least an initial complete response and partial response with reduction in need for immunosuppression was achieved in 36%. In addition, the data on HST for other autoimmune disease such as juvenile rheumatoid arthritis, chronic inflammatory demyelinating polyneuropathy, autoimmune cytopenia, bullous skin disease, celiac disease and so on were also reported.

Mesenchymal stem cell therapy for autoimmune disease

Recently emerging, another cellular-based therapy is to use another adult stem cell, the mesenchymal stem cell (MSC), as an anti-inflammatory and tissue protecting agent (23). MSC are multipotential nonhematopoietic progenitor cells (32). Recently, many *in vitro* studies have reported that MSC have immunomodulatory properties and immunosuppressive effects on MHC-mismatched lymphocytes proliferation by inhibiting naïve, memory and activated T cells, B cell, NK cells and dendritic cells. This concept is completely different from HSCT in that the patient does not need to be immunosuppressed prior to MSC transplantation, and that the therapeutic effect is considered to be delivered in the inflamed organ due to homing of MSC with a relatively short lived effect (23).

In 2009, Sun et al. reported bone marrow derived mesenchymal stem cell transplantation reverses multiorgan dysfunction in SLE mice and humans (33); MRL/lpr mice showed osteoblastic niche deficiency, which contribute in part to the pathogenesis of SLE-like disease, and allogeneic bone marrow derived MSC transplantation (BM-MSCT) can reconstruct the bone marrow osteoblastic niche and more effectively reverses multiorgan dysfunction compared with cyclophosphamide. Allogeneic MSCT treated SLE patients showed a stable 12～18 months disease remission. Disease activity was ameliorated and serological markers and renal functions were improved. Clinical trials using autologous BM-MSC are ongoing now in various autoimmune diseases.

Adipose tissue-derived Mesenchymal stem cells

Adipose tissue-derived MSC (AT-MSC) are becoming an alternative source of MSC for therapeutic applications because adipose tissues are abundant, easily accessible, easily obtainable with little patient discomfort and large amounts of AT-MSC can be easily obtained. Currently, AT-MSC were clinically applied for the regenerative treatment and wound healing; In the first clinical trial, autologous adipose tissue derived mesenchymal stem cells were used for the treatment of widespread traumatic calvarial bone defects (34). In this clinical trial, new bone formation and almost complete calvarial continuity was obtained.

In 2006, Yañez et al. reported AT-MSC have immunosuppressive properties that can be used to control graft-versus host disease (GVDH) in murin model (35). From this concept, AT-MSC were administered intravenously to patients with steroid-refractory acute GVDH. Acute GVDH resolved completely in five of six patients, four of whom were alive after a median follow-up period of 40 months without side effects (36).

Intravenous administration of AT-MSC before disease onset significantly reduces the severity of EAE by immune modulation and decreases spinal cord inflammation and demyelination (37). Administration of AT-MSC in chronic established EAE significantly ameliorates the disease course and reduces both demyelination and axonal loss, and induces a Th2-type cytokine shift in T cells (37). Inflammatory bowel diseases are associated with uncontrolled innate and adaptive immunity. Gonzalez-Rey et al. induced acute and chronic colitis in mice with dextran sulfate sodium (38). Colitic and septic mice were treated with hAT-MSC or murine AT-MSC intraperitoneally. Treatment of AT-MSC significantly ameliorated the clinical and histopathological severity of colitis by decrease of inflammatory cytokines and increase of IL-10 (38). In same group, González et al. reported systemic infusion of human AT-MSC significantly reduced the incidence and severity of experimental arthritis by inducing the generation and activation of regulatory T cells (39). Table 2 summarizes animal model, cell source and effects of mesenchymal stem cell therapy in autoimmune disease.

Table 2. Examples of mesenchymal stem cell therapy in animal model of autoimmune disease

Authors and reported year	Disease or Animal model	Species	Cell Source	Effect
Zappia et al, 2005 (40)	EAE	C57Bl/6 mice	Murine BM-MSC (syngeneic)	Before disease onset, strikingly ameliorated EAE after disease, stabilization, not effective
Zhou et al., 2008 (41)	SLE	MRL/lpr mice	Human BM-MSC	Significantly reduced serum levels of anti-dsDNA Abs, proteinuria and renal pathology
Sun et al., 2009 (33)	SLE	MRL/lpr mice	Murine BM-MSC (allogeneic)	Effectively reverses multiorgan dysfunction
Rafei et al., 2009 (42)	EAE	C57Bl/6 mice	Murine BM-MSC (syngeneic)	Ameliorate experimental autoimmune encephalomyelitis
Yañez et al., 2006 (35)	Graft-versus-host disease	Mice BM haploidentical transplantation (C57Bl/6(H2 $^{b/b}$) BM→B6D2F1(H2 $^{b/d}$))	Murine AT-MSC (syngeneic (B6D2F1))	Controlled the lethal GVHD
Constantin et al., 2009 (37)	EAE	C57Bl/6 mice	Murine AT-MSC (syngeneic)	Before disease onset significantly reduces the severity of EAE Chronic established EAE significantly ameliorates the disease course and reduces both demyelination and axonal loss
Gonzalez -Rey et al., 2009 (38)	Inflammatory bowel disease	C57Bl/6 mice	Human AT-MSC Murine AT-MSC (syngeneic, allogeneic)	Significantly amelioated the clinical and histopathological severity of colitis
González et al., 2009 (39)	collagen-induced arthritis	DBA/1 mice	Human AT-MSC Murine AT-MSC (syngeneic, allogeneic)	Significantly reduced the incidence and severity of experimental arthritis

Gene transfected stem cell therapy in autoimmune disease

Some studies on gene therapy using stem cells as a vehicle in autoimmune disease were reported. For examples, there were Brain-derived neurotrophic factor (BDNF) gene delivery in an animal model of multiple sclerosis using bone marrow stem cells (43) and human insulin gene transfected BM-MSC therapy in murine type 1 insulin-dependent diabetes (44). Xu et al. evaluated the effect of transplantation of bone marrow-derived stem cells expressing human insulin gene on murine type I insulin-dependent diabetes which induced by streptozoticin injection. After transplantation, the body weight increased and the average blood glucose level 7 day and 42 day were significantly lower compaired with control group. Immunohistochemistry showed secretion of human insulin in serum and liver. Makar et al. conducted BDNF gene transfected bone marrow stem cells therapy in experimental murine EAE, an animal model of multiple sclerosis. After therapy, EAE onset was significantly delayed and overall clinical severity was significantly reduced in mice which had received BDNF-transfected BM-MSC compared with control receiving BM-MSC transfected with an empty vector lacking the BDNF gene. Another study of human ciliary neurotrophic factor- overexpressed MSC therapy reduced demyelination and induced clinical recovery in murine EAE (45). Okada et al. reported that hepatocyte growth factor-overexpressed MSCT attenuated autoimmune myocarditis in rats (46).

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Potential Conflict of Interest

The authors have no conflicting financial interest.

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