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Current state of umbilical cord stem cells in humans

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Abstract

The umbilical cord is an unlimited source of mesenchymal stem cells (MSC) and hematopoietic stem cells (HSC). MSC obtained from the umbilical cord can be differentiated into different types of mesodermal cells, e.g. chondrocytes, osteocytes, adipocytes, and myocytes. It is also worth mentioning that there are reports of MSC differentiation into endo and ectodermal cells. The immunosuppressive properties of MSCs can protect against graft versus host disease as well as prevent rejection after transplantation. Umbilical cord stem cells can be frozen and then stored in liquid nitrogen for many years. In this work, we focused on the use of preclinical and clinical umbilical cord stem cells in disease entities such as type I diabetes, chronic renal failure, and multiple sclerosis. Furthermore, the anti-cancer properties of Wharton's jelly cells are described.

Running title: Umbilical cord stem cells in humans

Keywords: umbilical cord stem cells, Wharton's jelly, clinical trials, mesenchymal stem cells

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Introduction

In humans, the umbilical cord (UC) serves as a structure that allows nutrition of the developing fetus, as well as transportation of oxygenated and oxygen-free blood through the connection of the placenta and the fetus. Differentiation reports in the literature describe several compartments in the human umbilical cord. Fong et al. showed that UC couldbe divided into three major components: (a) the amnion (b) Wharton's Jelly, and (c) the vessels. The umbilical cord consists of three spirally twisted blood vessels (two arteries and one vein) enveloped in connective tissue called Wharton's jelly (WJ) and covered by epithelium [1].

In recent years, the research at preclinical and clinical levels on stem cells derived from the umbilical cord is conditioned by these cells self-renewal ability, high potential for differentiation, immunomodulatory properties, as well as their ability to restore tissues [2].

In this article, we try to present the latest reports on the use of umbilical cord stem cells in the treatment of common autoimmune diseases,such as type I diabetes or multiple sclerosis,and also the regenerative properties of UC stem cells in the treatment of chronic renal failure. We also discuss the controversial anti-tumor activity of mesenchymatic Wharton's jelly stem cells.

Treating type I diabetes

Type I diabetes is an autoimmune disease that results from the destruction of insulin-producing pancreatic β cells. As a result of the damage to Langerhans islands, patients lose control of regulating their blood glucose levels, and this leads to hyperglycemia [3]. At present, several exogenous insulin injections on a daily basis is the normal treatment for millions of diabetics. However, insulin administration only medicates the symptoms and does not eliminate the cause of diabetes in any way. Currently conducted clinical studies on the therapy of type I diabetes focus on combating the causes, i.e. autoimmune basics, and protecting β cells from destruction. Recent studies have shown that umbilical cord blood stem cells can treat type I diabetes by eliminating the autoimmune component and regenerating damaged β cells [4].

Cord blood contains up to 10% of stem and progenitor cells. Among umbilical cord blood cells, a beneficial therapeutic effect in the treatment of diabetes is shown by CD45 + umbilical cord blood-derived multipotent stem cells (UMB-SC) and CD90 + umbilical cord blood-derived mesenchymal stem cells (UMB-MSC) - they have the potential for differentiation and immunomodulation [5]. UCB-MSC has a multidirectional immunomodulatory effect on both innate and adaptive immune cells: T lymphocytes and B lymphocytes, dendritic cells and natural killer cells. UCB-MSC exhibit immunosuppressive activity on lymphocyte proliferation and inhibit the pro-inflammatory effect of cytokines [6].

Hu et al. (2013) in the results of their research indicate the clinical safety of using Wharton's jelly-derived mesenchymal stem cells from the umbilical cord of patients, as well as the restoration of pancreatic B-cell function in newly diagnosed type I diabetes [7]. In another study, patients were given UCB-MSC infusion for 24 months. The study group showed a lower postprandial glucose level, as well as a lower HbA1c level and a higher C peptide level compared to the control group [8].

The results obtained in the observed studies prove that MSCs under specific conditions can be differentiated into insulin-producing cells (IPCs), which can be a source of β-cells for replacement therapy [9**]**. Effective UCB-MSC differentiation protocols towards IPC were developed in 2012. The resulting IPCs responded to the presence of glucose both *in vitro* and *in vivo* by releasing insulin and C-peptide [10].

In summary, UCBs are an important biological source for the generation of pancreatic β cells, and also have immunomodulatory properties in the treatment of type I diabetes. Promising preclinical and clinical results indicate that transplantation of stem cells derived from umbilical cords can be a safe and effective treatment for diabetes.

Chronic renal failure

Mesenchymal umbilical cord stem cells (UC-MSC) secrete growth factors and cytokines that cause regeneration of adjacent tissues. UC-MSCs reduce the activation and proliferation of T lymphocytes, and also direct T cells to anti-inflammatory effects by increasing the number of regulatory T cells and inhibiting differentiation of Th17 cells [11]. In experimental models of diabetic nephropathy in rodents, administration of UC-MSC allowed to preserve renal function and reduce their damage [12].

In their case study, Rahyussalin et al. confirm the effectiveness of umbilical cord MSCs in the treatment of chronic kidney disease (CKD). A woman aged sixty-two had diabetes for over 10 years, a complication of which was chronic renal failure with a creatinine level of 11mg/dl and no urination. The woman underwent hemodialysis three times a week. The patient underwent six cycles (one dose every three months) of intrathecal and intravenous UC-MSC. Eight months after the first protocol of intrathecal and intravenous administration of 16 million human cord umbilical cord MSCs, the kidney function of the patient significantly improved. Creatinine levels decreased to 2mg/dl and the patient regained the ability to urinate [13].

