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Review

# New hope for type 2 diabetics: Targeting insulin resistance through the immune modulation of stem cells

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ABSTRACT

The prevalence of type 2 diabetes (T2D) is increasing worldwide, highlighting the need for a better understanding of the pathogenesis of the disease and the development of innovative therapeutic approaches for the prevention and cure of the condition. Mounting evidence points to the involvement of immune dysfunction in insulin resistance in T2D, suggesting that immune modulation may be a useful tool in treating the disease. Recent advances in the use of adult stem cells from human umbilical cord blood and bone marrow for immune modulation hold promise for overcoming immune dysfunction in T2D without many of the complications associated with traditional immunosuppressive therapies. This review focuses on recent progress in the use of immune modulation in T2D and discusses the potential for future therapies. New insights are provided on the use of cord blood-derived multipotent stem cells (CB-SC) in T2D.



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## 1. Introduction

Type 2 diabetes (T2D) is the most common type of diabetes, with prevalence rates exceeding 12.1% of the population in India, 9.7% in China, and 8.3% in the United States [1,2]. The incidence of T2D is increasing worldwide due to popularization of a Western lifestyle characterized by overnutrition and limited exercise. Diabetes-associated complications (*e.g.*, cardiovascular diseases, stroke, blindness, kidney

*Abbreviations:* CB-SC, cord blood-derived multipotent stem cells; GVHD, graft-versus-host disease; MSC, mesenchymal stem cells; TGF-β1, transforming growth factor-β1; T1D, type 1 diabetes; T2D, type 2 diabetes; Tregs, regulatory T cells.

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failure, and emotional stress) markedly decrease quality of life of T2D patients, limiting the productivity of individuals with the disease and creating significant economic and social burdens. Thus, finding a cure for T2D is a top priority.

In adults T2D has traditionally been characterized by elevated fasting blood glucose and an abnormal glucose tolerance test without evidence of autoimmune destruction of pancreatic islet β cells. However, evidence collected over the past decade indicates that the etiology of T2D includes an autoimmune component that initiates an inflammation affecting pancreatic islet β cells [3–8], which provides new insight into the mechanism and potential treatment of insulin resistance. These findings suggest T2D may be a candidate for some of the therapies in development for T1D, including the use of stem cell-based regeneration of pancreatic islet β cells and immune modulation by adult multipotent stem cells derived from cord blood or bone marrow [9–12]. While stem cell transplantation research faces many technical and ethical barriers, the use of adult multipotent stem cells to modulate immune response may provide a more universally acceptable and feasible approach. The use of adult multipotent stem cells in immune modulation has been widely explored in a variety of disciplines in animal studies and clinical trials to alter immune responses in graft-versus-host disease (GVHD), pancreatic islet transplantation, and various autoimmune diseases [9–11,13–16]. In this review, we highlight progress in the development of stem cell-based immune modulation for treating T2D.

## 2. Insulin resistance and immune dysfunction in type 2 diabetes

### *2.1. Pathophysiology of metabolic inflammation and insulin resistance*

Insulin, a hormone produced by pancreatic islet β cells, plays a key role in regulating cell metabolism, growth, differentiation, survival, and homeostasis through receptors expressed in all tissue cells. The neuro-endocrine network controls insulin regulation from synthesis to release to uptake and action in peripheral tissues. Obesity and lack of exercise are associated with increased risk for insulin resistance, and recent evidence indicates this increased risk is due at least in part to adipocyte-mediated immune dysfunction and inflammation that may affect insulin regulation and uptake. Inflammatory cytokines derived from adipocytes and macrophages promote the development of insulin resistance in T2D through JNK and/or IKKβ/NF-κB pathways, including changes in the levels of tumor necrosis factor-α (TNFα), interleukin-1 (IL-1), IL-6, IL-17, monocyte chemoattractant protein-1 (MCP-1), resistin, plasminogen activator inhibitor-1 (PAI-1) and others [8,17–19]. Despite the complexity and multifactorial nature of T2D, metabolic inflammation is the most common step leading to insulin resistance in the disease (Fig. 1). Although this relationship between insulin resistance and inflammation is a relatively recent finding, anti-inflammation therapy is rapidly gaining acceptance as an approach for the treatment of insulin-resistance in patients with T2D [5,8,20–22].

