

# New perspectives on treatment of gastrointestinal diseases: therapeutic potential of mesenchymal stromal cells

**Olga Payushina, Dibakhan Tsomartova, Yelizaveta Chereshneva, Marina Ivanova, Nataliya Pashina, Elina Tsomartova, and Sergey Kuznetsov**

I. M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University), ul. Trubetskaya, 8-2, Moscow, 119991, Russian Federation

Address correspondence and requests for materials to Olga Payushina, payushina@mail.ru

## Abstract

Mesenchymal stromal cells (MSCs) are a promising resource for cell therapy of different organs and systems, including the gastrointestinal tract (GIT). Therapeutic effect of MSC transplantation in GIT diseases may be partly due to their differentiation into various cellular components of the digestive tube. However, more significant is regulatory influence of MSCs on survival, proliferation, and differentiation of the gastric and intestinal epithelial cells, as well as their immunomodulatory, pro-angiogenic and antifibrotic effects. Data from experiments on animals and clinical trials indicate prospect of using MSCs in various diseases affecting any parts of GIT. However, effective and safe clinical use of MSCs requires an in-depth study of the mechanisms of their therapeutic effect, the development of optimal methods of administration, and risk assessment of adverse effects. This review analyzes MSC participation in regeneration of GIT and systematizes data on the potential of using MSCs in the treatment of gastroenterological diseases.

**Keywords:** mesenchymal stromal cells, gastrointestinal tract, esophagus, stomach, intestines, regenerative medicine, cell therapy

## Introduction

Regenerative medicine, which is aimed at restoring organs affected by various diseases by means of endogenous or transplanted stem cells, is the most urgent area for medical research. Its rapid development in the last two decades is largely due to the emergence of new knowledge about tissue-specific stem cells and their role in maintaining stable functioning of tissues and organs. In particular, significant progress has been achieved in understanding the biological significance of mesenchymal stromal cells (MSCs), which have become one of the main resources for cell therapy for a wide variety of diseases. Initially, MSCs were considered primarily as precursors of skeletal and other connective tissues capable of replacing lost cellular elements of these tissues by differentiating in an appropriate direction (Caplan, 1991). In this regard, the first examples of their clinical use were associated with treatment of pathologies of the musculoskeletal system, such as osteogenesis imperfecta (Horwitz et al., 1999), osteoarthritis (Wakitani et al., 2002), and large bone defects (Warnke et al., 2004). However, later the focus in the study of MSCs shifted towards the regulatory effects they have on tissues through the paracrine secretion of biologically active substances (Samsonraj et al., 2017; Pittenger et al., 2019). Almost ubiquitous distribution of MSCs throughout the body and a variety of regulatory molecules produced by them give reasons to consider these cells as universal regulators of tissue homeostasis and determine a wide scope of their potential therapeutic use. Additional advantages of MSCs

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**Authors' information:** Olga Payushina, Dr. of Sci. in Biology, Associate Professor, [orcid.org/0000-0001-8467-0623](https://orcid.org/0000-0001-8467-0623); Dibakhan Tsomartova, Dr. of Sci. in Medicine, Professor, [orcid.org/0000-0002-1381-0200](https://orcid.org/0000-0002-1381-0200); Yelizaveta Chereshneva, PhD, Associate Professor, [orcid.org/0000-0002-1046-6336](https://orcid.org/0000-0002-1046-6336); Marina Ivanova, PhD, Associate Professor, [orcid.org/0000-0001-8215-4609](https://orcid.org/0000-0001-8215-4609); Nataliya Pashina, PhD, Associate Professor, [orcid.org/0000-0002-8696-0023](https://orcid.org/0000-0002-8696-0023); Elina Tsomartova, PhD, Senior Lecturer, [orcid.org/0000-0002-8581-338X](https://orcid.org/0000-0002-8581-338X); Sergey Kuznetsov, RAS Corresponding Member, Dr. of Sci. in Medicine, Professor, Head of Department, [orcid.org/0000-0002-0704-1660](https://orcid.org/0000-0002-0704-1660)