Treatment of multiple sclerosis

Multiple sclerosis (MS) is a chronic, autoimmune inflammatory disease of the central nervous sys-

tem (CNS) that affects more than 2.3 million people around the world. The pathogenesis of the disease consists of demyelination occurring in the CNS under the influence of autoreactive lymphocytes [14]. Most people with multiple sclerosis (about 85%) have been diagnosed with relapsing-remission (RRMS). People with RRMS experience periods of deterioration (relapse) followed by periods when symptoms regress or completely disappear (remission). 10% of patients have primary progressive MS (PPMS). People suffering from PPMS do not experience relapses, however, they claim that the disease progresses over time. In the absence of RRMS treatment, 50-60% of patients may switch to so-called secondary progressive MS (SPMS) [15].

In recent years, therapeutic strategies have been introduced to delay the progression of MS through immunosuppression and immunomodulation. Stem cells (SC) are now also finding their place as a promising remedy for the disease. The ability of stem cells to proliferate and differentiate as well as immunomodulation can be used to slow down disease progression and improve the regeneration process of damaged neurons in the CNS. Studies have shown that autologous or allogeneic MSC transplantation as a result of neuroprotective and immunoregulatory effects improves the process of demyelination in the CNS [16].

The following MSC therapeutic mechanisms apply in the treatment of MS: ability to migrate to the site of injury, differentiate into neurons, and immunomodulation by secreting neurotropic and anti-inflammatory factors. MSC characterizes the ability to cross the blood-brain barrier. Environmental factors play an important role in guiding MSCs to damage sites. Research results indicate that culture conditions and time play a key role in expressing the targeting factors for damaged neurons. MSC subjected to more than 5 passages present a significantly lower chemotactic response [17]. Rossi et al. indicate that adipose tissue isolated MSC (Ad-MSC) and Wharton's jelly (USC-MSC) show greater expression of migration factors than bone marrow-derived MSC (BM-MSC). MSCs exhibit immunomodulatory properties through direct or paracrine interaction with immune cells. UC-MSC inhibit the production of pro-inflammatory cytokines and T cells and regulate the Th2 to Th1 ratio [18].

The biggest problem in the treatment of neurodegenerative changes in the CNS of MS patients is the inability of the nerve tissue to regenerate completely. Research suggests that MSC infusion can lead to stem cell migration to damaged tissues and reconstruction. MSCs also have the ability to differentiate into neurons, astrocytes, and oligodendrocytes. In addition, MSCs secrete immunosuppressive factors such as IL-10, PGE2, and TGFβ, among others, to suppress the proliferation of inflammatory immune cells [19].

In the case study of a patient with MS, done by Zong-Liu Hou et al., it is indicated that the use of allogenic UC-MSC in therapy has many advantages over autologous BM-MSC therapy. First of all, the UC-MSC collection procedure is painless and free from the possibility of infection compared to the aspiration procedure of 200ml bone marrow. Secondly, after two passages from one umbilical cord, $110x10^6$ cells can be obtained, whereasless than 30 x 106 cells can be collected from 200ml bone marrow. Many studies show that higher doses of MSC are more effective in treating MS. Allogenic UC-MSC is also much easier to obtain, and also does not require HLA class II antigen compatibility. The above-mentioned advantages indicate that allogenic UC-MSC can be a safe, effective, easily accessible, and universal source of MSC for the treatment of MS. The patient subjected to the above therapy achieved improvement in the Expanded Disability Status Scale (EDSS) from 3.5 to 2.0 and the extinction of many hypertensive changes in the MRI image. Case reports illustrate the great potential of MSC therapy in multiple sclerosis [20].

Therapy of patients with MS using UB-MSC is an important and valuable alternative to the currently widely used anti-inflammatory and immunosuppressive therapies. However, many studies need to be carried out to optimize the dosage and route of administration before widespread clinical use of MSCs [21].

Anticancer effect

WJMSC secrete many bioactive molecules, including cytokines, which affect the regulation of cancer cell cycle inducing growth attenuation and apoptosis. Many studies have proven the anti-tumor effect on solid tumors of human Wharton's jelly stem cells (WJSC) and their conditioned medium (WJMSC-CM) and cell-free lysate (WJMSC-CL). Gauthman et al. have shown the tumor-inhibiting properties of three cancer lines (breast adenocarcinoma, ovarian cancer, and osteosarcoma) by incubation with WJMSC-CM and WJMSC-CL [22]. The extracellular matrix of WJSC has also been shown to inhibit the proliferation of breast adenocarcinoma cells by suppressing the Wnt signaling pathway. The above results indicate the anti-tumor properties of WJMSC. This is a unique feature because the anti-cancer properties are controversial in the world of science. WJMSC have proangiogenic features and the ability to form functional vessels *in vivo*, which can accelerate the progression of some types of cancer. Therefore, caution should be exercised when implementing WJMSC in cancer therapy, as their properties have been proven to induce the development of kidney and esophageal cancer [23].

Conclusions

Until the 1990s, the umbilical cord did not arouse clinical interest and was considered as waste material. The low number of bone marrow mesenchymal cells and their limited proliferative potential were

the reasons for searchingfor new sources of MSCs. Currently, Wharton's jelly cells appear to be the most promising source of mesenchymal stem cells. Wharton's jelly cells are characterized by a non-invasive acquisition procedure that does not raise ethical problems, as well as a very high proliferative potential and the possibility of differentiation into meso, endo and ectodermal cell lines [2].

The world is now conducted over four international clinical trials using umbilical cord stem cells. Most clinical trials are in phase 1 or 2, only some are in phase 3 and 4. Umbilical cord stem cells in clinical studies are most often used to treat immune, hematological, and central nervous system diseases [24].

Ethical approval

The conducted research is not related to either human or animal use.

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Conflict of interest statement

The authors declare they have no conflict of interest.

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