

Stem cell therapy in the treatment of inflammatory bowel disease

Abstract

The application of cell therapy in the treatment of inflammatory bowel disease currently is of increasing scientific interest. Cell therapy in the treatment of Crohn's disease and ulcerative colitis includes 2 approaches: immunosuppressant followed by hematopoietic stem cells transplantation and systemic or local application of mesenchymal stem cells. The latter were reported to exhibit immunosuppressive and regenerative effect. Actually more than 1,500 patients with inflammatory bowel disease have been treated with mesenchymal stem cells worldwide. The introduction of cell therapy into gastroenterology will significantly expand the arsenal of therapeutic arrangements for the treatment of inflammatory bowel disease, in particular resistant forms of the disease and will allow to increase the effectiveness of treatment.

Keywords: crohn's disease, ulcerative colitis, stem cells

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Abbreviations: IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, crohn's diseases; TNF- α , tumor necrosis factor α ; IL-12/23, interleukin 12/23; IL-6R, interleukin 6R; iRNA, information ribonucleic acid; SC, stem cells; CT, cell therapy; MSC, mesenchymal stem cells; HSC, hematopoietic stem cells; 2,4,6-TNBA, 2,4,6-trinitrobenzene sulfonic acid; SDF-1, stromal derived factor-1; VEGF, vasculoendothelial growth factor; EGF, epidermal growth factor; DSS, dextran sulphate sodium; HSCT, hematopoietic stem cells transplantation; EPC, endothelial progenitor cells

Introduction

Achievements of modern science changed the ideas about etiology and pathogenesis of IBD, mainly UC and CD, what resulted in the emergence of novel approaches to the treatment of these disorders.¹⁻⁶ Environmental, genetic factors and microbial flora were elicited to play an important role in the development of inflammatory process in the intestinal wall, activating immune response.^{1,7,8} The disruption of balance between proinflammatory and anti-inflammatory factors in intestinal mucosa becomes the trigger of the development of pathologic process in which numerous cellular and molecular mechanisms are involved.^{1,7} Genetic nature of IBD is confirmed by wide studies of human genome and studies on twins.³ The efficiency of conventional methods of UC and CD treatment leaves much to be desired.^{1,9-11} Modern therapy of IBD includes biological therapy (antibodies to TNF- α , adhesion molecules, IL-12/23, IL-6R, endoscopic application of artificially grown pieces of tissues etc) and gene therapy (iRNA-technologies aimed at inhibition of the necessary genes).^{2,3,7,12,13} The application of nanoparticles for the transportation of drugs despite its high cost is also promising.²

In recent years an increasing number of experimental and clinical studies are devoted to the evaluation of therapeutic potential and effectiveness of SC in the treatment of UC and CD.^{7,9-11,14,15} According to experts' prognoses, CT will become the next generation of therapeutic arrangements in the treatment of IBD, in particular for patients with the secondary resistance to anticytokine therapy.^{4,12}

Discussion

Actually several tens of adult SC is distinguished, that in health

contribute to natural processes of tissues regeneration, play crucial role in wounds healing.¹⁶⁻¹⁸ SC derived from bone marrow, peripheral and cord bloods, tissue of umbilical cord, amniotic fluid, adipose tissue have got wide use.^{4,16,17,19} Remedial effect of SC is explained both by paracrine effect- stimulation of regenerative processes through the synthesis of growth factors and other biologically active compounds and ability to transformation into damaged tissues cells.^{14,17,18,20,21} Effectiveness of MSC in the treatment of autoimmune diseases is mediated by their potent immunosuppressive effect.²²⁻²⁴

Immunosuppressant followed by transplantation of allogeneic Hematopoietic Stem Cells (HSC) is a promising method of radical treatment of many autoimmune diseases, including CD and UC.^{5,11,23-25} Another direction of CT of IBD is the use of MSC due to their immunosuppressant effect, what was mentioned above.^{9,10,23,24} *In vivo* and *in vitro* studies showed the interaction of MSC with regulatory T-lymphocytes.²² *In vitro* studies also showed that MSC inhibit proliferation and cytotoxicity of T-lymphocytes, in particular natural killer cells, dendritic cells, production of cytokines, antibodies and antigen presentation what provides basis for the use of MSC in the treatment of autoimmune pathology.^{23,24}

The decrease of clinical and histopathological signs of 2,4,6-TNBA-induced colitis, treated with MSC was accompanied by redistribution of regulatory T-lymphocytes from tissues to circulation.²² SDF-1, produced by MSC was reported to play important role in chemo taxis regulation and SC engraftment in tissues, interacting with specific chemokine receptors.²⁰

Another mechanism of therapeutic effect of MSC is their prominent regenerative effect as these cells are the precursors of the connective tissue.^{14,15,19} MSC were revealed to release numerous trophic factors (VEGF, EGF etc) and affect all stages of the complex process of wound healing - inflammatory, proliferative and tissue remodeling.²¹ The advantage of MSC use is the lack of immunogenicity what allows wider allogeneic application.¹⁴ MSC above all are recommended to patients with fistulizing CD.¹⁴ Systemic MSC therapy was shown to be effective in resistant radiation colitis, decreasing pain, diarrhea, inflammation, bleeding, increasing the number of T-regulatory lymphocytes and decreasing of activated effector cells.¹⁴

