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## Cell membrane and bioactive factors derived from mesenchymal stromal cells: Cell-free based therapy for inflammatory bowel diseases

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### Abstract

Inflammatory bowel diseases (IBD) are chronic inflammatory disorders of the gastrointestinal tract associated with multifactorial conditions such as ulcerative colitis and Crohn's disease. Although the underlying mechanisms of IBD remain unclear, growing evidence has shown that dysregulated immune system reactions in genetically susceptible individuals contribute to mucosal inflammation. However, conventional treatments have been effective in inducing remission of IBD but not in preventing the relapse of them. In this way, mesenchymal stromal cells (MSC) therapy has been recognized as a promising treatment for IBD due to their immunomodulatory properties, ability to differentiate into several tissues, and homing to inflammatory sites. Even so, literature is conflicted regarding the location and persistence of MSC in the body after transplantation. For this reason, recent studies have focused on the paracrine effect of the biofactors secreted by MSC, especially in relation to the immunomodulatory potential of soluble factors (cytokines, chemokines, and growth factors) and extracellular vehicles that are involved in cell communication and in the transfer of cellular material, such as proteins, lipids, and nucleic acids. Moreover, treatment with interferon- $\gamma$ , tumor necrosis factor- $\alpha$ , and interleukin-1 $\beta$  causes MSC to express immunomodulatory molecules that mediate the suppression *via* cell-contact dependent mechanisms. Taken together, we present an overview of the role of bioactive factors and cell membrane proteins derived from MSC as a cell-free therapy that can improve IBD treatment.

**Key words:** Bioactive factors; Cell membrane; Mesenchymal stem cells; Cell-free therapy; Inflammatory bowel diseases

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**Core tip:** Recent experimental studies have suggested that both bioactive factors and surface proteins of mesenchymal stem cells demonstrate great therapeutic potential for overcoming the deficiencies of current therapies for inflammatory bowel diseases. Our goal in this review is to describe cell-free therapy based upon the therapeutic potential of mesenchymal stem cells, while avoiding the practical issues associated with the use of living cells.

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## INTRODUCTION

Inflammatory bowel diseases (IBD) comprise ulcerative colitis (UC) and Crohn's disease (CD), both of which are chronically multifactorial inflammatory disorders of the gastrointestinal system. Although the pathogenesis of IBD remains unclear, mounting evidence suggests that abnormal immune regulation in genetically susceptible individuals and/or environmental factors contribute to mucosal inflammation<sup>[1-3]</sup>. Conventional treatments for IBD involve immunosuppressive drugs that lead to the remission of intestinal inflammation and related symptoms. However, there is no known medical/surgical cure for IBD<sup>[4,5]</sup>. Therefore, additional therapeutic strategies, such as cell-based therapy, are required for unresponsive patients.

In this way, mesenchymal stromal cells (MSC) are a promising strategy for treating inflammatory diseases, immune disorders, and tissue regeneration due to their immunomodulatory properties, ability to differentiate into several tissues, and homing to inflammatory sites, by which they control inflammation and the production of cytokines<sup>[6-8]</sup>. However, there are conflicts in the literature regarding the location and persistence of MSC in the body after transplantation. Cell-tracking studies have shown that most MSC are localized in the lungs after intravenous infusion and have a short-term survival span<sup>[9-12]</sup>. After 24 h of infusion, MSC tend to disappear from the lungs, suggesting that they probably transmit their effects to resident cells<sup>[9]</sup>. Based on this, MSC may interact with resident cells through the secretion of paracrine factors or cell-cell communication<sup>[13-15]</sup>.