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as a resource for cell therapy are minimally invasive procedures for their isolation, for example, from bone marrow, subcutaneous adipose tissue and dental pulp (Zhou et al., 2019; Yoshida et al., 2020), their availability from perinatal sources, such as placenta and umbilical cord (Beeravolu et al., 2017), high capacity of *in vitro* proliferation with relative low demands on cultivation conditions (Han et al., 2019), low probability of tumor transformation and non-immunogenicity allowing allogeneic cell transplantation without the need for careful selection of a donor (Samsonraj et al., 2017). The data obtained to date in animal experiments and clinical trials indicate the promising use of MSCs in treatment of cardiological, neurological, immunological diseases, skin defects, pathologies of the musculoskeletal system, liver, kidneys, and other organs (Han et al., 2019; Pittenger et al., 2019). Encouraging results were obtained, including those in the study on applicability of MSCs in the treatment of various gastrointestinal diseases. These diseases, caused by unhealthy diet, environmental factors, harmful working conditions, sedentary lifestyle, infections and other causes, are now widespread throughout the world and represent an urgent medical problem. This review analyzes the effects of MSCs on regenerative processes in the gastrointestinal tract (GIT) and systematizes the data available in the world literature on the possibility of using these cells in the treatment of gastroenterological pathologies.

### The rationale for using MSCs in gastroenterology

According to the criteria of the International Society of Cellular Therapy, the category of multipotent MSCs includes cells which, along with the ability to adhere to culture plastic and a certain surface phenotype (the presence of CD73, CD90 and CD105 antigens in the absence of hematopoietic markers), have the potential to differentiate into osteoblasts, adipocytes and chondroblasts (Dominici et al., 2006). However, at least some of them have shown the ability to differentiate into other mesenchymal derivatives. This feature can partly determine their regenerative effect in damage to the GIT organs. The repeatedly demonstrated ability of MSCs to differentiate into cells of smooth muscle tissue (Hegner et al., 2016; Yeh et al., 2019; Zhang et al., 2020), myofibroblasts (Hegner et al., 2016; Liu, 2018), endothelial cells (Wang et al., 2020a; Zhang et al., 2020) and pericytes (Wang et al., 2016a) suggests that they can give rise to connective tissue cells of the mucosal lamina propria and submucosa in the GIT organs, as well as the cells of the vascular wall. Participation of MSCs in the repair of the damaged muscular tunica by their differentiation in myogenic direction cannot be completely excluded. This possibility is confirmed by the discovery of muscle cells of donor origin in the re-

generating esophagus of experimental animals after MSC transplantation (Kantarcioglu et al., 2014). Moreover, hypothetically, their direct involvement in the replacement of lost epithelial cells is also possible. According to some reports, the potential of MSCs is not limited to differentiation into cells of mesenchymal origin; under certain conditions, their transdifferentiation into ectodermal and endodermal derivatives such as precursors of epithelial cells of the salivary glands (Mona et al., 2020), hepatocytes (Hwang et al., 2012; Yu et al., 2012), and insulin-producing cells (Wang et al., 2020b) is shown. The ability of MSCs to differentiate into enterocytes *in vitro* under the influence of microRNA and growth factors (Ye et al., 2018) or upon co-cultivation with intestinal epithelial cells (Jiang et al., 2020) has been reported, and upon injection of fluorescently labeled bone marrow MSCs into the stomach of an experimental mouse, their differentiation into gastric epithelial cells was observed (Okumura et al., 2009). However, as evidenced by the results of MSC transplantation in experimental animals (Okumura et al., 2009; Hwang et al., 2012; Yu et al., 2012), “unorthodox” *in vivo* differentiation of MSCs into epithelial cells of endodermal origin is a rather rare event. It is unlikely to contribute significantly to the improvement of the GIT condition. The ability of MSCs to differentiate into components of the epithelial stem cells niches in the stomach and intestines seems to be more significant. These niches regulating the homeostasis of the GIT organs include several cell types of mesenchymal origin which are histogenetically related to MSCs. Thus, the microenvironment of intestinal epithelial stem cells includes subepithelial myofibroblasts which control self-renewal and differentiation of adjacent epithelial cells by producing Wnt ligands and other regulatory factors (Horiguchi et al., 2017; Pastuła, Marcinkiewicz, 2019), and various populations of fibroblast-like cells. Among the latter, some cells, located at the bottom of crypts (trophocytes), support proliferation of epithelial stem cells by secreting canonical Wnt ligands and inhibitors of bone morphogenetic proteins (BMP), while others, located in the region of the crypt-to-villus transition (telocytes), secrete non-canonical Wnt ligands and BMP and induce epithelial differentiation (Brügger et al., 2020; McCarthy et al., 2020). The cellular composition of the gastric epithelial stem cell niche is less studied, however the available experimental data indicate an important functional role of fibroblasts (Chen et al., 2019), myofibroblasts (Sigal et al., 2019), and pericyte-like cells similar in markers to intestinal crypt telocytes (Kim et al., 2020b). Cells with a myofibroblast phenotype capable of producing regulatory molecules, such as interleukin (IL)-6 and BMP-4, are also found in the esophageal mucosa (Shaker et al., 2013).

