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REVIEW

Mesenchymal Stromal Cells: New Generation Treatment of Inflammatory Bowel Disease

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Abstract: Inflammatory bowel disease (IBD) is a chronic inflammatory disease of the gastrointestinal tract, which has a high recurrence rate and is incurable due to a lack of effective treatment. Mesenchymal stromal cells (MSCs) are a class of pluripotent stem cells that have recently received a lot of attention due to their strong self-renewal ability and immunomodulatory effects, and a large number of experimental and clinical models have confirmed the positive therapeutic effect of MSCs on IBD. In preclinical studies, MSC treatment for IBD relies on MSCs paracrine effects, cell-to-cell contact, and its mediated mitochondrial transfer for immune regulation. It also plays a therapeutic role in restoring the intestinal mucosal barrier through the homing effect, regulation of the intestinal microbiome, and repair of intestinal epithelial cells. In the latest clinical trials, the safety and efficacy of MSCs in the treatment of IBD have been confirmed by transfusion of autologous or allogeneic bone marrow, umbilical cord, and adipose MSCs, as well as their derived extracellular vesicles. However, regarding the stable and effective clinical use of MSCs, several concerns emerge, including the cell sources, clinical management (dose, route and frequency of administration, and pretreatment of MSCs) and adverse reactions. This article comprehensively summarizes the effects and mechanisms of MSCs in the treatment of IBD and its advantages over conventional drugs, as well as the latest clinical trial progress of MSCs in the treatment of IBD. The current challenges and future directions are also discussed. This review would add knowledge into the understanding of IBD treatment by applying MSCs.

Keywords: mesenchymal stem cells, immunomodulation, inflammatory bowel disease, ulcerative colitis, Crohn's disease, cell therapy

Introduction

Mesenchymal stromal cells (MSCs) are a population of stromal cells capable of self-renewal and differentiation into various cell lineages given specific environmental cues.[1] MSCs can be extracted from various human tissues which is a pluripotent stem cell that are widely present in adult bone marrow and can differentiate into other cell types and related lineages of mesenchymal tissue.[2] MSCs differentiate into various cells at the single cell level in vitro including osteocytes, cartilage tissue cells,[3] cardiomyocytes[4] and epithelial cells.[5] The umbilical cord (including the Wharton's jelly, a gelatinous substance found inside the umbilical cord),[6,7] fetal tissue,[8] dental pulp[9] and placenta[10] have been investigated as sources of various MSCs types. Furthermore, the induced pluripotent stem cells (iPSCs)[11] have attracted much attention as a new source of MSCs, which are becoming an emerging cell therapy product.

Due to their ability to self-renew, be pluripotent, and have immunomodulatory properties, MSCs are frequently utilized in adoptive cell therapy, tissue engineering, and regenerative medicine.[12,13] Of particular note, MSCs as an adoptive therapy exhibit vast potential in alleviating inflammation-related diseases including inflammatory bowel disease

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(IBD). Many clinical trials demonstrate both the safety and efficacy of MSCs therapies on IBD. MSCs and their secreted bioactive factors (eg, extracellular vesicles (EVs), proteins, RNAs) could regulate immunity, repair inflamed tissues as well as modulate gut microbiota, thereby showing a protective effect on IBD. Although there have been great progresses on promoting MSCs for IBD therapy, several challenges emerge.

Therefore, this review aims to comprehensively discuss the current understanding of applying MSCs on IBD treatment based on their actions and mechanisms. Importantly, through a review of clinical trials of MSCs therapy, insights on current challenges and future directions are provided. This review will advocate a safe and effective treatment of MSCs in IBD in future.

An Overview of IBD

IBD is a chronic inflammatory disease that can be divided into ulcerative colitis (UC) and Crohn's disease (CD) by its etiology and pathogenesis, which has a high recurrence rate and is not easily curable, seriously affecting patients' quality of life. The clinical symptoms of IBD include gastrointestinal symptoms such as diarrhea, abdominal pain, blood in the stool and systemic symptoms such as weight loss, fatigue, anemia, etc.[14] IBD is currently prevalent in Western countries, particularly northern Europe and north America, with approximately 1.6 million Americans affected by IBD, including about 700,000 for CD patients and 900,000 for UC patients.[15] Up to 2 million people in Europe suffer from the disease, with the frequency being higher in wealthy Western countries.[16] In contrast, the prevalence of IBD is lower in newly industrialized countries in Asia, and in epidemiological studies of IBD in Asia-Pacific countries, the highest IBD prevalence was in India at 9.3/100,000 person per year, and in China at 3.3/100,000 person per year.[17] Overall, IBD has created tremendous financial pressure on the families of patients. The etiology of IBD has not been well studied, and genes, environment, gut microbiome and immune system all contribute to the development of IBD.[18–21] Among them, environmental factors are key factors in the pathogenesis of IBD, as most environmental triggers can mediate the pathogenesis of IBD through their effects on the gut microbiome.[22]

Pathogenesis of IBD

Pathogenesis of IBD is related to genetic inheritance, intestinal mucosal barrier, environment, gut microbes, immune system, and potentially other factors.[23] The main causes and symptoms are shown in Figure 1. Further exploration of the pathogenesis of IBD can contribute to a better comprehension of the function of current treatments and provide new ideas for the future development of new therapeutic drugs.

Genetic Factor

It is reported that first-degree relatives of IBD patients have a 3–20 times higher risk of developing the condition than first-degree relatives without the condition in the general population.[24] Studies have confirmed that IBD has some family heritability and its pathogenesis is closely related to genetic inheritance.[25] Identical twin concordance in UC is 10–15%, but concordance in CD is 30–35%, indicating that CD is more likely to be genetically influenced than UC, and that monozygotic twins are more likely to have IBD than dizygotic twins.[26] It is identified that *NOD2* is a susceptibility gene for CD through positional cloning and candidate gene approaches.[27,28] The identification of NOD2 opens up research direction for the study of the pathogenesis of IBD at the genetic level. New genotyping and sequencing technologies have aided to identify 242 common susceptibility loci for IBD, with 45 of them being identified as statistically conclusive causative variations, while 50 genes being linked to inflammatory disorders.[29] Notably, most of the genes in the loci associated with IBD, although shared in different ancestral groups, are only partially present in people with IBD. For instance, most European patients have variations in the *NOD2* and *IL23R* genes, but southeast Asian patients rarely do so.[30] Similarly, there were genetic IBD risk scores disparities between African Americans and Europeans, identifying genetic heterogeneity in populations of different ethnic origins.[31]

Despite substantial progress in determining the genetic inheritance of the IBD gene, there is still a long way to go before the cause of IBD is fully understood.

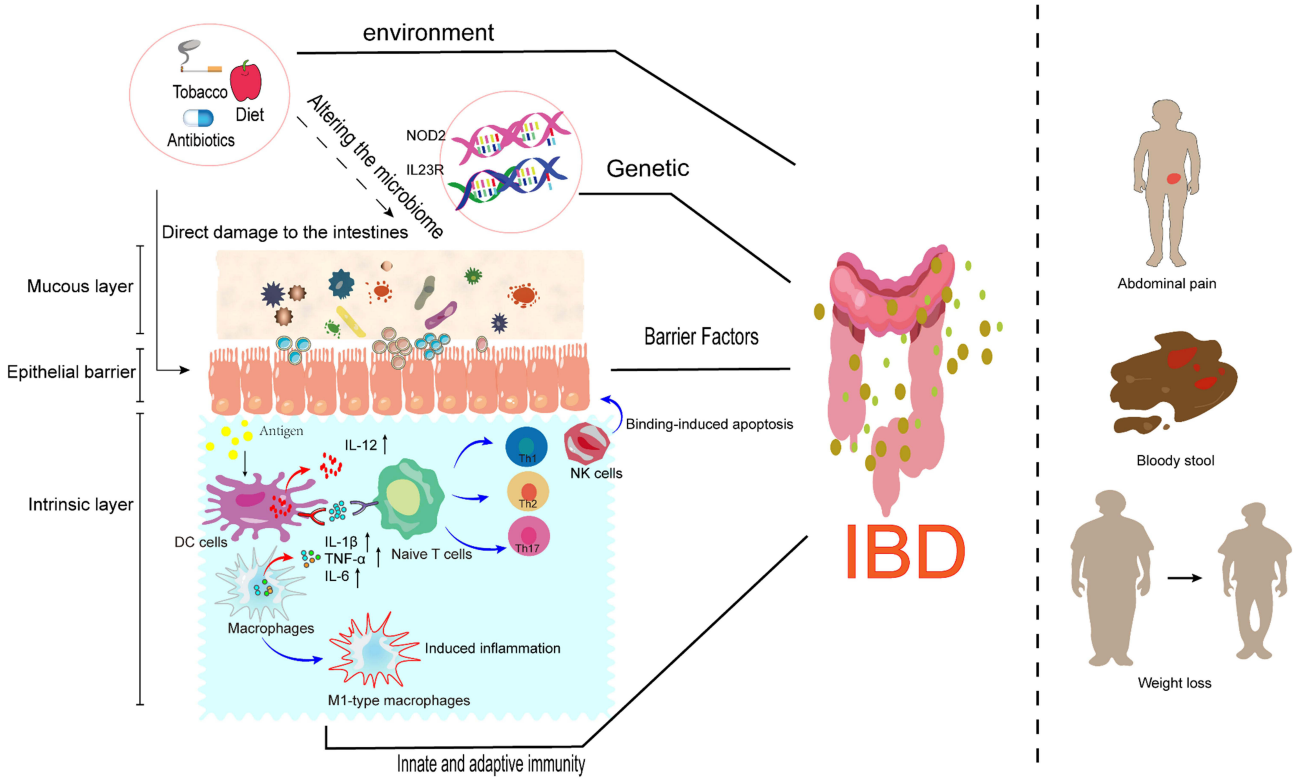

Figure 1 Pathogenesis and main symptoms of IBD. The interaction among environment, genetic inheritance, intestinal mucosal barrier, immune system and underlying factors leads to the development of IBD. The main clinical symptoms are diarrhea, abdominal pain, blood in the stool, and weight loss due to loss of appetite.
Abbreviations: DC cell, dendritic cell; IBD, inflammatory bowel disease; NK cell, natural killer cell.

