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Current Perspectives of Umbilical Cord Stem Cell Therapy for Treating Autoimmune Diseases

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Abstract

Multipotent adult stem cells have been promoted and utilized in the treatment of autoimmune diseases. Autoimmune diseases (AD) are unquestionably debilitating, not only by diminishing quality of life, but also these disorders significantly reduce life span. To date, prevalent drug treatments acting to curb AD seem to be ineffective, thus there is a critical need to find alternative treatments. Stem cells derived from the umbilical cord blood and tissue, bone marrow, adipose, amniotic fluid, placental, and dental pulp have been recently used for treating some of these diseases. Here we highlight the current use of umbilical cord mesenchymal stem cells (UCMSC) on Rheumatoid Arthritis, Lupus, Inflammatory Bowel Disease, Multiple Sclerosis, Type I Diabetes, and Psoriasis.

Keywords: Autoimmune diseases; Stem cell therapy; Umbilical cord; T lymphocytes; Multipotent adult stem cells.

Editor's Note

Rheumatoid Arthritis (RA) is a systemic and chronic disease in which abnormally activated T lymphocytes, especially due to an imbalance in Th17 and Treg population, causes an abnormal immune response associated with progressive joint disintegration. This effect is irreversible, and most treatments are geared towards inhibiting the function of these immune cells. Studies have administered over 100 million UCMSCs (cord blood and/ wharton's jelly) intravenously and intra-articularly into patients with advanced RA [1]. Scientists have found significant decreases in joint pain and stiffness, limb mobility increased, and an overall improvement in activities of daily living after 6 months [2]. UCMSCs can curb the symptoms of RA directly or indirectly by enhancing immunomodulation by downregulating T-cell activation and proliferation markers and increasing Tregs, increasing homing potential, activating macrophages with reparative properties, increasing Th2 population (anti-inflammatory), and a significant decrease in the mean of disease activity joint score [1].

Systemic Lupus Erythematosus (SLE) may stem due to genetic, epigenetic and environmental factors causing overproduction of dysfunctional B cells, T cells (mitochondrial dysfunction), dendritic cells and activation of certain antinuclear autoantibodies, inducing extreme tissue injury leading to multi organ failure. Although symptoms are typically heterogeneous, humoral autoimmunity seems to be a distinctive indicator of SLE. The use of UCMSCs from wharton's jelly has been shown to modulate the immune response via the activation of Tregs by TGF- expression and inhibition of immature dendritic cells (iDCs) to mature dendritic cell (mDC) production, autoreactive NK cells, T cells and B cells and mitochondrial biogenesis and transfer in activated T cells [3]. Multiple ongoing phase I to phase III clinical trials with intravenous infusions of UCMSCs (1-5 million cells/kg body weight) have shown remission rates of more than 28% within the 1st year to 50% within 4 years (clinicaltrials.gov, Identifiers - NCT03562065, NCT03219801, NCT03580291, NCT03171194, NCT02633163). Overall, the outcomes of UCMSC treatment seem promising, and elucidating detailed mechanisms will help us understand the impact of UCMSCs on SLE [4].

Typically affecting the gastrointestinal (GI) tract, Inflammatory Bowel Disease (IBD) may be caused by sectional GI inflammation, macrophage overproduction, and free radicals involved in GI lesions. One suggested mechanism for IBD is through the pathological activation of CD4 positive thymic helper cells (CD4+T cells) which promote them to differentiate into CD4+Th1 and CD4+Th17, that consequently trigger intestinal epithelial inflammatory cells by releasing inflammatory cytokines [5]. Research has suggested that UCMSCs from wharton's jelly used in treatment for patients with IBD can suppress abnormal immune function, alleviate stomach ulcers, and promote mucosal healing [6]. Treatment with UCMSCs have shown to decrease proliferation of Th1, Th17, neutrophils and CD3+T cells and regulate tight junction proteins through NF-kB and Wnt/β catenin pathways [5]. Additionally, there does not seem to be any safety concerns with UCMSC therapy in patients with IBD, even after treatment with 10 million cells/kg body weight.

Multiple Sclerosis (MS) is a neurological disease that affects the central nervous system by progressively deteriorating the myelinated sheaths of neurons. This phenomenon may be caused by cytotoxic cells (CD8+T cells), along with CD4+ T cells that blunt myelin sheath repair and also trigger oligodendrocyte apoptosis through the binding of the FasL on Fas receptors. Cell based therapy for MS has been focused on slowing the progression of neurodegeneration. For example, one study showed that 83% of MS patients injected with approximately 150 million UCMSCs from wharton's jelly did not exhibit disease progression for one year [4]. Another trial found that patients infused with 1 to 2×10^6 cells/kg of UCMSCs exhibited decreased cytokine levels associated with central nervous system inflammation [7]. The suppressive functions of Tregs which are impaired in MS are shown to be reversed by UCMSC treatment. Additionally, anti-inflammatory molecules including TGF-β1, IL-10 and PGE2 were increased and pro-inflammatory IFN-γ decreased with UCMSCs (wharton's jelly) [8].

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Often beginning at childhood, Type I Diabetes results in severe damage to the insulin-producing -cells caused by pathogenic CD8 T-cells leading to an altered Treg population. UCMSCs from blood have been shown to differentiate into pancreatic β-cells by activating Pdx-1 and can restore insulin to euglycemic levels. Human leukocyte antigen G (HLA-G) released by UCMSCs can trigger expansion of Treg cells which helps rebalance the Teff/Treg ratio and reduce Th1 effector cells. Additionally, wharton's jelly may have a superlative potential to differentiate into mature β-cells which produce insulin [9]. Currently, encapsulated pancreatic endodermal cells preserve stability in c-peptide levels, and the synergistic use of differentiated UCMSCs towards insulin producing cells along with intravenously infused UCMSCs can be a potential cure for T1D.

Psoriasis is an obscure autoimmune disorder that affects the skin and joints. The exact etiology is not clear, however the proliferation and activation of Th1 and Th17 cells from the expression of the HLA-Cw6 gene may enhance systemic inflammation to organs and tissues. Additionally, it is hypothesized that Th1 and Th17 cells directly signal certain cytokines (IFN-γ, IL-17A, IL-17F, and IL-22) responsible for the alteration in keratinocyte generation [10]. Recent studies utilizing UCMSCs as a treatment for Psoriasis seem advantageous. Approximately 1-2 million/kg of UCMSCs from cord blood were infused into patients with Psoriasis, and it has been suggested to alleviate skin lesions, improve immunomodulation, and regulate cytokine production for up to four years [11].

Conclusion

In conclusion, treatment of autoimmune diseases with multipotent adult stem cells derived from the umbilical cord shows promising outcomes in most studies and clinical trials. Although UCMSC therapy seems to be safe, favorable, and a viable treatment option, further studies are warranted to elucidate the mechanisms of immunomodulation, optimal dosages, suitable transfusion methods, and appropriate standardized protocols. It is now known that UCMSCs decrease the production of mast cells, NK cells, B cells, T17, and monocytes which consequently decrease the activation of iDC and mDC, and UCMSCs also enhance the activation of Treg, Th2 and Native T cell. Moreover, a better understanding of the etiology of these autoimmune disorders are necessary to improve treatment options using UCMSCs. Thus, umbilical cord stem cell therapy may become a primary treatment option for a multitude of autoimmune disorders.

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