In addition to differentiated cells of mesenchymal origin, cells with characteristics of multipotent MSCs are also present in the stromal microenvironment of the

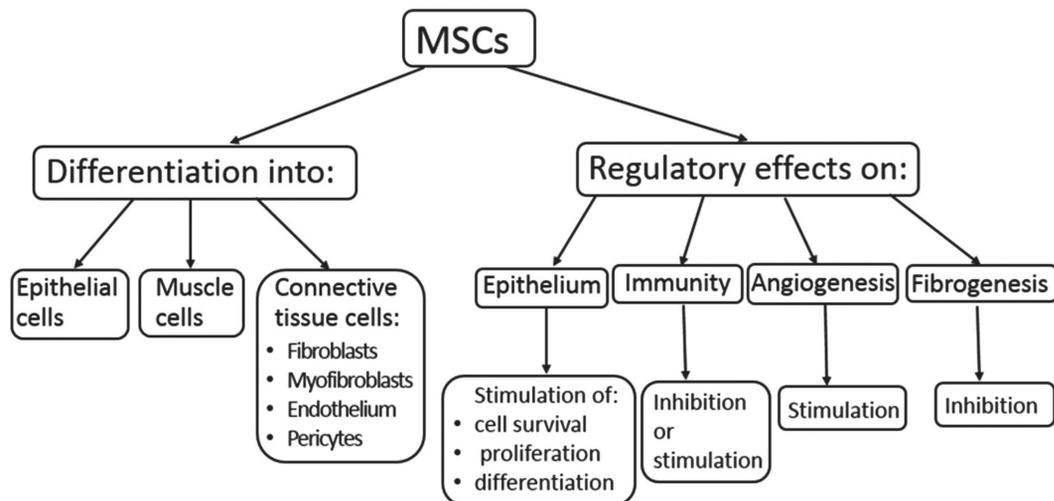
GIT. Thus, they were found in the large intestine (Tao et al., 2016), where they are localized around the crypts (Signore et al., 2012) and in the submucosa (Lanzoni et al., 2009). In patients with gastric cancer, they were isolated from both the tumor stroma and adjacent parts of the organ not affected by the tumor process (Xu et al., 2011). Despite some peculiarities related to the expression of differentiation potencies and surface markers, the main characteristics of the resident MSCs of the stomach and intestines are similar to those obtained from such a clinically significant source as bone marrow (Lanzoni et al., 2009; Xu et al., 2011; Signore et al., 2012; Tao et al., 2016). This suggests that the additional introduction of exogenous MSCs into the damaged area can affect the state of epithelial stem cells contributing to its regeneration. This assumption is supported by the fact that MSCs secrete factors which affect self-renewal and proliferation of gastric and intestinal stem cells. It is known, in particular, that such molecules as IL-1 $\alpha$ , IL-11, and stem cell factor (SCF), basic fibroblast growth factor (bFGF) and transforming growth factor  $\beta$  (TGF  $\beta$ ) are important for the survival of intestinal epithelial stem cells (Proskuryakov et al., 2009). These factors were found in the secretome of MSCs from the tissue sources most often used in cell therapy — bone marrow, adipose tissue, dental pulp, umbilical cord tissue, and umbilical cord blood (Yang et al., 2017; Baberg et al., 2019; Miranda et al., 2019; Al-Hakami et al., 2020). The ability of MSC secretory products to prevent apoptosis of the intestinal epithelium was shown in experimental models of Crohn's disease (Gao et al., 2020) as well as radiation (Accarie et al., 2020; Luo et al., 2020) and ischemic (Liu et al., 2020) intestinal injuries. Antiapoptotic effect of factors secreted by MSCs has also been established with regard to the gastric epithelium (Xia et al., 2018). An increase in the proliferation of epithelial cells in the stomach (Xia et al., 2018; Donnelly et al., 2014) and intestines (Soontarak et al., 2018; Accarie et al., 2020; Gao et al., 2020; Luo et al., 2020; Xu et al., 2020; Lim et al., 2021) under the influence of MSCs or factors secreted by them was also noted. Moreover, in irradiated rats which received an injection of MSC conditioned medium, an increased number of intestinal epithelial stem cells identified by the Lgr5 marker was found as compared with the reference group (Luo et al., 2020). The same effect was observed when MSCs were administered to animals with experimental colitis (Soontarak et al., 2018). In addition, the ability of MSCs to enhance differentiation of intestinal epithelial cells has been shown (Lanzoni et al., 2009; Lim et al., 2021).