Gut Microbiota

The balance of the gut microbiome plays an important role in maintaining the health of the organism and mediating disease development, which is influenced by both environmental and host factors.[32–34] Over-immunization to bacteria in genetically susceptible hosts disrupts the gut homeostatic environment, which is one of the reasons for the development of IBD. When gut microbiota diversity is reduced or altered, in which case the host becomes more susceptible to pathogens or pathogenic microorganisms, as well as the IBD.[23,35] Reflecting on the fact that the incidence of IBD has been rising in industrialized nations over the past decades, it is more likely that lifestyle, diet and environmental changes other than the genetic inheritance or natural selection are to blame for this sudden rise.[36] These dietary and environmental changes can exacerbate immunological imbalances in the body and promote the development of IBD in genetically predisposed people, because the composition and function of the human gut microbiome are particularly sensitive to these changes.[37,38]

Several studies comparing the intestinal microbial diversity and the abundance of specific bacteria in IBD patients found differences in the composition of the intestinal microbiota between IBD patients and healthy individuals. IBD patients had reduced biodiversity, reduced abundance of some bacteria belonging to the thick-walled phylum (eg, *Enterococcus faecalis*) and increased bacteria belonging to the Aspergillus phylum (eg, *Escherichia coli*) compared to healthy individuals.[39–41] Schaubeck et al colonized already ecologically dysregulated microbiota in inflamed mice into healthy mice and found inflammation in healthy mice.[42] Meanwhile, in another animal experiment investigating the effect of sugar on the pathogenesis of colitis, major alterations in the intestinal microbiota were discovered in mice fed sugar by short-term gavage.[43,44] When mice were treated with antibiotics or kept in a germ-free environment, there was no sugar-induced exacerbation of colitis, but transfer of the intestinal microbiota from sugar-treated mice to germ-free mice resulted in an exacerbation of colitis, indicating that changes in the microbes play an essential part in the

development of colitis.[43] All these studies in animal models provide strong arguments for the role of microbiome in inducing intestinal inflammation.[38,45]

While most of the current studies have focused on bacteria and less on the role of fungi and viruses, some studies have shown that the role of viral and fungal communities in the pathogenesis of IBD cannot be underestimated as well.[39,46] Notably, intestinal inflammation promotes fungal proliferation, and conversely, some fungi can modulate host susceptibility to inflammation.[47] Although the exact role and mechanism of the virus in IBD has not been fully explored, some evidence suggests that it may be indirectly involved in the development of intestinal inflammation. For future directions of IBD research, modulation of the intestinal microbiota and local immune response can be indirectly achieved by altering viral diversity.

Environmental Factor

Recent findings in the epidemiology of IBD suggest that the environment is one of the key pathogenic mechanisms of IBD.[48] Among the environmental factors, diet is the main contributor to IBD.[49] Genetically susceptible individuals have intestinal dysregulation and abnormal immune responses, a process that may be caused by changes in environmental factors, including diet.[23] Excessive intake of simple sugars is the main culprit of IBD because ingestion of large amounts of simple sugars can cause changes in gut microbes.[44] Interestingly, rectal insulin drip reduces colonic inflammation in mice,[50] suggesting that increased intake of simple sugars is an environmental risk factor for colitis.[43,44]

In addition, vegetables and fruits can help decrease the occurrence of CD.[51] Increased dietary intake of animal protein was considered a factor in the development of CD decades ago.[52,53] The harmful effects of animal proteins are also evident in chronic colitis and are associated with significant changes in intestinal bacteria and fungi.[54] Other environmental factors influence the development of IBD, such as sterility,[55] antibiotics, and other appendectomies and smoking.[56–58] In general, environmental factors trigger IBD mainly by disrupting the balance of the intestinal microbiome, and another possible cause is the destruction of intestinal epithelial cells.

Barrier Factors

The disturbance of the epithelial barrier is the root cause of IBD. The colonic epithelium facilitates host-microbe interactions, regulates mucosal immunity, coordinates nutrient circulation, and generates a mucus barrier to maintain the intestinal environment in equilibrium.[21,59] Existing studies have reported increased intestinal epithelial cell permeability and impaired intestinal mucosal barrier function in patients with IBD compared to normal subjects.[60] Furthermore, mucin and antimicrobial proteins secreted by mucus create a physical barrier to microbial contact, and the formation of internal and external mucus layers is crucial for maintaining homeostasis in the body. Of particular note is that goblet cells produce mucus to form the intestinal mucus layer, which is a crucial part of intestinal epithelial cell protection.[61,62] The intestinal flora and immune system's dysbiosis may be impacted by impaired intestinal mucosal barrier function, which could lead to an ongoing immunological response and chronic intestinal inflammation. Therefore, a key factor in the etiology of IBD is the breakdown of the intestinal mucosal barrier.[15]

Innate and Adaptive Immunity

The innate immune system clears foreign pathogens and activates the body's immune response, which consists of natural barriers such as the mucosal epithelium, immune cells such as neutrophils and natural killer cells (NKs), pattern recognition receptors, complement proteins and cytokines that allow for a rapid and effective response to foreign pathogens.[63] In rats with trinitro-benzene-sulfonic acid-induced colitis, dendritic cells (DCs) in the medullary lineage of mesenteric lymph nodes increased inflammatory responses by using IL-12 to polarize T helper cells into pro-inflammatory Th1 subpopulations.[64] In addition, immature DCs caused local intestinal inflammation, a process that is mediated by the production of IL-23.[64] Macrophages can target the antigenic specificity of pathogens and cause inflammation by activating the adaptive immune response of the body.[65] Based on their function and amount of inflammatory factor release, macrophages are classified into two subpopulations: M1-type and M2-type macrophages, M1 being associated with the induction of inflammation, while M2 being associated with inhibition of inflammation and stimulation of tissue healing.[66] The role of NKs is to induce and maintain inflammation by producing IFN-γ and IL-15,

which stimulates the recruitment of additional NKs and thus enhances the immune response. The IL-12 and IL-18 from macrophages can amplify the NKs-mediated immune response.[67]

Adaptive immunity is also crucial in the etiology of IBD, mainly involving T cells and their subpopulations. Abnormal activation of naive T cells lead to differentiation of different cell subtypes and the production of inflammatory cytokines, thereby mediating inflammation.[67,68] DCs stimulate T cells after they have taken up antigen, causing them to transform into Th1, Th2, or Th17 cells, which participate in the inflammatory response.[69] In these subtypes, cytotoxic T cells are stimulated by Th1 cells to become active, and assault infected intestinal epithelial cells, resulting in impaired intestinal epithelial barrier function. IL-18 is a key inflammatory factor involved in the activation of Th1 cells and NKs.[70,71] Th2 cells activate B cells by transmitting activation signals, proliferate and differentiate into plasma cells, and secrete antibodies against pathogen invasion, but on the other hand, when IL-13 is present in the organism, Th2 cells are induced by it and secrete IL-4, IL-5 and IL-13 that are involved in the pathogenesis of UC.[70] Th17 cells can be induced by TGF-β, IL-6, and IL-23 and produce a range of cytokines such as IL-17A and IL-21/22 to mediate inflammation.[72]

Current Treatments for IBD Including MSCs

Since the current research on the process of IBD pathogenesis is not well studied, and there is a lack of effective drugs. In CD, medical treatment is aimed at reducing abdominal pain, normalizing bowel movements, and promoting ulcer recovery, whereas in UC, the purpose of treatment is to stop the symptoms of rectal bleeding and obtain endoscopic remission.[73] Traditionally, conventional treatments include 5-amino salicylic acid, corticosteroids, immunomodulators, etc. It is worth noting that with the gradual maturation of drug development technology, the development of TNF-specific inhibitors as biologics is a milestone achievement that enables IBD patients to achieve long-term remission.[74] An increasing number of drugs, including biological agents and small chemical molecules, have been developed to treat IBD, which has also led to an increasing variety of drug options for the treatment of IBD.[20,75]

However, these treatments do not respond well to a large proportion of patients or are too difficult to tolerate due to adverse reactions, and clinical studies face significant challenges due to the efficacy and safety of existing medicinal medicines. For refractory disease, patients urgently need effective alternatives, and the heterogeneity of UC and CD clinical manifestations also make it difficult to find the best treatment for all patients.[76,77] Therefore, it is crucial to use the right and effective therapy, and further development and research of IBD treatment drugs are needed to obtain the best treatment options.

Recently, the MSCs provide more therapy ideas for IBD, which will help in the long-term management of IBD in future. The newer treatment for IBD, MSCs differentiate into different cells depending on their extensive differentiation and self-renewal capacity, and are infused after ex vivo expansion to reduce the production of intestinal inflammation by balancing the immune system and repairing the intestinal mucosa, as shown in Figure 2. In addition, it is worth noting that MSCs have low immunogenicity and immunomodulatory properties and have active therapeutic effects in a variety of inflammatory diseases.[78] Numerous animal experiments have shown the alleviating effect of MSCs and its exosomes on intestinal inflammation in mice.[79,80] Various clinical trials are also underway.[81,82] The safety and short-term efficacy of MSCs administration has been demonstrated, and the potential challenges associated with the treatment of MSCs are slowly being addressed.[83,84]

Application of MSCs exhibits distinct mechanisms of action compared to conventional drug interventions, as shown in Table 1. Firstly, MSCs can selectively migrate to damaged intestinal tissues through homing effects and replace damaged tissues. Secondly, MSCs secrete growth factors via paracrine action to facilitate intestinal epithelium regeneration and angiogenesis and reduce intestinal inflammation. Finally, MSCs can also encourage T cells and macrophages to develop anti-inflammatory characteristics through regulation of the immune system, regulating the inflammatory response.