Recent studies have focused on the paracrine effect of the biofactors secreted by MSC, especially in relation to the immunomodulatory potential of soluble factors (cytokines, chemokines, and growth factors)<sup>[16-18]</sup>. Also, MSC alter their immune function in response to the inflammatory environment, especially by the stimulation of proinflammatory cytokines interferon- $\gamma$  (IFN- $\gamma$ ) and the tumor necrosis factor (TNF)- $\alpha$ <sup>[19,20]</sup>. After activation, MSC upregulate the expression of interleukin (IL)-6, IL-10, indoleamine 2,3 dioxygenase (IDO), transforming growth factor (TGF), prostaglandin E2 (PGE-2), hepatocyte growth factor (HGF), nitric oxide, and heme oxygenase-1<sup>[20-23]</sup>. It is also known that MSC are capable of releasing extracellular vesicles (EVs) that are involved both in cell communication and in the transfer of cellular material, such as proteins, lipids, and nucleic acids<sup>[24-26]</sup>. Moreover, MSC express immunomodulatory molecules in their cell membrane such as ATPases, CD73, and Toll-like receptors (TLRs)<sup>[27-29]</sup>, and, under inflammatory conditions, they express the programmed death ligand 1 (PD-L1) and the Fas ligand<sup>[22,30-34]</sup>. For this reason, both biofactors secretion and cell contact may be required for efficient MSC immunomodulation<sup>[14,35]</sup>.

Therefore, the study of bioactive factors and cell membrane molecules of MSC becomes important in the search for new cell-free therapeutic methodologies that aim to reduce the complications associated with the administration of MSC but while preserving the immunological properties of these cells.

## IBD

IBD are chronic inflammatory disorders of the gastrointestinal system associated with multifactorial conditions, such as UC and CD. Although the underlying mechanisms of UC and CD remain uncertain, growing evidence has shown that failure of the epithelial barrier and dysregulation of the immune system in genetically predisposed individuals contribute to mucosal inflammation<sup>[1-3]</sup>. These diseases are characterized by the dysfunction of mucosal T cells, alteration in the production and secretion of cytokines, and cellular inflammation affecting the digestive tract, especially the distal small intestine and colon mucosa<sup>[36]</sup>. While CD may affect any part of the gastrointestinal segment and is characterized by an inflammatory process that recruits macrophages and forms granulomas, UC is generally limited to the colon and rectum, characterized by neutrocytic infiltrate with formation of cryptic abscesses and epithelial ulceration<sup>[37]</sup>. Patients with UC experience continuous inflammation confined to the mucosal layer. In CD, the inflammation is discontinuous and affects all intestine layers<sup>[2]</sup>.

At the clinic, patients with IBD have recurrent episodes of abdominal pain, diarrhea, bloody stools, and weight loss. Moreover, they may present extra intestinal manifestations in the skin, joints, eyes, and less frequently in the abdominal organs, for example, the biliary tract<sup>[38]</sup>. Treatment of IBD is based on the severity, site, clinical manifestations, and complications of the disease in each case. Several cellular and molecular pathological pathways have been identified as targets for IBD treatment<sup>[39]</sup>. The exacerbated progression of IBD requires a scale ranging from anti-inflammatory treatment to biological agents, usually with limited success<sup>[40]</sup>. Furthermore, medical treatments are expensive and common drugs are toxic and ineffective for most patients, making surgical resection of the parts of the intestine necessary in many cases<sup>[2,41]</sup>. Regarding the progress achieved by intensive clinical-drug treatment, approximately 20% of patients with UC and 50% of patients with CD require surgical intervention within 10 years of diagnosis<sup>[41]</sup>. Accordingly, some studies have addressed MSC therapy as a promising approach for treating IBD<sup>[42]</sup>.

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## MSC

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MSC are multipotent cells capable of differentiating into mesodermal lines, particularly osteoblastic, adipogenic, and chondrogenic strains<sup>[43,44]</sup>. There is controversy over the naming and definition of MSC in the scientific community. The term “mesenchymal stromal cell” is used in parallel with the terms “mesenchymal stem cell” and “multipotent mesenchymal stromal cell”<sup>[45]</sup>. MSC are indeed a heterogeneous population of cells characterized immunophenotypically by the expression of CD73, CD90, and CD105 and do not present the expression of CD45, CD34, CD11, CD14, CD19, CD79A, and human leukocyte antigen (HLA)-DR hematopoietic lineage markers<sup>[46]</sup>. Most of the knowledge about these cells was generated from bone marrow-derived MSC. However, the origin of MSC production has been expanded to other tissues, including muscle, adipose, and neonatal tissues<sup>[47,48]</sup>. Recently, Soontararak *et al.*<sup>[49]</sup> demonstrated that MSC derived from induced pluripotent stem cells are equivalent to MSC derived from adipose tissue in terms of improving the intestinal healing in IBD model.