In addition to the direct effect on tissue-specific stem cells, MSCs also have a general impact on the state of the tissue. First of all, they modulate inflammatory reactions through contact interactions and secretion of cytokines influencing the functional activity of the im-

mune cells such as B-lymphocytes, T-helpers, regulatory T-cells, natural killer cells, macrophages, neutrophils, dendritic and mast cells. With insufficient activity of the immune system, MSCs stimulate the development of inflammation, attracting neutrophils and lymphocytes to the lesion and activating them due to the release of proinflammatory factors, and in case of a strong severity of the inflammatory reaction, on the contrary, suppress it (Jiang and Xu, 2020). For the treatment of gastrointestinal diseases, the pathogenesis of which in many cases is associated with inflammation, the immunosuppressive properties of MSCs are especially important. In particular, in an experimental model of inflammatory bowel diseases, it was shown that under the influence of MSCs, the expression of proinflammatory cytokines, such as tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), interferon- $\gamma$ , IL-1 $\beta$ , IL-6, IL-8 and IL-17, decreases in the affected tissue (Song et al., 2017 a, b; Zheng et al., 2019), while the level of anti-inflammatory cytokines IL-4 and IL-10 increases (Wang et al., 2016b; Song et al., 2017b), neutrophil infiltration diminishes (Banerjee et al., 2015), the content of regulatory T-cells rises (An et al., 2018), and macrophages acquire anti-inflammatory phenotype M2 (Song et al., 2017b; Wu et al., 2020).

The immunomodulatory properties of MSCs are of particular interest from the point of view of the prospects for their use in the treatment of the coronavirus infection caused by the SARS-CoV-2 virus, the pandemic of which is currently the most serious problem in global health. Originally thought to be a respiratory disease, COVID-19 affects many systems in the body, including the digestive system. Binding of the SARS-CoV-2 virus to molecules of angiotensin-converting enzyme 2 on the epithelial cells in the esophagus and intestines, as well as a systemic inflammatory reaction (“cytokine storm”) in some patients, lead to gastrointestinal injury, which is manifested by nausea, vomiting, diarrhea, abdominal pain and anorexia, and is detected during endoscopic examination, biopsy and autopsy as an inflammatory damage to the mucous membrane with its infiltration by lymphocytes (Ma, Cong, and Zhang, 2020). Encouraging results from the use of MSCs for respiratory manifestations of COVID-19 (Lanzoni et al., 2021) and the multiple organ failure caused by it (Yilmaz et al., 2020) have been reported. There are reasons to hope that cell therapy using MSCs will also give a positive effect in case of damage to the GIT organs, although this issue has not been researched to date.

Under pathological conditions, the ability of MSCs to stimulate the growth of blood vessels, primarily due to the paracrine secretion of vascular endothelial growth factor (VEGF), is of great importance because it improves the blood supply to the damaged tissue. The angiogenic effect of MSCs or their secretory products, accompanied by intensification of the regenerative pro-



**Fig. 1.** Possible ways of MSC involvement in gastrointestinal tract regeneration.

cess, was shown in experimental injuries of the gastric (Hayashi et al., 2008; Xia et al., 2018) and colonic (Manieri et al., 2015) mucosa, as well as in a model of radiation enteropathy (Chang et al., 2013, 2017; Van de Putte et al., 2017; Kim et al., 2019). The antifibrotic action of MSCs also contributes to the full regeneration of the affected organs. In particular, there is evidence that the factors they produce suppress the activation of myofibroblasts after endoscopic resection of the submucosa of the esophagus (Mizushima et al., 2017) and the rectum (Tsuda et al., 2018), and also reduce the expression of fibrogenic factors and collagen deposition in the rectal mucosa after local irradiation (Linard et al., 2013).

Thus, MSCs have a complex effect on various aspects of the regenerative process in the pathologically altered GIT organs, which makes them a promising resource for the treatment of diseases of these organs (Fig. 1).