Actions of MSCs for IBD Treatment and the Underlying Mechanisms

Traditional therapies for IBD have many side effects and poor efficacy, while MSCs, as an emerging cell therapy, have a wide range of prospects in the treatment of IBD. Because of their strong proliferation and differentiation,

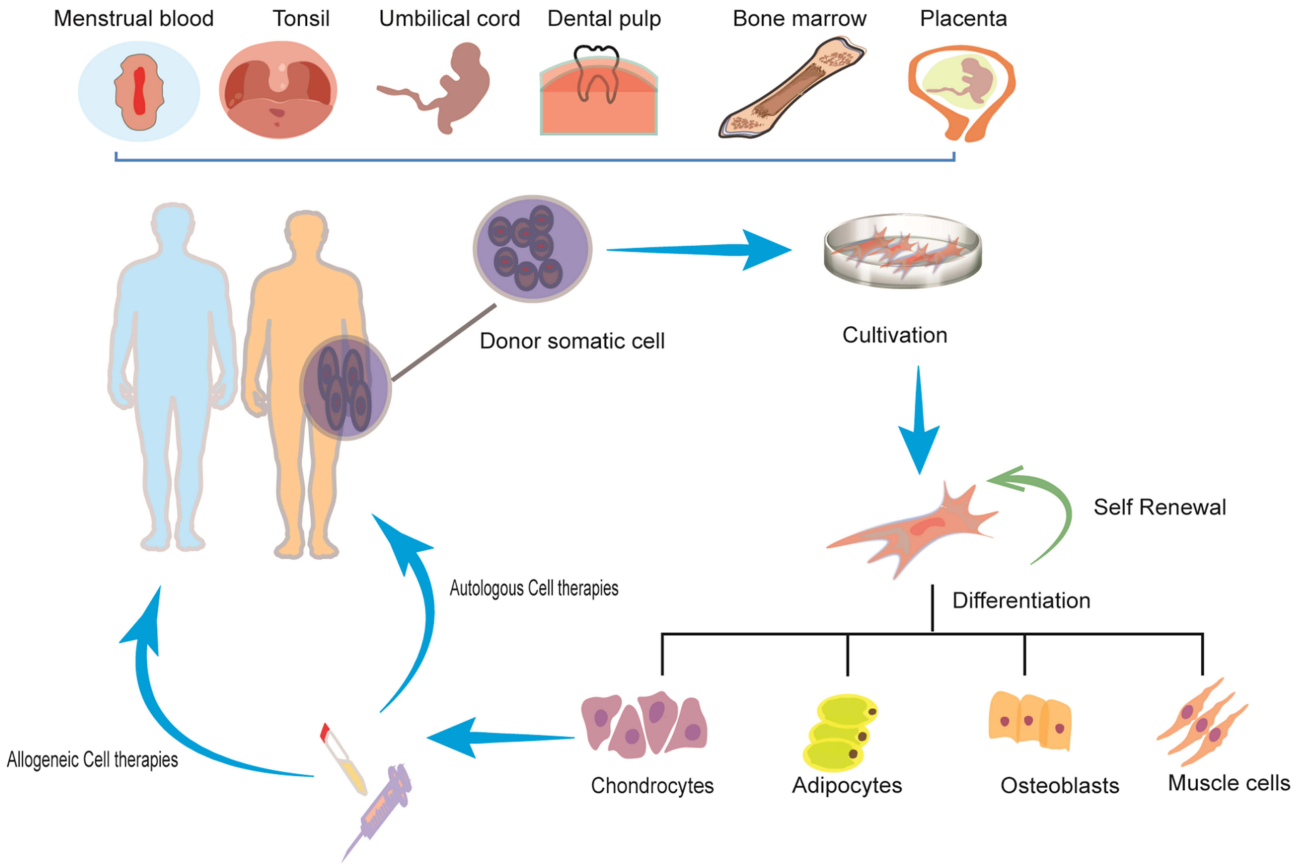

Figure 2 Different origins of MSCs possess self-renewal effect enabling allogeneic and autologous cell therapy. MSCs of different origins treat diseases through their broad differentiation potential. MSCs are widespread in the umbilical cord, tonsils, bone marrow, placenta, and dental pulp, and MSCs are able to self-renew and differentiate into various cell lineages in specific environments, and allogeneic or autologous mesenchymal stem cells cultured in vitro are infused into the body for rapid remission of disease symptoms and therapeutic effects.

immunomodulation and ability to repair damaged tissues, MSCs show strong IBD alleviating effects in preclinical and clinical studies.[85] MSCs are considered as the most promising cellular drug for IBD.[86]

MSCs have low immunogenicity because MSCs induce an immune tolerance phenotype through cell-to-cell interactions, as evidenced by low to moderate levels of MHC class I, lack of expression of MHC class II antigens and no expression of co-stimulatory molecules (CD40, CD40L, CD80 and CD86).[87] Regarding this, MSCs avoid clearance by the immune system and allows for better migration, differentiation and regulation in the body. Through its paracrine action, MSCs can release EVs, anti-inflammatory factors, growth factors, anti-apoptotic factors and soluble enzymes to suppress inflammation, promote healing of damaged intestinal tissues and regulate host immune response.[88] Herein, this review will summarize the modes of action of MSCs as well as the underlying mechanisms.

Modes of Action of MSCs

Homing Effect

The arrival of a certain number of MSCs in the damaged tissue is a prerequisite for their active function, The homing of MSCs targeting damaged tissue is key to MSC therapy for various inflammatory diseases, including IBD.[89] So far, only a few studies have studied the aggregation of MSCs in intestinal epithelial tissue, and some of these studies have elucidated homing patterns of intravenous MSC in animal models. MSC homing refers to the directional movement of MSC to the damaged tissue site under the influence of various factors and the replacement of damaged cells in the tissue site.[90] The homing effect workflow is shown in Figure 3. In brief, the homing effect of MSCs is divided into five steps:[89]

Table 1 Characteristics of IBD Treatment: Conventional Therapeutic Drugs and MSCs Therapy

Category	Mechanism	Agent	Side Effects
5-ASAs	Regulation of cyclooxygenase and lipoxygenase pathways to reduce prostaglandin and leukotriene synthesis	Sulfasalazine, mesalamine	Depression, dental caries, insomnia, kidney damage, heart damage
Corticosteroids	Reducing TNF-α, IL-1β, IL-6, IL-8, and GM-CSF generation and blocking NF-κB	Budesonide, beclometasone dipropionate	Osteoporosis, adrenal insufficiency, hyperlipidemia, pancreatitis, headache
Immunomodulators	Inhibiting immune cell differentiation and producing immunosuppression thereby reducing inflammation	Azathioprine, methotrexate, 6-mercaptopurine	Hepatotoxicity, vomiting, nausea, pancreatitis
Biologics	Blocking key cytokines of the immune inflammatory process and interfering with the immune inflammatory response in IBD	Infliximab, golimumab, risankizumab, filgotinib	Bacterial infections, primary and secondary non-responding
MSCs	Homing differentiation and immunomodulation of immune cells and secretion of growth factors through paracrine action to promote intestinal epithelial tissue regeneration and reducing the production of pro-inflammatory factors	UC-MSCs, BM-MSCs, AD-MSCs	Insomnia, loss of taste, fever, proctalgia
MSC-derived products	Regulating the immune system by secreting cytokines, restoring the normalization of the intestinal microbiome and promoting the regeneration of intestinal epithelial cells	Remestemcel-L, placental MSC derived exosomes, BM-MSC exosome isolated products	No adverse or serious adverse events related to the investigational product

Abbreviations: AD-MSC, adipose derived stem cell; BM-MSC, bone marrow mesenchymal stem cell; 5-ASAs, 5-Amino salicylic acid; GM-CSF, granulocyte-macrophage colony stimulating factor; IBD, inflammatory bowel disease; UC-MSC, umbilical cord mesenchymal stem cell.

1. Rolling: MSCs express CD44, which captures the selection and drives the cells to start rolling along the blood vessel wall.[91]
2. Activation: This step is typically advanced by G protein-coupled chemokine receptors in response to inflammatory signals, and the chemokine receptor CXCR4 ligand stromal cell-derived factor-1 is critical in this process as they allows MSCs to homing more smoothly to target tissues through binding.[92]
3. Firm adhesion: Integrins determine the adhesion process. MSCs express very late appearing antigen-4, which is then activated by chemokines such as stromal cell-derived factor (SDF)-1. After activation, in endothelial cells, vascular cell adhesion molecule-1 then produces a firm bond with very late appearing antigen-4 integration.[93]
4. Crawling: After the adhesion process is finished, MSCs scurry along the blood vessel's interior wall in search of an appropriate spot for focused migration.[94]
5. Transendothelial migration: In this process, any migrating cells must cross the endothelial cell layer and the basement membrane, and MSCs break down the endothelial basement membrane by secreting matrix metalloproteinases;[93] Finally, MSCs migrate through the mesenchyme to the damaged tissue. This step is guided by chemotactic signals released in response to tissue injury.[95]

The completion of the homing process requires the involvement of molecules such as adhesion molecules, chemokines and metalloproteinases.[96] Chemokine CXCR4 is an important molecule involved in MSCs homing.[97] CXCR4 stimulates the transfer of MSCs to damaged tissues, and MSCs homing and survival are reduced when CXCR4 is knocked out.[98] Notably, the expression of CXCR4 can be increased by upregulation of pro-inflammatory factors stimulation, such as IL-3, TNF-α, IL-1β, etc. so that MSCs show better homing and migration properties in vivo.[99–101] The homing rate of MSCs is related to various aspects, such as the degree of aging of MSCs, intercellular oxidative damage, and the pathway of transplantation.[102] In addition, the MSCs amplification process in vitro affects the expression of homing molecules and also affects the homing rate.[103] This leads to the inspiration that MSCs could be pretreated in vitro by gene therapy for MSCs to improve their homing efficiency.

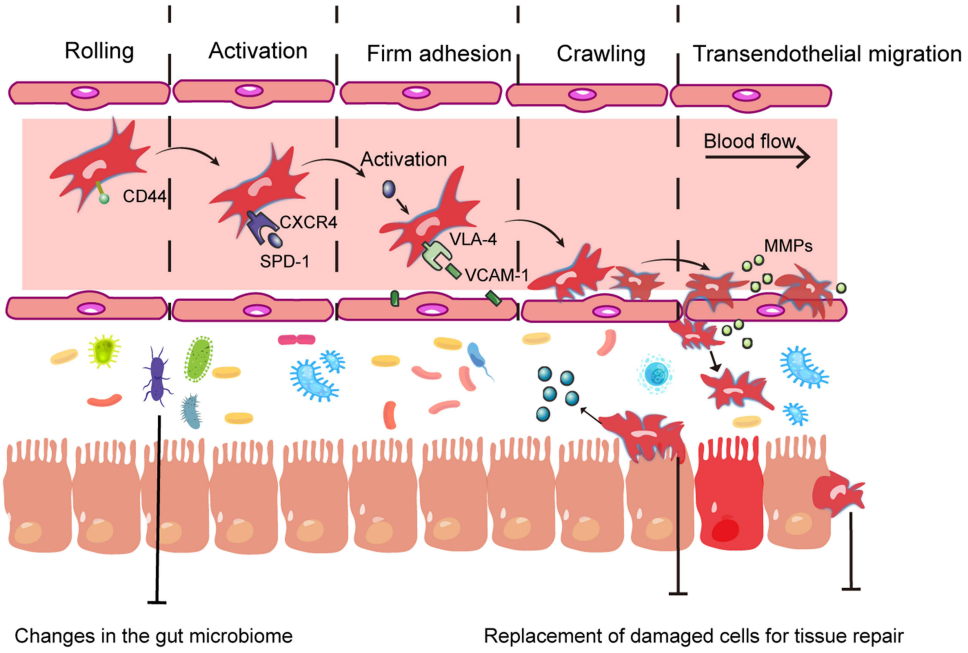

Figure 3 Non-immunomodulatory mechanisms of MSCs in the treatment of IBD. The non-immunomodulatory mechanisms of MSCs in IBD mainly include homing effect, mitochondrial transfer and improving gut microbiome balance. Through homing effect, MSCs acts directly on intestinal epithelial cells to replace injured cells to play a therapeutic role. In addition, healthy mitochondria of MSCs transfer to replace damaged mitochondria in the intestine, produce ATP to treat IBD, and finally change the intestinal microbiome and improve the intestinal microenvironment to promote the regression of inflammation.
Abbreviations: CXCR4, C-X-C chemokine receptor type 4; VCAM-1, vascular cell adhesion molecule 1; MMPs, matrix metalloproteinases.