### *2.2. Metabolic abnormalities cause atypical immune dysfunction in T2D*

The human immune system does not normally recognize single glucose and/or lipid molecules as antigens unless they occur in glycolipids or lipoproteins capable of stimulating an immune response. Like other cells, cells of the immune systems rely on insulin signaling to utilize glucose and/lipid as regular fuels for energy to perform their normal functions. Overnutrition-related hyperglycemia and/or hyperlipidemia cause chronic toxicity to multiple body systems including the immune system and interfere with the normal response to insulin. The resulting oxidative stress, mitochondrial dysfunction, and endoplasmic reticulum (ER) stress impair intracellular homeostasis and can alter both innate and adaptive immune responses and promote inflammation [6,23–25].

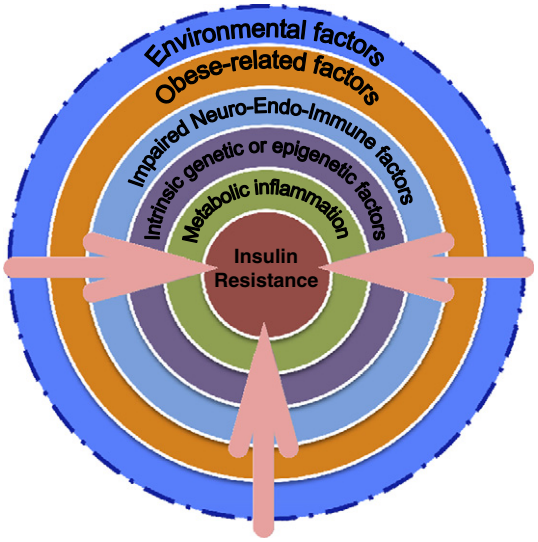


**Fig. 1.** Outline the multipotential factors that contribute to insulin resistance. The metabolic inflammation is the common step for these factors leading to insulin resistance, the key issue for the onset of T2D.

### *2.3. Metabolic abnormalities cause autoimmunity in T2D*

Healthy pancreatic islets are protected by a specialized basement membrane that serves as a barrier against immune cells and assists in maintaining homeostasis [26,27]. Studies using humanized immune-mediated diabetic mouse model demonstrate that immune cells cannot cross the basement membrane into pancreatic islets unless triggered by antigen-presenting cells (APCs) [28]. Donath and Shoelson [23] found infiltrated macrophages inside of pancreatic islets of T2D subjects. These macrophages may present islet β cell antigens to T cells and initiate the autoimmune responses, which is supported by evidence of autoimmune response in T2D similar to the response observed in T1D [3,4]. About 10% of subjects with T2D are diagnosed with "latent autoimmune diabetes in adults (LADA)" following a positive test for at least one of the known T1D-related autoantibodies (*e.g.*, islet cell antibodies (ICA), anti-protein tyrosine phosphatase-like protein IA2, anti-insulin, and anti-glutamic acid decarboxylase 65 (GAD65)) [7,29]. In addition to these humoral autoimmune responses, Brooks-Worrell and colleagues reported that some T2D patients who test negative for islet autoantibodies have T cells responsive to islet proteins in the peripheral blood [4]. Thus, it is appears that autoimmune responses contribute to the pathogenesis of T2D in some, if not all, patients.

The specific mechanisms underlying these autoimmune responses are not yet well characterized. A large body of evidence demonstrates that regulatory T cells (Tregs) play an essential role in control of peripheral tolerance and the development of autoimmune-caused diabetes [30–35]. Reports have shown the dysfunction of regulatory T cells (Tregs) in obese-related inflammation [36–38]. To better understand the molecular mechanism underlying the autoimmunity in T2D, we focused on the transcription factor autoimmune regulator (Aire). Aire, usually expressed in thymic medullary epithelial cells, plays an important role in immune tolerance by mediating the ectopic expression of peripheral self-antigens and the deletion of auto-reactive T cells [39]. Increasing evidence shows the expression of Aire in peripheral tissues and organs [40]. Interestingly, we found the Aire expression in human peripheral blood-derived multipotent stem cells (PB-SCs). *In vitro* studies demonstrated that both high fat and glucose significantly alter the bioactivity of PB-SCs (Fig. 2A and B), and high glucose markedly reduces expression of Aire expression in these stem cells (Fig. 2B). Down-regulation of Aire expression may be a primary contributor to