## Key directions in the therapeutic use of MSCs

### Esophagus

Most of the experimental works devoted to the use of MSCs in the treatment of esophageal diseases are associated with the creation of tissue-engineered constructs for the restoration of an organ after its resection, the need for which arises, for example, in malignant tumors, burn strictures or esophageal atresia. The possibility of creating transplant constructs by cultivating MSCs on scaffolds made of biocompatible synthetic materials (La Francesca et al., 2018; Jensen et al., 2019; Kim et al., 2020a) or decellularized matrix of the GIT organs has been shown (Carty et al., 2017; Wang et al., 2018a; Marzaro et al., 2020). It was also possible to obtain a tubular structure suitable for reconstruction of the esophagus from MSCs combined with other cell types using the

3D printing method without any scaffold (Takeoka et al., 2019). Upon transplantation of tissue-engineered constructs based on MSCs into experimental animals, proliferation of squamous epithelium along the inner surface of the graft and formation of muscle tissue in it were revealed (Carty et al., 2017; La Francesca et al., 2018; Jensen et al., 2019; Takeoka et al., 2019; Kim et al., 2020a); some authors also report on vascularization of the transplanted construct (La Francesca et al., 2018; Kim et al., 2020a). It should be noted that the implantation of scaffolds of the same composition not seeded with MSCs did not allow to restore epithelial and muscle tissues of the esophagus (Carty et al., 2017; Marzaro et al., 2020).

In experiments on animals, the possibility of cell therapy for the esophagus diseases is also being researched by local transplantation of MSCs in the form of a suspension or cell spheroids into the affected area. On the model of esophageal anastomosis leakage, it was shown that the introduction of MSCs in fibrin gel into the lesion improves its closure, while reducing inflammation and collagen deposition (Xue et al., 2019), and when injecting MSC-derived spheroids into the irradiated esophagus, a decrease in fibrosis and better preservation of the muscular tunic, as compared to the reference animals, were noted (Kim et al., 2021). At the same time, with a burn of the esophagus (Kantarcioğlu et al., 2014) and strictures caused by dissection of the submucosa (Juhásová et al., 2019), the transplanted MSCs, despite their engraftment in the damaged tissue, did not significantly affect the course of the pathological process. However, in the latter case, it was possible to reduce inflammation and prevent stricture formation by applying MSC conditioned medium containing products of cell secretory activity to the wound bed (Mizushima et al., 2017). The successful clinical use of MSCs in a patient with esophageal-pleural fistula has also been reported.

Transplantation of autologous MSCs into the submucosa of the esophagus allowed achieving the closure of the fistula that did not respond to conservative treatment (Porziella et al., 2020).

### Stomach

The ability of MSCs to stimulate tissue regeneration and suppress inflammatory processes gives hope for their successful therapeutic use in gastric ulcer disease, which is one of the most pressing gastroenterological problems due to its widespread prevalence and incurability. It has been shown that MSC transplantation to experimental animals with ulcerative lesions of the gastric mucosa improves healing of the defect by reducing inflammatory infiltration and enhancing re-epithelialization and neovascularization (Hayashi et al., 2008; Xia et al., 2019; Alazzouni et al., 2020). A similar effect is exerted by the introduction of MSC conditioned medium into the damaged area (Xia et al., 2019). In case of gastric ulcer perforation, MSCs in combination with surgical treatment are also capable of ensuring a therapeutic effect. This is evidenced by the results of their local injection in rats after suturing the perforated hole, which led to the accelerated healing and a decrease in the incidence of complications such as dehiscence of the wound edges, formation of adhesions and abscesses in the abdominal cavity (Liu et al., 2015). The efficiency of intraperitoneal MSC administration was also shown on the model of surgical wounds of the stomach: in this case, in experimental animals, inflammation decreased and the quality of wound healing improved, which was manifested in the absence of erosions and hemorrhages in the suture region (Trubicyna et al., 2016). Attempts are also being made to create MSC-based tissue-engineered constructs for closing gastric wall defects. In particular, it was reported about the successful restoration of the stomach muscular tunic using a scaffold made of MSC-seeded small intestinal submucosa (Nakatsu et al., 2015).

### Intestines

One of the most actively developed areas of MSCs use in gastroenterology is associated with the treatment of the inflammatory bowel diseases such as Crohn's disease and ulcerative colitis. Although etiology of these diseases is not fully determined, there is no doubt that abnormal activation of the immune system leading to a chronic inflammatory process plays a role in their development. In this regard, the immunomodulatory, mainly immunosuppressive properties of MSCs are of particular value for their treatment. In numerous experiments on animals, in which inflammatory bowel diseases can be modeled by oral administration of sodium dextran sulfate (Soontarak et al., 2018; Zheng et al., 2019; Xu et al., 2020; He et al., 2021; Nishikawa et al., 2021; Yang