Paracrine Effect

MSCs were capable of secreting many bioactive factors which facilitate MSCs to exert beneficial effect. These bioactive factors include the EVs and EVs-contained components, apoptotic bodies, chemokines, cytokines, soluble enzymes and membrane-bound active proteins.

MSCs-Derived EVs (MSC-EVs)

MSC-EVs have strong biological activity similar to that of MSCs, which are cell-secreting nanoscale vesicles with a phospholipid bilayer structure that secrete proteins, microRNAs, mRNAs, and other substances involving various bioactive components under certain conditions.[104] Studies have shown that MSC-EVs are highly effective in treating a variety of inflammatory disorders, suggesting that MSC-EVs as a cell-free therapy may have high research value in the treatment of IBD.[105] This is because EVs-based therapy has some advantages over cell-based therapies. For example, it is previously reported that there is an increased risk of cancer associated with MSC therapy, which has not been reported for EVs. EVs have a more stable nature compared to MSCs.[106]

Adipose-derived MSC-EVs reduce the secretion of the pro-inflammatory cytokines IL-1β and TNF-α, increase the proportion of Treg cells and reduce the production of helper T cells, maintaining homeostasis in the body.[107] It was shown that EVs derived from umbilical cord MSCs (UC-MSCs) were injected intraperitoneally into mice with enterocolitis, and by increasing TNF-α-stimulated gene 6 protein (TSG-6) expression, MSC-EVs dramatically decreased mortality and relieved symptoms of IBD in colon tissue.[108] Additionally, olfactory ecto-derived MSC-EVs prevented T cells from differentiating into Th1 and Th17 cells, and also exerted its immunosuppressive function by aggregating Tregs cells to alleviate enteritis.[109] In addition to the effect on adaptive immunity, MSC-EVs can also act on innate immunity by polarizing macrophages and producing M2-type macrophage changes to improve intestinal inflammation, and by increasing the level of the cellular immunosuppressive factor IL-10 through macrophages.[110]

It is reported that microRNAs in MSC-EVs are associated with inhibition of inflammatory development.[105] In addition, MSC-EVs contain several important enzymes involved in glycolysis: glyceraldehyde-3P dehydrogenase, phosphoglycerate kinase, phosphoglucomutase, enolase, and pyruvate kinase M2 isoform, which are speculated to be

involved in glycolysis to produce ATP.[111] Surprisingly, MSC-EVs have been reported to increase the level of ATP in myocardial tissue,[112] which results in a decrease in oxidative stress and a decrease in local and systemic inflammation.[113] CD73 may be present in MSCs, which can dephosphorylate adenosine monophosphate to adenosine, and the same process has been observed in MSC-EVs.[114] Notably, transmembrane proteins are also found in MSC-EVs, which mainly includes tetraspanins and integrins (CD9, CD63, CD81 and CD82). These transmembrane proteins are essential for cell targeting and adhesion,[111,115] showing the importance of transmembrane proteins in mediating the biological activity of MSC-EVs.

Recently, attention has been paid to apoptotic bodies that are the main products of MSCs apoptosis. Apoptotic bodies are EVs rich in deoxyribonucleic acid, ribonucleic acid, proteins, and organelles.[116,117] Interestingly, it has been found that a large number of MSCs exhibit apoptosis after transplantation into a skin wound healing model, and it is speculated that apoptosis plays an important role in activating the inflammatory regulation ability of MSCs.[118] Moreover, a research team successfully isolated apoptotic bodies derived from MSCs. In their study, these MSC-derived apoptotic bodies demonstrated significant efficacy in reducing bone loss in an animal model of periodontitis.[119] MSC-derived apoptotic bodies have been found to show similar biological activity to MSCs, which can promote muscle growth, skin healing, angiogenesis, and exhibit powerful anti-inflammatory and tissue regeneration effects.[120,121] Preliminary evidence suggests that apoptotic bodies may serve as a potential therapeutic strategy to help improve the symptoms and disease progression of IBD.

In conclusion, the study of MSC-EVs can help us to further investigate the mechanism of action of MSCs-based cell therapy. The new cell-free EVs-based therapy is emerging that can overcome some limitations of cellular therapies, and IBD treatment will take on new meaning with the help of cell-free therapy and may have the same therapeutic effect in future.

Secretion of Chemokines, Cytokines & Growth Factors

Chemokines are chemical inducers of the body's immune cells.[122] In the presence of certain inflammatory factors such as TNF-α and IFN-γ, MSCs are stimulated to produce chemokines. The C-X-C chemokine receptor 3 and C-C chemokine 5 ligands are the most common chemokines generated by MSCs triggered by cellular inflammatory stimuli.[123] These chemokines produce chemotaxis to recruit T cells in the vicinity of MSCs, which subsequently exert immunomodulatory effects on T cells by expressing inducible nitric oxide synthase or indoleamine 2,3-dioxygenase (IDO).[124] The mechanism of inhibition is that inducible nitric oxide synthase acts on the JNK signaling transducer and the activator of transcription signaling pathway through catalytic production of NO, which causes cell cycle arrest in T cells.[125] In addition to its effect on T cells, NO production acts on macrophages to reduce the production of pro-inflammatory cytokines, and the regulation of NF-κB and mitogen-activated protein kinase activity may be the underlying mechanisms.[126]

In addition to the chemokines, MSCs can also secrete a variety of cytokines. MSCs are capable of reacting to inflammatory or harmful signals from the body and are stimulated by the release of soluble bioactive substances, which can serve as feedback signals to encourage MSCs' immunomodulation.[127] In a study, IL-10 released by MSCs prevented immature $CD4^+$ T cells from differentiating into Th17 cells in vitro by downregulating $ROR\gamma^+$ T and the related signaling pathways.[128] Interestingly, the recently reported soluble mediator IL-10 is not directly produced by MSCs, but indirectly regulates the release of IL-10 through cell-to-cell communication mechanisms that affect the function of other cells.[129] One study suggests that MSCs may promote IL-10 secretion by inducing monocytes and macrophages in the presence of high levels of TNF-α and IFN-γ. MSCs may indirectly produce anti-inflammatory effects by acting on neutrophils during inflammatory episodes.[130] In addition, inflammation-activated MSCs also act on macrophages, causing them to polarize to anti-inflammatory macrophages and secrete the anti-inflammatory factor IL-10.[131,132] Research investigating MSC interaction with T cells revealed that while MSCs cultured in isolation did not secrete IL-10, co-culture with T cells induced IL-10 production by MSCs. Additionally, IL-10 levels were notably elevated in T cells co-cultured with MSCs.[133] This change in perspective provides us with a deeper understanding of the role of MSCs in immunomodulation and therapy that does not simply directly produce and release mediators, but influences the release of mediators by

regulating the functions of other cells. This contributes to a more comprehensive understanding of the mechanism of action and clinical application of MSCs.

In the presence of inflammatory cytokines, MSCs produce a range of growth factors including vascular endothelial growth factor, basic fibroblast growth factor, keratinocyte growth factor, insulin-like growth factor and hepatocyte growth factor, which activates the regenerative potential of resident stem cells, promotes angiogenesis, inhibits apoptosis and remodels the stroma.[134,135] The embryonic-derived MSCs were found to alleviate Dextran Sulfate Sodium-induced enteritis in mice, improve colonic epithelial proliferation and barrier integrity, and increase the level of insulin-like growth factor-1 in the body circulation, which was found with no improvement in enteritis by MSCs with insulin-like growth factor-1 receptor inhibitors.[136]

Secretion of Soluble Enzymes and Other Proteins

MSCs express heme oxygenase-1, which is an important soluble enzyme in heme metabolism, with antioxidant and anti-inflammatory effects. Its potential regulatory mechanisms include regulation of toll-like receptors (TLRs)-dependent cytokine gene expression and regulation of inflammatory vesicle-dependent cytokine maturation, and macrophage polarization.[137–139] IDO as a soluble enzyme is one of the key factors of immune regulation in MSCs. MSCs induce differentiation and maturation of anti-inflammatory Th2 cells by increasing the expression of IDO, resulting in tryptophan depletion, tryptophan metabolite synthesis, and Th1 cell apoptosis.[140,141] Species-specific differences exist in the immunosuppressive mechanisms mediated by MSCs. In humans, MSC-mediated immunosuppression in response to inflammatory cytokines is primarily mediated by IDO, whereas in mice, it is mediated by NO. Similarly, MSCs, regardless of their origin, secrete several factors in the presence of inflammatory factors, with NO and IDO being the most active.[142] The research team found that MSC-EVs overexpressed by IDO had better cell proliferation than MSC-EVs and inhibited renal tubular cell apoptosis and fibrosis.[143] It has been shown that IDO-depleted MSCs do not have the ability to modulate immune responses.[144]