Preclinical studies on the models of necrotizing colitis as well as experimental colitis induced by DSS and 2,4,6-TNBA showed positive effect of systemic and local use of MSC derived from the bone marrow, amniotic fluid, cord blood, adipose tissue on the course of colitis and stimulation of reparation.^{15,16,19,26} CT was shown to increase survival and stimulate reparation of the damaged mucous membranes of the large intestine of newborn rats with necrotizing colitis. Animals were divided into 2 groups: control group was intraperitoneally injected bone marrow MSC and investigation group was treated with amniotic fluid SC. Positive effect of CT was accompanied by modulation of cyclooxygenase-2 expression in stromal cells of lamina propria of colonic mucosa. In amniotic fluid SC differentiated expression of genes of Wnt/beta-kinine pathway was detected as well as the migration of these cells and production of growth factors contributing to regeneration of colonic mucosa.¹⁵

In mice with DSS-induced colitis intraperitoneal injection of bone marrow or cord blood MSC was shown to decrease inflammation in colonic mucosa. Simultaneously the regulatory impact of MSC on the course of immune processes in spleen and mesenteric lymphatic nodes was noted.²⁷ The application of adipose tissue MSC mixed with thrombin and fibrin significantly facilitated reparative processes in walls of the colon due to angiogenesis stimulation, what was proved in ischemia-induced colitis in mice.¹⁹ Immunosuppressive effects of MSC in the treatment of experimental colitis in mice were reported to be potentiated by interferon- γ .²⁶

Currently more than 200 clinical trials on MSC are registered worldwide, from which 22 trials are devoted to the treatment of autoimmune diseases and 27- IBD.¹⁴ Due to literary data 1500 patients with IBD were carried out systemic and local treatment with MSC worldwide. The 1st and 2nd phases of clinical studies confirmed the safety of CT in the treatment of IBD and its advantages above the fibrin glue in fistulizing colitis.^{4,14}

As mentioned above, CT is of special importance for the treatment of Patients with the resistance to anticytokine drugs. The level of anticytokine drugs antibodies was shown to correlate with the severity of clinical and endoscopic picture.¹² CT was also reported to decrease the need for glucocorticosteroid therapy and other drugs, what results in the decrease of treatment cost.²⁸

MSC therapy was carried out in a group of 39 patients with UC and 11- with CD. Control groups included 20 patients with UC and 11 with CD. Treatment with immunodepressing drugs was stopped 2-3 days before MSC introduction. Glucocorticosteroids dose was decreased up to 15-20mg/day and aminosalicylates up to 2g/day. After MSC transplantation significant decrease of inflammation signs was noted in 39 patients with UC and 11 patients with CD compared to control groups. In 40 patients clinical and morphological remission was stated. MSC therapy was ineffective in 8 patients with UC and 2 patients with CD. In 34 from 50 patients with hormone-dependent or hormone-resistant forms of UC and CD MSC use allowed to decrease prednisolone dose up to 5mg/day. Thus, the authors consider MSC therapy as a novel strategic direction in the treatment of IBD due to its potent immunomodulating effect, decrease of autoimmune inflammation and stimulation of reparation processes in mucous membranes.⁹

Results of clinical studies give evidence that allogeneic MSC transplantation significantly increases remission duration, decreases the risk of relapse and efficiency is comparable with TNF α antibodies. In majority of patients MSC treatment allowed to discontinue 5-acetylsalicylic acid administration. Positive effect of CT was noted

in hormone-resistant and hormone-dependent IBD.¹⁰ Another study reports about 3 patients with the active form of CD, resistant to conventional therapy with the presence of antibodies to anti-TNF α drugs. These patients either refused from surgery or such treatment was not an acceptable alternative. 2 patients were successfully transplanted hematopoietic stem cells (HSC) with CD34+ selection. At the moment of examination 5 and 6 years after transplantation the patients were in remission. 1 patient got into remission after conditioning so HSCT was not performed.¹¹

Effectiveness of SC was also noted in genetically mediated diseases of the intestine. HSCT was shown to restore gluten tolerability in patients with celiac disease. 2 clinical cases of successful HSCT after myeloablation in celiac disease were reported. After this treatment introduction of gluten-containing diet did not cause any clinical, serological or histological markers of the disease during 5 year follow-up period.⁵

Inherited deficiency of IL-10 and its receptors cause immune dysregulation in patients with the development of severe colitis, resistant to standard methods of treatment. HSCT was reported to be effective in patients with colitis on the background of deficiency of IL-10.²⁵ Recent research data also gives evidence about the decrease of EPC number in patients with UC. Although, actually there is no data on the impact of infusion of EPC on the processes of mucosa regeneration.⁶

Conclusion

Introduction of CT into gastroenterology significantly expands the arsenal of therapeutic arrangements for IBD treatment, in particular forms of the disease resistant to conventional therapy. Results of long-term observations and improvement of protocols of SC application in patients with CD and UC will allow increasing the effectiveness of IBD treatment.

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Conflicts of Interest

The author declares that there is no conflicts of interest.

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