et al., 2021) or 2,4,6-trinitrobenzenesulfonic acid (Gao et al., 2020; Yang et al., 2021), it has been shown that under the influence of MSCs or the factors secreted by them, not only inflammation is mitigated (Soontarak et al., 2018; Zheng et al., 2019; Xu et al., 2020; He et al., 2021; Nishikawa et al., 2021; Yang et al., 2021), but also the survival rate increases (Yang et al., 2021), severity of such symptoms as weight loss, diarrhea and blood in the feces is reduced (Soontarak et al., 2018; Zheng et al., 2019; Gao et al., 2020; He et al., 2021; Nishikawa et al., 2021; Yang et al., 2021), shortening of the colon is prevented (Zheng et al., 2019; He et al., 2021; Nishikawa et al., 2021), damaged mucosa structure is restored (Xu et al., 2020; Yang et al., 2021), tight junctions between epithelial cells are better preserved (Nishikawa et al., 2021; Yang et al., 2021), and the intestinal microflora is normalized (Soontarak et al., 2018; He et al., 2021). In addition, MSCs in these animals suppress the development of colon cancer caused by chronic inflammation (Zheng et al., 2019; He et al., 2021).

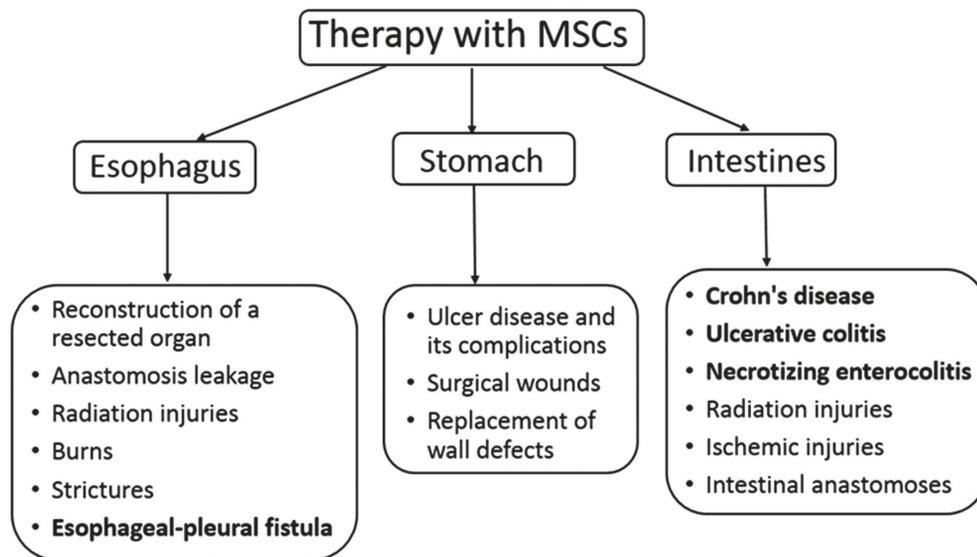
Cell therapy for inflammatory bowel diseases seems to be all the more reasonable since these diseases are accompanied by dysfunctions of resident MSCs which are important components of the microenvironment of the intestinal epithelium. Thus, increased proliferative activity of MSCs of the colon mucosa was found in patients with ulcerative colitis, and in patients with Crohn's disease, a loss of the ability of these cells to clonal growth was reported; in both cases, differentiation potentials of MSCs were altered (Grim et al., 2021). There is a fairly large experience of clinical use of MSCs in complex therapy in patients with Crohn's disease and ulcerative colitis. ClinicalTrials.gov contains data on a variety of completed and ongoing clinical trials involving local or systemic MSCs transplantation in these diseases (Table 1). As a rule, patients receive autologous or allogeneic MSCs derived from bone marrow and adipose tissue whereas umbilical cord derived cells are used less often. The available clinical trial data do not yet give a complete picture of MSC efficiency in inflammatory bowel diseases, however, preliminary data published by a number of authors are encouraging. Thus, after local injections of MSCs, it was possible to achieve closure of perianal fistulas caused by Crohn's disease in many patients (Cheng, Huang and Li, 2019; Barnhoorn et al., 2020). Systemic administration of these cells in the luminal form of Crohn's disease and ulcerative colitis alleviated the course of the disease, reduced the risk of relapse and increased the duration of remission (Lazebnik et al., 2011; Zhang et al., 2018; Shi, Chen and Wang, 2019; Konopljannikov, Knjazev and Baklaushev, 2021).