MSCs can also help to relieve inflammation by promoting the secretion of anti-inflammatory factors such as prostaglandin E2 (PGE2), TSG-6, and IL-10.[145] PGE2 promotes the production of Treg cells, enhances their activity and inhibits the activity of NKs and DC cells.[146,147] Besides, TSG-6, a hyaluronan-binding protein produced by MSCs in response to TNF-αstimulation, plays a key role in various immune-mediated inflammatory diseases.[40] TSG-6 has multiple anti-inflammatory functions, regulating lymphocyte migration and adhesion through binding to the cell surface receptor CD44, and inhibiting the migration of neutrophils, monocytes and macrophages to inflammatory tissues.[134,148] Recently, it was discovered that TSG-6 might speed up mucosal regeneration and encourage epithelial cell proliferation in iPSC-derived MSCs, reducing the signs of enteritis in mice.[149]

Cell-to-Cell Contact

In addition to paracrine effects, MSCs control immune response mechanisms by interacting with other cells. MSCs engage with cell surface molecules and receptors, and they directly control a number of immune cell downstream pathways that have an impact on immune cell survival, proliferation, and production of effectors.[134] The PD-1/ PD-L1 axis is crucial for intercellular interactions. PD-1 is triggered to be expressed on the surface of some activated immune cells, and PD-L1 is the ligand of PD-1, which is expressed in T cells, B cells, DCs, macrophages and some non-hematopoietic cells.[150] However, it has been shown that the expression of PD-L1 and PD-L2 in MSCs,[151] therefore, MSCs can inhibit T cell activity by binding to PD-1 and its MSC-expressed ligands on the surface of immune cells to achieve immunosuppression and control the development of inflammation.[152]

In addition, MSCs also have beneficial effects on cell-to-cell contact with non-immune cells. One study found that direct cell-to-cell contact between MSCs and endothelial progenitor cells induces MSCs differentiation into a pericycle-like phenotype, promoting angiogenesis.[153]

Cell Fusion

Cell fusion mechanism refers to the replacement of damaged cells by cell fusion for tissue repair when cells are damaged in tissues, which occurs widely in prokaryotes and eukaryotes under both natural and pathological conditions, such as in

tissue and organ repair, immune response, and tumorigenesis.[154] In a prior study, bone marrow derived MSCs (BM-MSCs) from a healthy donor group were transplanted into an injury model group, and long-term proliferation of donor-derived cells was seen in major intestinal epithelial lineages, including cupped cells and enterocytes, suggesting that BM-MSCs are engaged in the repair of damaged intestinal epithelial tissues and also demonstrating that this process occurs through cell fusion.[155]

Mechanisms of Action

Immune Regulation

Numerous studies have shown that MSCs have a wide range of immunomodulatory capabilities. Its immunomodulatory function interacts with immune cells mainly through cell-to-cell contact and paracrine activity. The detailed immunoregulatory mechanisms are shown in Figure 4. For example, MSCs are involved in immune regulation, acting on immune cells, recruiting Treg lymphocytes and reducing Th1, Th17 and B cell differentiation to treat IBD.[156] Similarly, it has also been extensively studied in refractory systemic lupus erythematosus,[157] graft-versus-host disease[158] and rheumatoid arthritis.[159]

MSCs show a dual role in immunoregulation. MSCs recognize different danger signals through TLRs.[160] On the one hand, through their specific recognition pattern, MSCs can cause inflammation by activating the immune system when the host's immune system is underactive, and on the other hand, MSCs mediate immune regulation to avoid excessive self-attack when the immune system is overactive.[161] The initial line of defense is TLR recognition from harmed cells or

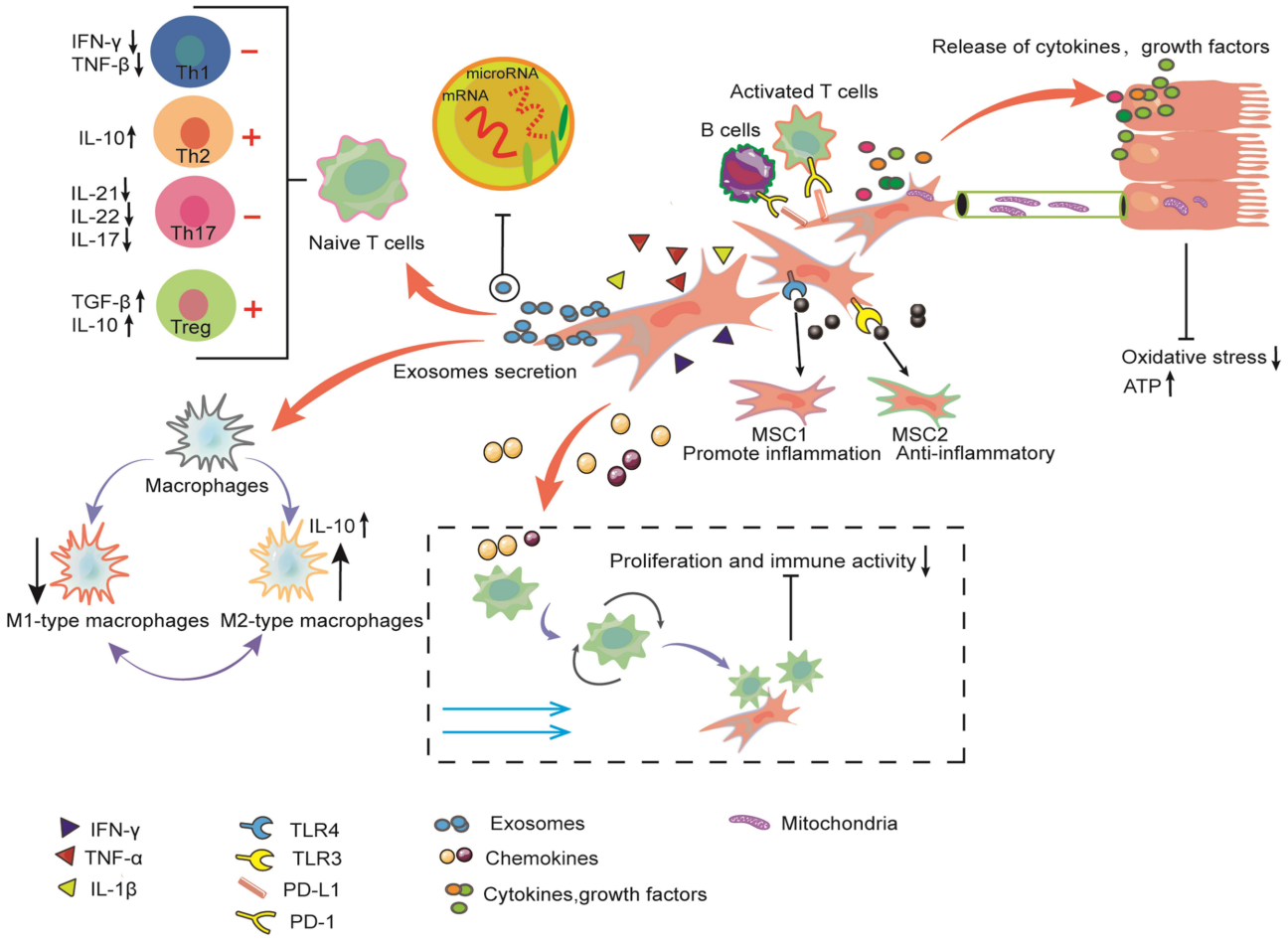

Figure 4 Immunomodulatory mechanisms of MSCs in the treatment of IBD. MSCs produce immunomodulatory effects by secreting chemokines, extracellular vesicles, and a series of cytokines interacting with immune cells such as T cells, B cells, natural killer (NK) cells, macrophages, and dendritic cells (DCs). In addition, MSCs can mediate the immune process through mutual contact with immune cells.

pathogens, and TLR activation can increase immune system stimulation and activated MSCs respond to TLR ligands and release anti-inflammatory substances. Therefore, in MSCs, TLR is essential for controlling immune responses and signal reception.[162] Interestingly, differences in the type of TLR activation also differentially affect the generation of anti-inflammatory or pro-inflammatory phenotypes in MSCs.[163–165] TLR3 induces an anti-inflammatory phenotype in MSCs, namely MSC2, and secretes inflammatory mediators such as IL-6 and IL-8. Conversely, TLR4 activation induces a pro-inflammatory phenotype, namely MSC1, and secretes anti-inflammatory mediators like IFN-γ inducible protein-10 and IL-1 receptor antagonist, which inhibits T lymphocyte proliferation through expression of PGE2 and IDO.[163,166] TLR also has an important role in that when exogenous MSCs are transplanted into the host, which are slowly removed by NKs, while TLR can activate MSCs and regulate their susceptibility to NKs, thus avoiding the killing of NKs.[167] This is why MSCs can be present in the body and produce immunomodulatory effects.[167]

Several factors can affect the immunomodulatory process of MSCs. For example, there is a difference in immunosuppressive effect between tissue-resident and newly infused MSCs, and the speculation is that its potential could be due to a change in the number of MSCs. Studies have shown that the immunosuppressive ability of MSCs is not inherently expressed, but requires stimulation by inflammatory factors. In certain infections, injuries, or immune-related conditions, MSCs can dampen the immune response when exposed to environments abundant in inflammatory cytokines. Interestingly, this specific performance of MSCs in the presence and absence of inflammatory mediators is called MSC polarization.[168] The levels of pro-inflammatory factors such as IFN-γ, TNF-α and IL-1β affect their immune processes and inflammation tend to change in the active state of the disease, which may alter the immune properties of MSCs.[166,169–171] When levels of inflammatory factors such as IFN-γ and TNF-α are low, MSC demonstrate a pro-inflammatory phenotype, and MSCs produce chemokines such as MIP-1α/β, CCL5, CXCL9 and CXCL10 to activate T cells to regulate immunity.[124] In addition, in the presence of IFN-γ and IL-1, the production of pro-inflammatory M1 macrophages is induced, and M1 further responds to T cell activation.[172] Conversely, in the case of high levels of inflammation, MSCs can inhibit the activation and proliferation of T lymphocytes.[173] In addition to the above-mentioned inflammatory factors, alarmins like IL-1α,[174] IL-33,[175] and heat shock proteins[176] all have an impact on MSC biology and show a potent ability in tissue repair and showed positive promoting effects on MSCs. MSCs also produce a large number of cytokines such as IDO, PGE2, and TGF-β, which are directly involved in the activation of Treg cells.[177] Pro-inflammatory MSCs and anti-inflammatory MSCs have opposite biological functions, and they play different roles depending on the inflammation status in the body, helping to maintain immune balance and tissue health. Therefore, inflammatory status and tissue location are the main factors determining immune regulation of MSCs.