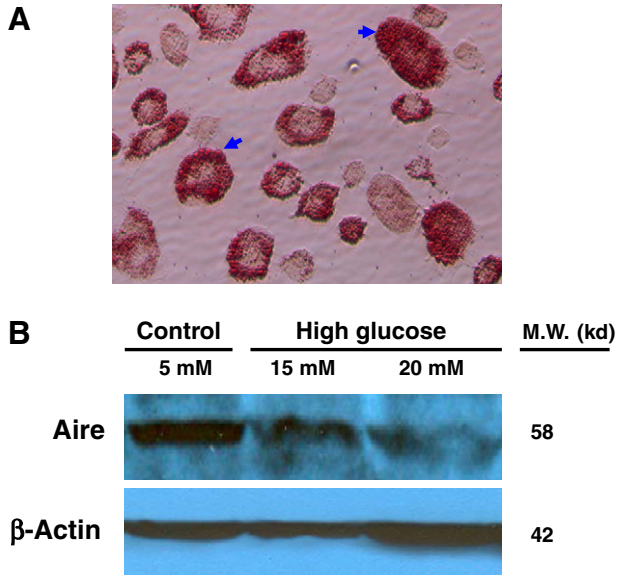


**Fig. 2.** Metabolic abnormalities affect the function of stem cells. Peripheral blood-derived multipotent stem cells (PB-SCs) were isolated from buffy coat blood of healthy humans, by using the as previously described method [73,89]. (A) Oil red O staining shows numbers of lipid droplets (blue arrow) in VLDL-treated PB-SCs. PB-SCs were treated with very-low-density lipoprotein (VLDL, 500 μg/ml) for 24 h in regular cell culture medium. (B) Western blot shows the dose-dependent reduction of Aire following high glucose treatments in PB-SCs. The β-actin served as internal control.

the autoimmune response that occurs in T2D subjects. These data provide a molecular link between T2D and autoimmune disease [3,4,41–43].

## 3. Immune modulation of stem cells and approaches for clinical application

### *3.1. Current clinical approach for insulin resistance: PPAR-γ agonists as insulin sensitizer*

A growing body of evidence demonstrates that metabolic inflammation plays a key role in the development of insulin resistance. Targeting inflammation through the peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists (thiazolidinediones, TZDs) is one of the major pharmacological approaches for clinical treatment of T2D that directly improves insulin sensitivity. The presence of PPAR-γ in adipocytes and macrophages has been shown to directly contribute to the regulation of insulin sensitivity in response to PPAR-γ agonists [44]. TZDs have been widely prescribed as the frontline insulin-sensitizing drugs to treat T2D patients in recent years, but the risk of adverse effects with long-term use of these compounds is cause for concern. For example, the use of Rosiglitazone (Trade name: Avandia) has been strictly limited due to an increased risk of heart attack [45], and use of pioglitazone (Trade name: Actos) is associated with an increased risk of bladder cancer [46]. Thus, additional assurances of safety will be necessary in the discovery and development of next-generation selective PPARγ modulators and/or non-TZD insulin sensitizers.

### *3.2. Current clinical approach: application of conventional immunotherapy*

While multiple factors contribute to risk for T2D (*e.g.*, environmental factors, genetic predisposition, obese, and lifestyle factors), metabolic inflammation is the final common step leading to insulin resistance and the development of T2D (Fig. 1). Therefore, overcoming metabolic inflammation is the major challenge in developing preventative or therapeutic approaches for T2D. A number of strategies for overcoming inflammation-mediated insulin resistance have been proposed and tested in animal studies and clinical trials [5,20,21,23,47–49]. For example, blockade of IL-1 with antibodies or IL-1 receptor antagonist has been shown to improve metabolic control of T2D in clinical trials [23,50–53]. However, these efforts are complicated by the role of inflammatory cytokines in the normal immune response against viruses, bacteria, and tumors. Recent clinical trials of conventional immunotherapies (*e.g.*, blocking with monoclonal antibodies) by targeting and blocking a single molecule have not been successful in treating autoimmunity in T1D [54–57]. Thus, additional research on alternative approaches will be needed to address the role of inflammation in the development and maintenance of T2D.