Another urgent medical problem is radiation enteropathy, which occurs after radiation therapy of oncological diseases due to the high radiosensitivity of intestinal epithelial stem cells. The effect of ionizing radiation on

**Table 1. Clinical trials of MSC transplantation in inflammatory bowel diseases**

Disease	Way of cell delivery	Source of MSCs	Phase	Number of patients	Year of completion	NCT Number
Ulcerative colitis	Intravenous	Umbilical cord	I/II	50	2012	NCT01221428
				30	2017	NCT02442037
				20	2020	NCT03299413
	Intraarterial	Autologous adipose tissue	I	20	2022	NCT04312113
	Local	Allogeneic bone marrow	I/II	24	2023	NCT04543994
		Allogeneic adipose tissue	I/II	8	2013	NCT01914887
			50	2021	NCT03609905	
Crohn's disease and ulcerative colitis	Intravenous	Allogeneic bone marrow	I	8	2017	NCT01851343
Crohn's disease	Intravenous	Allogeneic bone marrow	I/II	13	2015	NCT01540292
				III	98	2011
			73		2014	NCT01233960
			330	2014	NCT00482092	
		Autologous bone marrow	I	16	2015	NCT01659762
		Allogeneic adipose tissue				NCT02580617
		Umbilical cord	I/II	82	2015	NCT02445547
		Not specified	II	21	2015	NCT01090817
	Local	Allogeneic bone marrow	I/II	24	2023	NCT04548583
		Autologous bone marrow	I	10	2018	NCT01874015
		Allogeneic adipose tissue	I	6	2012	NCT01440699
		Autologous adipose tissue	I/II	15	2013	NCT01157650
				III	98	2011
		36	2021		NCT04612465	
		Not specified	I/II	60	2023	NCT03901235
Perianal fistulas in Crohn's disease	Local	Allogeneic bone marrow	I/II	21	2014	NCT01144962
				40	2022	NCT04519671
		Allogeneic adipose tissue	I/II	24	2010	NCT01372969
				III	278	2016
			22		2023	NCT03706456
			554		2023	NCT03279081
			IV	50	2026	NCT04118088
		Autologous adipose tissue	I	20	2019	NCT01915927
				II	10	2018
			84		2023	NCT04010526
			60		2025	NCT04847739
		Autologous (tissue source is not specified)	I	7	2019	NCT03209700
				5	2022	NCT03449069

The information is taken from the website ClinicalTrials.gov



**Fig. 2.** Scope of using MSCs in gastroenterological diseases. Diseases in which the therapeutic efficacy of MSCs has been clinically proven are shown in bold.

the intestine leads to ulceration of its mucous membrane, destruction of crypts, impairment of the barrier function of the epithelium, leukocyte infiltration and fibrosis. Administration of MSCs to irradiated experimental animals can reduce these manifestations of radiation damage to the intestine (Chang et al., 2013; Linard et al., 2013; Han et al., 2017; Kim et al., 2019; Usunier et al., 2021). Similar effects are achieved by using MSC conditioned medium (Chang et al., 2017) and extracellular vesicles isolated from it (Accarie et al., 2020). At the same time, with the help of MSC transplantation, both prevention of the destructive changes in the intestine and treatment of already developed radiation injury are possible (Han et al., 2017).

Other intestinal pathologies, in which MSCs show therapeutic efficacy in preclinical trials, include ischemic injury (Jiang et al., 2013; Shen, Zhang, Song and Zheng, 2013; Markel et al., 2015; Jensen, Drucker, Ferkowicz and Markel, 2018; Liu et al., 2020) and necrotizing enterocolitis (Tayman et al., 2011; Rager et al., 2016; McCulloh et al., 2017). A clinical case of allogeneic MSC transplantation to a newborn with necrotizing enterocolitis, which led to an improvement in the condition of the remaining intestine after resection of the necrotic area, has also been described (Akduman et al., 2021). The pro-regenerative, pro-angiogenic and anti-inflammatory properties of MSCs allow using them to improve the healing of intestinal anastomoses (Caziuc, Calin Dindelegan, Pall and Mironiuc, 2015), including those cases when tissue regeneration is hampered, namely under conditions of ischemia (Adas et al., 2013) or after irradiation (Van de Putte et al., 2017).

The principal areas of using MSCs in gastroenterological diseases are summarized in Fig. 2.

### Potential risks associated with MSCs

Despite the obvious pro-regenerative effects of MSCs, their clinical use, in particular, in gastrointestinal diseases, should be treated with caution due to possible risks to the patient. Along with the abovementioned ability to suppress inflammation and prevent fibrosis development, MSCs placed in pathological microenvironment may, on the contrary, exhibit pro-inflammatory and fibrogenic properties, thereby worsening the course of disease. In particular, some authors report these adverse effects of MSCs in the model of sodium dextran sulfate-induced colitis (Tolomeo et al., 2021). Mode of the action of MSCs is probably determined by cytokine milieu in the affected tissue, patient's immune status and other factors that are difficult to assess. These circumstances hamper predictions of the clinical outcome of MSC transplantation.