Intestinal Epithelial Repair

MSCs produce the epithelial repair effect through cell fusion mechanism and paracrine action. By intravenously injecting human embryonic stem cell-derived MSCs into Dextran Sulfate Sodium-induced colitis mice, elevated insulin-like growth factor levels were detected. Through the elevated insulin-like growth factor levels, the intestinal epithelial cells were repaired and the epithelial cell integrity was maintained.[136] In an in vitro experiment, by co-culturing colon tissue with iPSCs, it was found that iPSCs could also promote the proliferation of colon in vitro.[149] In addition, MSCs also improve colitis by promoting intestinal epithelial repair and reducing epithelial cell apoptosis through the derived EVs.[178]

MSC-Mediated Mitochondrial Transfer

MSCs may also be used in the treatment of IBD through mitochondrial transfer. It has been shown that MSCs can replace damaged mitochondria and leave them intact through replacement, making mitochondrial transfer a potential strategy to promote tissue repair and regeneration.[179] Mitochondrial transport in MSCs requires a key Rho-GTPase, and MSCs are capable of expressing high levels of mitochondrial transport protein. It is with the help of this enzyme that the smooth transfer of mitochondria is possible.[180] Healthy mitochondria from MSCs can be transferred to target cells in a variety of ways, replacing damaged mitochondria, restoring energy supply and ensuring cell survival.[181] The mitochondria transferred by MSCs can act on intestinal epithelial cells, increase ATP levels, provide epithelial cells with the necessary bioenergy for growth and differentiation, reduce oxidative stress, and alleviate the intestinal symptoms of IBD in multiple aspects.[85,182]

MSCs mediate mitochondrial transfer mainly through tunneling nanotubes, gap junctions, microvesicles, and cell fusion.[183] Among them, tunneling nanotubes are a new mode of intercellular communication, and tunneling nanotubes are also the most common mode of mitochondrial transfer.[184] There are numerous studies on MSCs-mediated tunneling nanotubes transfer of mitochondria for tissue repair. For example, by implanting MSCs into the injured cerebral vascular system, MSCs transferred healthy mitochondria to cells in the injured tissue sites by means of tunneling nanotubes, which significantly improved the mitochondrial activity of blood vessels, enhanced angiogenesis, and promoted tissue repair and functional recovery.[185] In addition, BM-MSCs-derived mitochondria were transplanted into the damaged spinal cord of rats, and mitochondrial transfer through gap junctions could reduce neuronal apoptosis and promote neurological recovery.[186] As a new organelle-derived therapy, MSCs-mediated mitochondrial transfer has great promise in promoting epithelial cell survival and reducing apoptosis in IBD patients. However, further studies are needed to understand the precise mechanism of MSCs transfer in mitochondria for the treatment of IBD and the influencing factors that affect the transfer.

Regulating Gut Microbiome

MSCs can achieve the anti-IBD goal by altering the gut microbiota. Variation in the composition of the gut microbiota, ie abundance and species, is a key pathogenic factor in the prevalence of IBD, and it is possible that the gut microbiota may change in the early stages of IBD.[35] In one study, intraperitoneal injection of UC-MSCs into mice with enteritis effectively alleviated colitis, and analysis of mouse feces by 16S rRNA sequencing revealed that the variety and number of gut microbes were altered by UC-MSCs.[187] Another study found that MSCs changed the gut microbiome, reversed the abnormal microbiome to normal, improved overall gut health and healing, and alleviated enteritis by administering adipose-derived MSCs (AD-MSCs) to mice with colitis.[188] However, it is not known whether MSCs act directly on the microbiota to improve enteritis or whether MSCs administration promotes epithelial cell repair and thus normalizes the microbiome. The mechanisms responsible for the altered microbiota have not been determined. The potential mechanisms may be the improvement of host metabolic processes by restoring intestinal microbial diversity and abundance, as intestinal bacteria usually target host metabolism, thereby further activating the immune system and promoting inflammation.[189]

Anti-Fibrosis, Anti-Bacteria and Angiogenesis

In the early stages of intestinal inflammation, fibrosis is the initiating factor. The therapeutic potential of MSCs has been extensively studied in various organs to combat fibrosis. The expression of immune cells and their cytokines plays a key role in the progression of intestinal fibrosis, the TGF-β signaling pathway is a fundamental driver of intestinal fibrosis. Studies have shown that IL-10, as an anti-inflammatory factor, can reduce the expression of collagen 1 and TGF-β, which plays an important role in inhibiting fibrosis.[190] However, their specific role in addressing intestinal fibrosis remains relatively underexplored.[191] Different types of T cell subsets, including Th1, Th17, Th22, and Treg cells, along with the cytokines they produce, have been implicated in the progression of intestinal fibrosis, among them, MSCs and their EVs can reduce fibrosis by modulating the immune system.[190,192] In addition, MSCs and their derived EVs secrete hepatocyte growth factor and TGF-β to reduce fibrosis, and also inhibit dermal fibroblast-myofibroblast transformation by inhibiting the TGF-β1/Smad2/3 signaling pathway.[193,194]

Antibiotics can target bacterial infections in the gut, reduce inflammation, and may help improve symptoms.[195] The cytokines hepatocyte growth factor, IL-6 and IL-8 secreted by dental pulp MSCs have good antibacterial effects.[196] In addition, a preclinical study found that BM-MSCs have good antimicrobial effects on infection of *Mycobacterium avium* in vivo and in vitro. In addition, the study also found that MSCs and their secretions can enhance the efficacy of antibiotics and reduce side effects.[197] These results suggest that MSCs combined with antibiotic therapy is expected to reduce patients' dependence on long-term antibiotics and is expected to be a promising treatment. We speculate that on the one hand, MSCs may reduce the occurrence of intestinal inflammation through antimicrobials, and on the other hand, MSCs may fight against harmful intestinal bacteria and regulate microbiota balance.

MSCs and their derived EVs can promote endothelial cell proliferation and migrate to form new blood vessels, and are widely used in diabetic wound and infectious wound repair research.[198,199] MSCs secrete vascular endothelial growth

factor, platelet-derived growth factor, TGF-β, and angiopoietin-1 to promote the regeneration of blood vessels.[200,201] Intestinal epithelial tissue regeneration requires the formation of new blood vessels to provide oxygen and nutrients,[202] and it is hypothesized that the induction of angiogenesis by MSCs is another major mechanism of action of MSCs in promoting tissue regeneration.

Clinical Trial

Due to their varied actions, MSCs have been demonstrated in preclinical research to be effective for the treatment of IBD.[203] However, the data from animal studies are not necessarily applicable to human clinical trials, so the safety and efficacy of MSCs in human IBD treatment still need to be further verified in clinical trials. Therefore, clinical studies of stem cell therapy for IBD are underway and have been reported. In 2003, García-Olmo et al pioneered AD-MSCs for IBD in a woman with a rectovaginal fistula,[204] and since then, the effectiveness and safety of MSCs in the treatment of IBD have been shown in an increasing number of Phase I, II, and III clinical studies.[205–207] In 2012, a Phase III randomized, double-blind, parallel-group, placebo-controlled trial is underway in Europe and Israel using expanded allogeneic adipose-derived stem cell type to assess the efficacy of treatment of perianal fistula CD at 24 weeks and up to 104 weeks of follow-up.[207] It was eventually approved for marketing in the Europe for the treatment of perianal fistula CD.[208] As of December 2022, a broad count of clinical trials in MSCs found that the NIH Clinical Trials Database (https://ClinicalTrials.gov/) registered more than 1400 clinical trials for MSC-based treatments, with more than 700 trials for immune-related diseases, accounting for about half of the overall trials. A total of 50 trials are for IBD, including 40 trials for CD and 10 for UC. The current findings suggest that no serious complications have been reported in the clinical trials that have been conducted with MSCs for IBD. However, different MSCs sources, administration methods and doses may have different degrees of clinical symptom improvement. The sources of MSCs varied among studies, including both autologous and allogeneic differences, differences in the tissues taken, insufficient number of randomized controlled studies, unclear criteria for the assessment of side effects, and inconsistent healing criteria, all of which require further pilot studies with more rigorous and rational design and clearer criteria to provide convincing findings.[209]

Representative clinical trials of MSCs for IBD are shown in Table 2. Currently registered MSCs clinical trials for the treatment of IBD are mainly in the following directions: 1) Different tissue sources of MSCs for CD and UC. 2) Validation of the efficacy and safety of autologous and allogeneic sources of MSCs in IBD. 3) MSCs for the treatment of IBD administration modalities, doses administered, interval of injection and number of injections and clinical trials related to cell-free therapies.

MSCs Transplantation in CD

Most clinical trials have used autologous or allogeneic MSCs for transplantation and local injections for fistula CD. Allogeneic MSCs are more convenient to use because they can be expanded in vitro in large numbers to obtain fully characterized and adequate cell doses.[202] Ilse Molendijk et al[210] used MSCs of allogeneic bone marrow origin to study 21 patients with refractory perianal fistula CD (Clinical Trials ID: NCT01144962). This trial consisted of four randomly assigned groups: the first group with local injections of 1×10^7 cells (n = 5), group 2 with 3×10^7 cells (n = 5), group 3 with 9×10^7 cells (n = 5) BM-MSCs and group 4 with placebo injections (n = 6), and examined for healing after 6, 12 and 24 weeks, respectively. The results showed that the healing rate reached 80% at the 6th week of BM-MSCs treatment, showing a good therapeutic effect, and that BM-MSCs also showed a dose-related response in the treatment of refractory perianal fistula, and that in comparison to placebo, local therapy with lower doses of BM-MSCs increased the pace of fistula healing, and the therapeutic impact of 9×10^7 cells of BM-MSCs was comparable to that of the control group. Additionally, all patients accepted the local BM-MSCs injection well. Only one patient in group 2 experienced post-procedure hyperthermia and only some local reactions were observed, with no serious adverse events occurred.