### *3.3. Novel clinical approach: application of MSC as immunotherapy*

Mesenchymal stem cells (MSCs) are rare cell populations typically located in the bone marrow and in connective tissues. MSCs cultured *in vitro* usually display fibroblast-like morphology and adhere to the tissue culture-treated plastic devices. These cells are positive for CD73, CD90, and CD105 and negative for blood lineage markers [9]. Despite the morphological similarity of *in vitro* cultures, MSCs are a highly heterogeneous population with different phenotypes and passages. MSCs share many characteristics with bone marrow-derived stromal cells (BMSCs) and tissue-derived fibroblasts [10] making it difficult to generate a pure MSC culture. Contamination with BMSCs, fibroblast, and hematopoietic cells (especially in mice) is typical [10]. However, the immune modulation activity of MSCs warrants the effort to establish and study pure cultures.

Mounting evidence demonstrates that MSCs can alter the activity of most types of immunocytes including $CD4^+$ T cells, $CD8^+$ T cells, B cells, monocytes/macrophages, DCs, and NK cells [10,12]. The molecular mechanisms underlying this activity in mice are fairly well understood, but the mechanisms for human MSCs are different [58–60]. For example, nitric oxide (NO) plays a key role in mouse MSCs, but not in human MSCs. Importantly, Waterman et al. reported that specific TLR-activation polarizes hMSCs into two distinct sub-populations (MSC1 and MSC2) that display different immune modulating activities. Sub-population MSC1 primed by TLR4 primarily releases pro-inflammatory factors and activates lymphocytes, whereas MSC2 primed by TLR3 produce predominantly immunosuppressive effects [61].

The immune modulating activity of MSCs may be harnessed for clinical application in T2D. For these applications, MSCs can be derived from bone marrow, adipose tissue, umbilical cord, or placenta. In most studies reported to date, MSCs are expanded through *in vivo* culture, collected, and administered through interventional therapy such as intravenous delivery or direct infusion into pancreatic islets via transfemoral cannulation under angiography. MSCs are under study for use in treating graft versus host disease (GVHD) in islet transplantation [13,14]. However, a significant placebo effect has been observed in some studies, and larger-scale, placebo-controlled clinical trials will be necessary to prove the concept [10].

While these approaches show some promise, researchers must overcome several challenges before IV or direct infusion of MSCs can be used clinically: 1). Safety in chromosome stability after *ex vivo* expansion [62]. 2). Tumorigenicity after *ex vivo* expansion. Yang and colleagues found the tumor formation of mouse MSCs after transplant into the diabetic mice (personal communication). 3). Immunogenicity of MSCs post transplant. Increasing evidence from animal and clinical studies indicates that allogeneic MSCs can cause immune rejections [12,63,64]. Importantly, MSCs may function as antigen-presenting cells (APCs) in the presence of interferon-γ (IFN-γ) [65,66]. 4). Pulmonary passage effect [67,68]. 5). Cell fusion between MSCs and tissue cells post transplant [69,70]. 6). Exposure of new tissue antigens after gene reprogramming in fused cells, which may promote immune responses.