Even more significant concerns are related to the possible role of MSCs in tumorigenesis. MSCs are not prone to tumor formation, but their spontaneous malignant transformation during prolonged *in vitro* cultivation cannot be excluded (He et al., 2016). Another potential mechanism of MSC involvement in carcinogenesis may be due to their ability to stimulate the growth of an existing tumor. Although it was reported that bone marrow-derived MSCs, after repeated administration to mice with chronic *H. pylori* infection, reduce the progression of gastric mucosal dysplasia due to their immunomodulatory properties (Yang et al., 2014), there is also evidence that, in pathological conditions, under the influence of an inflammatory microenvironment, stomach-resident MSCs can promote growth of cancerous tumors by stimulating the proliferation of epithelial cells, including malignantly

transformed ones, as well as the epithelial-to-mesenchymal transition and migration of tumor cells (Donnelly et al., 2014; Yang et al., 2014; Bie et al., 2017; Ji et al., 2017). Statistical analysis shows that the presence of cells with phenotypic markers of MSCs (CD73, CD90, and CD105) in the stroma of gastric tumors is associated with a large tumor size, advanced cancer and lymph node metastasis, and is an unfavorable prognostic sign (Numakura et al., 2019). Their source can be not only resident gastric MSCs (Ning, Zhang, Wang and Song, 2018), but also cells migrating from the bone marrow (Wang et al., 2018b). Being incorporated into the tumor stroma, gastric MSCs are subjected to paracrine influence from cancer cells, which significantly alters their profile of genes expression and cytokine production (Ning, Zhang, Wang and Song, 2018; Wang et al., 2018b; Shamai et al., 2019). Such MSCs promote self-renewal of cancer stem cells and increase their resistance to chemotherapy (He et al., 2019; Sun et al., 2020), induce pro-tumor activation of macrophages (Li et al., 2019), and suppress immune responses (Wang et al., 2017).

There is also evidence of a possible involvement of MSCs in the development of colorectal cancer. They have tropism towards colon cancer stem cells and undergo transformation into cancer-associated fibroblasts under their influence (Ma et al., 2021). As a part of colorectal tumor microenvironment, MSCs promote angiogenesis, stimulate growth and metastasis of the tumor, and allow it to avoid immune attack (O'Malley et al., 2016; Wang et al., 2018c).

Thus, MSCs are key components of the stroma of malignant neoplasms largely responsible for the tumor progression. This circumstance limits the possibilities of their use in the cell therapy of gastrointestinal diseases, but, on the other hand, allows considering resident MSCs as targets for therapeutic impacts on the tumor process. In particular, attempts are being made to suppress their production of factors that enhance tumor growth and metastasis, as well as to switch the immunosuppressive phenotype to the immunostimulating one, which should enhance tumor rejection by the immune system (Poggi, Varesano and Zocchi, 2018; He et al., 2019; Yin et al., 2020).

## Conclusion

The results of numerous experimental studies indicate that cell therapy using MSCs can improve the condition of the digestive system in a wide range of diseases. The beneficial effect of MSCs on the pathologically altered organs of GIT is complex in nature and is primarily due to the ability of these cells to create a pro-regenerative microenvironment by paracrine production of the factors that have mitogenic, antiapoptotic, immunomodulatory, angiogenic and antifibrotic effects. Such a multi-

faceted influence of MSCs on the regenerative process, as well as the availability of their tissue sources, ease of cultivation, lack of pronounced tumorigenicity and immunogenicity, determine the advantages of their therapeutic use. However, many issues related to the use of MSCs in the treatment of gastroenterological diseases require further research. In particular, a comparative assessment of the therapeutic efficiency of the MSCs obtained from various tissue sources and the development of optimal methods for their transplantation into patients (number of cells, routes, timing and frequency of administration) are required. When assessing the potential for the clinical use of MSCs, it should be borne in mind that, along with obvious advantages, it also has serious limitations. Thus, the low survival rate of MSCs under unfavorable conditions of the affected tissue reduces their therapeutic efficacy. Moreover, there is a risk of their adverse effects on the recipient's body due to the manifestation of pro-inflammatory or pro-fibrotic properties, differentiation in an undesirable direction, malignant transformation, or stimulation of the tumor growth. In view of the predominantly paracrine mechanism of MSC action, a safer alternative to cell transplantation can be the administration of their secretory products, such as conditioned media or extracellular vesicles, to the patient. In any case, the effective and safe use of MSCs in the treatment of gastroenterological diseases requires an in-depth study of the cellular and molecular mechanisms underlying their therapeutic effects.

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