In a trial of 82 CD patients with intravenous UC-MSCs, 41 patients in the treatment group showed varying degrees of reduction in CD activity index scores, corticosteroid dosage, and Harvey Bradshaw index. No serious adverse events were identified at the end of the final follow-up.[211]

Recently, in a meta-analysis on CD anal fistulas,[212] it was reported that patients with complex perianal fistulas who received MSCs injections had a healing rate of 62.8% (95% CI, 53.5–71.2%, I2=54.05%), while it was about 64% in patients with

Table 2 Clinical Trials of MSCs for Inflammatory Bowel Disease

ClinicalTrials.gov Identifier	Status	Cell Type	Dose	Phase	Outcomes
NCT01541579	Completed	AD-MSCs	1.2×10^{10}	3	Outcome Measures: Assessing the effectiveness of eASCs sourced from healthy donors in the treatment of complex anal fistulas in Crohn's disease patients, with a study duration of 24 weeks. Results: At week 24, a higher percentage of patients (50%) who received either Cx601 injection alone or in addition to their current medical treatment experienced combined remission, whereas only 34% of patients in the placebo group achieved the same outcome.
NCT01144962	Completed	BM-MSCs	3×10^{7}	1/2	Outcome Measures: Various parameters were evaluated to determine the safety and efficacy of the intervention, including fistula closure rates, clinical scores, endoscopic scores, quality of life assessment, CRP levels, incidence of surgical intervention, and infection rates. Results: No severe adverse events were observed with the local administration of allogeneic MSCs in patients with perianal fistulizing Crohn's disease. Interestingly, the injection of 3×10^{7} MSCs have potential to promote healing.
NCT01157650	Completed	AD-MSCs	/	1/2	Outcome Measures: Feasibility, safety, and tolerability assessment of AD-MSC implantation in fistulized Crohn's disease patients to monitor and document adverse events occurring during the study. Results: not published
NCT02445547	Completed	UC-MSC	1×10^{6}	1/2	Outcome Measures: Evaluation of the potential of UC-MSC therapy in patients with CD treated with hormonal medications, monitoring its therapeutic efficacy, changes in hormonal medication dosage, and adverse effects. Results: UC-MSC therapy demonstrated significant and safe improvement in disease condition among CD patients who were receiving a stable dose of steroids and had reduced steroid doses.
NCT01540292	Terminated	BM-MSCs	$1.5–2.0\times10^{6}$	1/2	Outcome Measures: Safety, clinical response, incidence of infections, CDAI, CRP, fecal calprotectin levels, and immune modulation investigation studies. Results: The MSC infusions exhibited excellent tolerability and safety profiles. No signs of infusion-related toxicity or serious adverse events were detected. However, one patient did experience a mild upper respiratory tract infection, which responded well to antibiotic treatment. Additionally, there were no notable changes observed in the blood cell counts or creatinine levels.
NCT01090817	Completed	MSC	2.0×10^{6}	2	Outcome Measures: Clinical response to MSC, incidence of infusional toxicity, induction of remission, improved quality of life, endoscopic improvement. Results: Among 15 patients with moderately to severely active disease who did not respond to anti-tumor necrosis factor therapy, infusion treatment demonstrated positive results. It led to a clinical response in 12 patients (80%), with 8 patients (53%) achieving clinical remission. Furthermore, 7 patients (47%) experienced improvement in their endoscopic findings. The CDAI also showed signs of improvement, along with a notable enhancement in the patients' quality of life.

(*Continued*)

https://doi.org/10.2147/JIR.S458103 DovePress

Table 2 (Continued).

ClinicalTrials.gov Identifier	Status	Cell Type	Dose	Phase	Outcomes
NCT01372969	Completed	AD-MSCs	2.0×10^6/ 4.0×10^6	1/2	Outcome Measures: Comprehensive monitoring to assess the incidence of treatment-emergent adverse events, change in the number of draining fistulas, change in the number of closed fistulas, rate of closure of perianal fistulas externally, percentage of subjects with healed fistulas by MRI, percentage of subjects with recurrent lumen. Results: There was a high rate of fistula closure, and two patients experienced adverse effects, namely "sepsis" and "perianal abscess".
NCT03803917	Completed	AD-MSCs	/	/	Outcome Measures: Clinical healing, ceased or reduced fistula secretion, complications to the treatment. Results: Injection of freshly harvested autologous MSC resulted in complete healing in the majority of patients (57%), demonstrating the safety and tolerability of the treatment.
NCT02520843	Completed	AD-MSCs	/	1/2	Outcome Measures: Efficacy, safety, improvement of quality of life (assessed by questionnaire). Results: At week 12, 70% of patients demonstrated a clinical response, which increased to 80% by week 48. Composite remission was achieved by 20% of patients at week 12 and by 60% at week 48. Throughout the study, three serious adverse events were reported, including two recurrent cases and one incident of a new fistula.
NCT05003947	Recruiting	UC-MSC	1×10^{10}	1	Outcome Measures: Clinical monitoring of possible adverse events or complications, efficacy. Results: not published
NCT04543994	Recruiting	BM-MSC	1.5/ 3×10^{10}	1/2	Outcome Measures: Assessed several outcomes, including clinical and endoscopic remission, clinical and endoscopic response, partial clinical and endoscopic response, lack of response, and the Mayo Clinic score. Results: not published
NCT04073472	Withdrawn	BM-MSC	7.5×10^5	1	Outcome Measures: Safety and feasibility, radiographic healing, clinical healing, alloimmune response to MSCs. Results: not published
NCT01914887	Unknown	AD-MSCs	6.0×10^5	1/2	Outcome Measures: Drug-related adverse events of study and the efficacy of treatment for inducing remission in moderately active ulcerative colitis. Results: not published
NCT01915927	Completed	AD-MSCs	2.0×10^5	1	Outcome Measures: Evaluating the safety and toxicity of autologous MSC for the treatment of patients with Crohn's disease fistulas, with a preliminary assessment of the response of MSC-containing cells to promote fistula healing. Results: At the 6-month follow-up, majority (83%) of the patients (10 out of 12) achieved complete clinical healing and showed positive radiographic markers of treatment response. Furthermore, the application of MSC-coated matrix fistula plugs in patients with chronic perianal fistulas demonstrated both safety and efficacy, leading to clinical healing and radiographic response in 10 out of the 12 patients.

Abbreviations: AD-MSC, adipose-derived mesenchymal stem cell; BM-MSC, bone marrow mesenchymal stem cell; CDAI, Crohn's disease activity index; CRP, C-reaction protein; MSC, mesenchymal stem cell; UC-MSC, umbilical cord mesenchymal stem cell.

uncomplicated perianal fistula. It is important to note that the healing rates were 69.4% and 50.7% for autologous and allogeneic stem cell treatment, respectively (p = 0.020), suggesting that autologous stem cells have a higher clinical healing rate.[212] This is due to the fact that autologous-derived MSCs are host-derived, and there is no immune rejection after injection.[212] MSCs derived from CD patients have been found to have phenotypic and functional characteristics comparable to those of MSCs from healthy population.[212]

In addition, many other clinical trials are underway showing cure rates of 46% to 90% for anoperineal fistulas in CD after injection of autologous or allogeneic AD-MSC, a good safety profile with longer clinical remission in nearly 60% of cases was demonstrated in a phase III controlled trial using allogeneic AD-MSC for adoptive therapy.[213]

MSCs Transplantation in UC

A study from 2009 revealed for the first time that MSCs were successfully used in UC patients.[214] In a phase IB/IIA randomized controlled clinical trial investigating the safety and efficacy assessment of BM-MSCs in UC, six patients were studied and all received anti-TNF or anti-integrin therapy; four were treated with BM-MSCs and two with placebo. In the therapy group (n = 4), patients had decreased severity scores and reduced symptoms after two weeks of BM-MSCs treatment, and among the control group (n = 2), Mayo scores remained stable. After 3 months of treatment, according to the Inflammatory Bowel Disease Patient-Reported therapy Impact, all patients were either extremely happy or satisfied with their BM-MSCs therapy, and the therapy response of each patient was rated as outstanding or good. In terms of adverse events, there have been no significant adverse effects linked to the BM-MSCs treatment. Adverse events occurred in 5 patients within the initial three months; 3 reported abdominal pain, 1 reported knee pain, and 1 reported pain due to perianal fissure at 6 weeks, which were resolved spontaneously without treatment.[82]

In another clinical trial (Clinical Trials ID: NCT01221428), the safety and therapeutic effects of UC-MSCs in moderate-to-severe UC were investigated.[215] All patients had taken a stable dose of 5-aminosalicylate prior to MSCs treatment. In group I, 34 patients with UC were infused with UC-MSCs, and in group II, 36 patients were infused with saline as the control group. After 1 month of treatment, 30 out of 36 patients in group I had positive responses, with significant improvement in severe mucosal inflammation. The Mayo score and histology score of the patients in group I reduced during the course of the follow-up period, and in contrast to group II, there were no notable negative effects following infusion in group I. It is worth mentioning that throughout the monitoring period, there were no recurring adverse effects or consequences.[215] The use of UC-MSCs infusion therapy for UC may be a safe and successful option, according to adequate clinical research. Although a vast number of animal and clinical research have shown that MSCs may be safe and effective, further high-quality randomized controlled clinical studies are required to produce more conclusive data. The phase III clinical trial currently underway will also provide valuable data reference and treatment flow for future cell therapy for IBD.

Major Challenges of MSCs Therapy

Cell Source

The therapeutic effects of MSCs differ depending on their tissue origin. For instance, differences in proliferative capacity and paracrine mechanisms between AD-MSC and BM-MSC have been reported.[216] In terms of differentiation, BM-MSC and AD-MSC showed a greater tendency to differentiate towards osteoblasts, while UC-MSC lacked differentiation towards adipocytes.[217] In addition to having a higher angiogenic capacity than BM-MSC,[218] AD-MSC also has a higher immunomodulatory potential.[216] In contrast, UC-MSC has the highest cartilage differentiation capacity and therefore has the potential to be used for tissue engineering studies.[219]

Currently no studies have been performed to directly assess the differential effect of different sources of MSCs on IBD. However, based on current knowledge, different types of MSCs may exert similar yet different protective effects. With regard to the existing clinical application of MSCs on IBD, different sources seem to have no preferences on UC and CD. BM-MSCs and UC-MSCs are mostly investigated on IBD, followed by the AD-MSCs. On the other hand, it has been reported that different sources of MSCs secrete varied levels of factors and exhibit distinct suppressive activities.[220] It is important to note that the perinatal MSCs, including those derived from the placenta, chorion, and umbilical cord,