### 3.4. Novel clinical approach: Stem Cell Educator therapy

Based on evidence that cord blood-derived multipotent stem cells (CB-SC) can control autoimmune responses by altering Tregs and human islet β cell-specific T cell clones [9,71,72], we developed a novel Stem Cell Educator therapy (ClinitrialTrials.gov identifier: NCT01415726). Briefly, a 16-gage IV needle was placed in the left (or right) median cubital vein, and the patient's blood was passed through a Blood Cell Separator at 35 ml/min for 6 to 7 h to isolate lymphocytes. The collected lymphocytes were transferred into the Stem Cell Educator for exposure to CB-SCs, and other blood components were returned to the patient. The Stem Cell Educator functions as part of a closed-loop system that circulates a patient's blood through a blood cell separator, briefly co-cultures the patient's lymphocytes with CB-SCs *in vitro*, and returns the educated lymphocytes to the patient's circulation. CB-SCs attached to interior surfaces in the device present secreted and cell-surface signaling molecules to passing lymphocytes, and only the autologous lymphocytes are returned to the subjects. The Stem Cell Educator requires only two venipunctures, carries a lower risk of infection than a typical blood transfusion, and does not introduce stem cells or reagents into patients. In addition, CB-SCs have very low immunogenicity, eliminating the need for human leukocyte antigen (HLA) matching prior to treatment [9,73,74]. Thus, the Stem Cell Educator may provide CB-SC-mediated immune modulation therapy for multiple autoimmune and inflammation-related diseases while mitigating the safety and ethical concerns associated with other approaches. The relative simplicity of the approach may also provide cost and time savings relative to other approaches.

## 4. Efficacy of immune modulation of stem cells in the treatment of T2D

### 4.1. Efficacy in targeting immune dysfunction

Interleukin-17 (IL-17, also known as IL-17A) is a pro-inflammatory cytokine produced by activated $CD4^+$ T cells, $CD8^+$ T cells, γδT cells, and NKT cells. IL-17 promotes inflammation and autoimmunity by inducing the expression of genes encoding proinflammatory cytokines (TNF, IL-1, IL-6, G-CSF, and GM-CSF) and chemokines to recruit neutrophils, enhance antibody production, and activate T cells [75,76]. Recent studies indicate that obesity selectively promotes expansion of the Th17 cells and increases IL-17 production [77]. Subsequently, we found that expression of IL-17 in T2D patients was higher than that of healthy controls, and administration of Stem Cell Educator therapy markedly reduced levels of IL-17 in these patients. Examination of the effects of therapeutic approaches on other cytokines involved in the chronic low degree inflammation (*e.g.*, IL-1, IL-6, IL-17, and TNFα) will likely require sensitive intra-cellular staining techniques and flow cytometry analysis.

Tregs play a crucial role in controlling the immune balance and the maintenance of immune homeostasis through their inhibitory impacts on autoreactive effector T cells and reduction of inflammation. Compelling evidence demonstrates that Treg abnormalities are associated with initiation and progression of obesity-associated T2D, both in animal models and diabetic patients [36]. Using leptin-deficient ob/ob mice, Ilan and colleagues showed that treatment with anti-CD3 Ab + β-glucosylceramide (GC, a metabolic intermediate) decreases fat accumulation in the liver, decreases infiltration of macrophages in adipotissue, and increases $CD4^+Foxp3^+$ Tregs in fat [38]. A large body of literature from animal studies and other clinical settings (*e.g.*, GVHD studies) show that up-regulation of Tregs is one of the major mechanisms contributing to the immune modulation of stem cells [10–12,71]. Our clinical trial data on the use of Stem Cell Educator in T1D have demonstrated that the percentage of Tregs in the peripheral blood of T1D patients is significantly increased at 4 weeks following therapy. A better understanding of the role of Tregs in T2D may provide a novel approach for prevention and treatment of the disease.

### 4.2. Efficacy in improving islet β cell function and metabolic control

Reduction of insulin sensitivity is the hallmark of T2D. It is widely accepted that the inability of pancreatic β cell to function in compensating for peripheral insulin resistance leads to the onset of clinical diabetes. Progressive dysfunction of islet β cells leads to the absolute shortage of insulin-producing β cells due to the apoptosis of islet β cells. Therefore, overcoming a shortage of islet β cells is a major obstacle in the treatment of long-standing T2D subjects. Results from animal studies demonstrate that administration of MSCs can contribute to regeneration of islet β cells, albeit with a very low frequency of auto-transdifferentiation into insulin-producing cells [78]. MSCs also produce multiple trophic factors that contribute to repair and regeneration of tissues [79–81], including regeneration of islet β cells [82,83]. In this regard, the use of MSCs as feeder cells can improve the function of transplanted islets via revascularization and immune protection [83,84].

However, the recovery of islet function by administration of MSCs is effective due to targeting peripheral insulin resistance. Abraham and colleagues reported that bone marrow-derived MSCs in combination with an HO-1 (a cytoprotective antioxidant system) inducer can prevent T2D and restore insulin sensitivity and glucose tolerance after transplant into the bone marrow of obese mice [85]. Using human placenta-derived MSCs (PD-MSCs, intravenous infusion, and 3 doses for total $1.35\times10^6$ cells/kg of body weight), Jiang and colleagues showed improved metabolic control in a pilot study with T2D patients ($n=10$) [86]. Due to the challenges involved in *ex vivo* expansion of MSCs and potential contamination in the lab, whole bone marrow-derived mononuclear cells (BM-MNCs) have been tested in clinical trials. Bhansali and colleagues reported that direct infusion of BM-MNCs into pancreas via cannulation significantly increased β-cell function as measured by the homeostasis model assessment (HOMA-B) but failed to change the HOMA of insulin resistance (HOMA-IR) [87]. Notably, preliminary results from our ongoing clinical trials of Stem Cell Educator therapy indicate that T2D patients achieve improved metabolic control and reduced inflammation or autoimmunity that lasts at least 9 months following a single treatment. Median glycated hemoglobin ($HbA_1C$) was significantly reduced (−1.36 percentage points at 12 weeks post treatment), and more than 80% of subjects achieved the 7% standard recommended by the American Diabetes Association (ADA) for T2D treatment.

## 5. Conclusions

The prevalence of T2D is rising at an alarming rate. T2D and its associated complications (*e.g.*, cardiovascular diseases, stroke, blindness, and kidney failure) create huge burdens on families and societies. The identification of the role of inflammation in the development of insulin resistance and T2D offers an opportunity to develop novel anti-inflammation and immune modulation therapies to treat and potential prevent or cure the disease. However, efforts to address the role of immune response in T1D provide cautionary lessons for future efforts in T2D. In the past 25 years, tremendous efforts have been invested into T1D studies to find a cure, but clinical trials on conventional immunotherapy have not been successful in humans, despite being effective in mice [54–57,88]. The failures of these and other approaches to controlling inflammation in T1D should inform the development and testing of approaches in T2D. Recent advances in our understanding of stem cell-mediated immune modulation and advances in the use of minimally invasive autologous cell therapies may contribute to the development of successful therapies for overcoming inflammation and insulin resistance in T2D.

## Take-home messages

- Insulin resistance is the hallmark of T2D.
- Multiple immune dysfunctions contribute to insulin resistance in T2D.
- Adult stem cells (CB-SCs and MSCs) possess two major natures: differentiation potential for tissue repair and immune modulation for controlling inflammation.
- CB-SC-based Stem Cell Educator therapy functions as an immune modulator that can lead to control of the immune dysfunction of T2D and improve the metabolic control in clinic.
- T2D patients need to change their lifestyle: "control mouth, stride legs".

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### *The prevalence of anti-synthetase syndrome in patients affected with idiopathic interstitial pneumonias*

Antisynthetase syndrome (ASS) is characterized by interstitial lung disease, arthritis, Raynaud's phenomenon and the presence of autoantibodies to aminoacyl-tRNA synthetase. Watanabe K, et al. **(Respiratory Medicine 2011; 105 (8):1238–47)** retrospectively evaluated the prevalence of ASS in 198 Japanese patients with idiopathic interstitial pneumonia and found 13 cases, (6.6%) that tested positive for anti-syntetase antibodies. Anti-EJ was the most prevalent antibody, positive in 6 cases (3%) followed by anti-PL-12. Among ASS, the Authors found a 50% prevalence of non specific interstitial pneumonia (NSIP) and 46.2% of cases without extrapulmonary features and absence of myositis. On HRCT ground glass opacity and traction bronchiectasis were the major findings among patients with ASS, and honeycombing was absent.