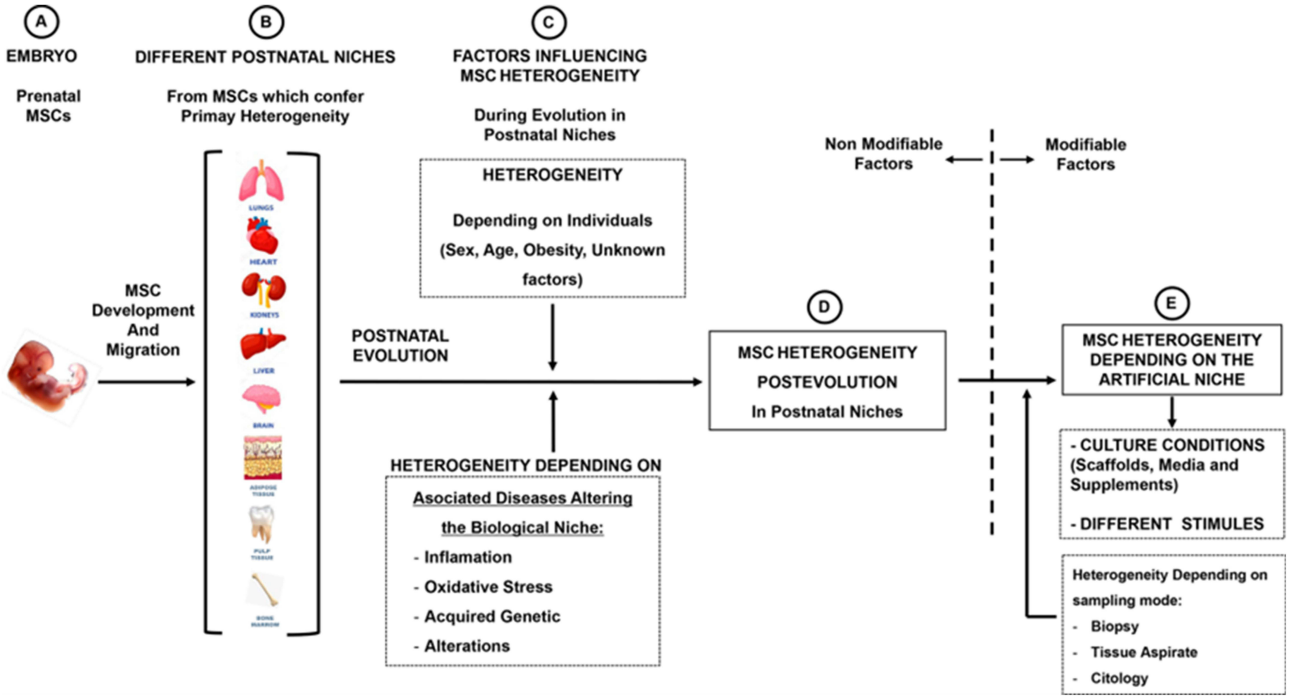

Figure 5 Key factors contribute to MSC heterogeneity in their different niches. Reprinted with permission from Costa LA, Eiro N, Fraile M, et al. Functional heterogeneity of mesenchymal stem cells from natural niches to culture conditions: implications for further clinical uses. Cellular and Molecular Life Sciences. 78(2):447–467. Copyright © 2020, Springer Nature Switzerland AG.[226]

may offer some advantages over somatic MSCs. Perinatal tissue-derived MSCs usually offer the advantage of a less invasive and more convenient sampling process compared to their adult-derived counterparts. Perinatal MSCs possess higher proliferation capacity in vitro, especially under hypoxic conditions.[221] The proliferation and differentiation ability of MSCs from bone marrow was decreased with the increase of donor age, while perinatal MSCs were more primitive and had strong differentiation ability and immunomodulatory properties.[222]

In addition, Wharton's jelly as a substance found in perinatal tissues, due to their proliferate and expand faster than MSCs from other sources and being immunogenic and nontumorigenic, has gained a great deal of attention.[6,7] Wharton's jelly is a mux-like connective tissue found in the umbilical cord that prevents vascular torsion and is similar to the umbilical cord with an abundance of MSCs.[223] It is important to note that Wharton's jelly MSCs are easy to collect painlessly and do not pose a risk to the donor. They are also less heterogeneous compared to adult MSCs, promising to have an encouraging role in future cell therapies.[224,225]

Donor age, sex, disease state, and other unknown factors can also lead to differences in MSC characteristics (Figure 5).[226] It was also found that MSCs from different sampling locations of the same subject had different characteristics. MSCs obtained from visceral white adipose tissue showed greater proliferation and were more likely to differentiate into adipose or osteogenic lineages compared to MSCs of subcutaneous white adipose tissue origin.[227] In the therapeutic treatment of IBD, selection of autologous and allogeneic MSCs is crucial. Due to their being more readily available and accessible than autologous MSCs and having the potential for broad-scale expansion and standardization, allogeneic MSCs are being used in clinical trials at an increasing rate.[134]

Therefore, it is crucial to take the source of MSCs into account while developing future IBD cell therapies.

Medication Management

In addition to the type of MSCs, the dose, the mode of administration, frequency of administration, and whether MSCs are pretreated or not may also lead to dynamic changes in the results of MSCs clinical application. The lack of retention

time and survival of MSCs at the site of administration after transplantation is a challenge, which affects the therapeutic efficacy.

The common modes of administration in current clinical trials of MSCs for IBD are circulatory administration and local injection. With circulatory delivery, the cells often do not reach the target tissue, making them insufficient to deliver therapeutic cells to the site of the disease. Local delivery, where the cells can be quickly localized to the lesion, is relatively more effective, but has the disadvantage of causing new trauma or complications.[228] Consequently, it is crucial to select the proper administration method for each indication. Molendijk et al[229] emphasized that in order to avoid wasting MSCs and to achieve standardized treatment, MSCs should be injected into the wall around the internal opening of the fistula rather than into the lumen of the fistula because MSCs are absorbed by the lungs after injection, resulting in a weakened absorbable dose at the location of intestinal inflammation in CD, and therefore having an impact on the therapeutic effect.

Dave et al[230] improved the success rate of BM-MSCs infusion into CD mice from the left ventricle and greatly reduced morbidity and mortality in mice. Currently, the dosage and duration of MSCs in the treatment of IBD are not standardized, and to examine the connection between efficacy, dose, and duration, the majority of contemporary clinical trials employ a dose-escalation strategy. Thus, the study of dose and frequency of administration is particularly important.[105] In a clinical trial using autologous BM-MSCs in 12 patients with CD, Dhere et al[231] set up infusion gradients of 2×10^6, 5×10^6, or 1×10^7 cells/kg and found that all patients were well tolerated without dose-dependent toxicity, suggesting that intravenous injection of 1×10^7 cells/kg is safe and practical. Various tissue sources for MSCs have varied migratory homing characteristics. It suggests that some pharmacokinetic studies can be performed. Pharmacokinetic studies can clarify the precise distribution, survival rate, and metabolism of various MSCs in vivo to establish the ideal dosage and timing, which is anticipated to increase the clinical effectiveness of MSCs and decrease their potential side effects.[232]

Preconditioning MSCs with pro-inflammatory cytokines like sub-IFN-γ, TNF-α, and IL-1β have been demonstrated to enhance their therapeutic potential by influencing their immunosuppressive properties.[86] BM-MSCs cultured under specific hypoxic conditions, such as near-hypoxia (0.1% oxygen), have been shown to have enhanced paracrine effects. Moreover, BM-MSCs cultured under near-hypoxic conditions exhibit improved chemotactic and pro-angiogenic properties of the conditioned medium and have been shown to reduce inflammatory mediators as well.[233] Although in vitro expansion of MSCs is widely used and in most studies, they are cultured in complete medium containing 2–10% fetal bovine serum, clinical application of MSCs is impeded by differences in serum batches and preservation issues which can lead to changes in the MSCs phenotype. As such, developing serum-free media is a necessary step towards standardized MSCs production for clinical purposes.[134]

Adverse Reactions

Although MSCs have shown beneficial effects in reducing inflammation through immunosuppression and aiding tissue repair and wound healing, their role in promoting tumorigenesis by mediating the immune system cannot be ignored.[234] It is important to consider the long-term safety of MSCs treatment, as this aspect has not yet been extensively studied. Therefore, there is a need to conduct more research on the potential risks and benefits of using MSCs as a therapeutic option. In a clinical study involving seven participants with IBD,[235] allogeneic UC-MSCs/ BM-MSCs infusion was investigated. Two of the patients experienced low-grade fever and insomnia following the infusion. Although their symptoms completely resolved in a short period of time without any medical intervention,[235] the findings demonstrate the potential safety concerns associated with this treatment modality and highlight the need for further research in this area.

In the context of IBD, MSCs have exhibited a favorable safety profile in the short-term, with only minor adverse effects or serious adverse effects being reported. This suggests that MSCs therapy may have value as a safe treatment option for IBD, but long-term clinical safety is difficult to conclude due to insufficient data from studies, which will require future long-term follow-up studies. The longest study period is the 4-year clinical study conducted by Barnhoorn, which showed that allogeneic BM-MSCs are safe and effective in the long-term treatment of patients with anal fistula CD.[236]

Conclusions

MSCs as an emerging therapeutic approach for IBD have demonstrated robust immunomodulatory and non-immunomodulatory effects in numerous preclinical studies, actively participating in tissue regeneration at inflammatory sites and mediating effective anti-inflammatory responses. While MSCs therapy for IBD is still in its early stages, a series of clinical trials have confirmed the safety and efficacy of MSCs infusion and its associated products.

The application of MSCs in treating IBD not only allows for the avoidance of potential side effects associated with conventional drugs but also enhances the quality of treatment and improves the overall life quality of patients. Various challenges remain to the use of MSC-based therapies that require evaluation of the long-term safety and efficacy of MSCs. Future research should prioritize the comparative evaluation of the therapeutic effects of MSCs from different sources, doses, treatment frequencies and different pretreatment methods. Notably, MSCs can be prepared into new drug delivery systems such as hydrogels and nanoparticles to improve efficacy. In the near future, novel MSC-based cell therapies may become the preferred method for the next generation of IBD treatments.

Abbreviations

AD-MSC, adipose-derived mesenchymal stromal cell; BM-MSC, bone marrow mesenchymal stromal cell; CD, Crohn's disease; DC, dendritic cells; EVs, extracellular vesicles; IBD, inflammatory bowel disease; IDO, indoleamine 2,3-dioxygenase; iPSC, induced pluripotent stem cells; MSC, mesenchymal stromal cell; NK, natural killer cells; PGE2, prostaglandin E2; TLR, toll-like-receptor; TSG-6, TNF-α-stimulated gene 6 protein; UC, ulcerative colitis; UC-MSC, umbilical cord mesenchymal stromal cell.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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