MSC exhibit great therapeutic potential in regenerative medicine owing to their ability to differentiate *in vitro*, homing (the process in which cells are able to migrate and graft to the tissues) to inflamed tissues after *in vivo* infusion, and the secretion of various bioactive molecules<sup>[8]</sup>. In addition, the immunomodulatory properties of MSC suggest that even MSC of the incompatible HLA may be suitable for a wide variety of new therapeutic applications, especially for cellular therapy of inflammatory and autoimmune diseases<sup>[50]</sup>. Traditionally, MSC are isolated from bone marrow, but other cellular sources may be of greater benefit due to the higher number of MSC or easier accessibility<sup>[13]</sup>. Moreover, MSC from different tissue sources share several phenotypic and functional features. Even so, there are subtle peculiarities in the expression and differentiation abilities of specific markers on cell surface<sup>[13,45]</sup>.

Studies have compared the ability of MSC from different tissues to suppress peripheral blood cells, and adipose tissue-derived MSC have demonstrated a greater immunomodulatory effect than MSC from other sources<sup>[51,52]</sup>. Although adipose and bone marrow-derived MSC share several properties, there are variation in gene expression and growth factor secretion profiles<sup>[53]</sup>. In addition, various types of adipose tissue may have distinct properties. MSC isolated from abdominal and mammary adipose tissue, for example, present discrepancy in the expression of fibroblast growth factor and receptor, suggesting variability in angiogenic potential<sup>[54]</sup>.

Neonatal tissues (cord blood, umbilical cord, placenta, amnion, and chorion) have been an alternative for MSC isolation. These tissues are usually discarded as a

residual product after delivery and can be obtained in large quantities in an easy and noninvasive way<sup>[55]</sup>. Another relevant advantage of neonatal tissues is that they supply immature cells, which present a lower risk of mutations and superior cell activity, such as increased differentiation, homing, and grafting ability<sup>[56,57]</sup>. Previous studies have shown that neonatal sources exhibit superior proliferation and immunosuppressive and regenerative potential when compared to adult tissues, for example, bone marrow and adipose tissue<sup>[47,58]</sup>.

### **Immunological properties of MSC**

MSC have demonstrated low levels of HLA or major histocompatibility complex (MHC) class I and insignificant levels of HLA class II. Moreover, they do not express co-stimulatory molecules such as CD40, CD40L, B7-1 (CD80), and B7-2 (CD86)<sup>[22,51,59-61]</sup>. Consequently, MSC present low immunogenicity and may “escape” the immune system due to their surface phenotypes that are not recognized by T cells. Absence of MHC II or T cell co-stimulatory molecules make the MSC immune-privileged cells and may explain the mechanism by which MSC are not recognized by T cells<sup>[62]</sup>. Interestingly, both syngeneic and allogeneic MSC are immunotolerable by the receptor<sup>[63]</sup>.

MSC have presented a high immunosuppressive capacity and interaction with immune cells through several mechanisms. Studies have shown that MSC-mediated immunosuppression may occur through the secretion of soluble factors and the presence of MSC membrane protein<sup>[51,64]</sup>. Regarding soluble factors, important anti-inflammatory molecules, such as transforming TGF- $\beta$ , PGE-2, and HGF, have been enrolled<sup>[21,23]</sup>. Through secretion of TGF- $\beta$  and other factors, MSC promote the induction of regulatory cells, including T cells<sup>[65]</sup>, macrophages<sup>[66]</sup>, and B cells<sup>[67]</sup> and thus transmit their immunosuppressive effects to different types of cells that exert several mechanisms of immune suppression. MSC can also be induced to produce IDO enzyme, which has an effective ability to inhibit lymphocyte proliferation by metabolism of L-tryptophan to L-kynurenine. Thus, low levels of L-tryptophan and high levels of L-kynurenine impose a block of lymphocyte proliferation<sup>[68]</sup>.

Moreover, MSC exert their immunomodulatory function through molecules in their cell membrane, such as ATPases and CD73 (ecto-5'-nucleotidase, Ecto5'NTase)<sup>[28,69]</sup>. ATPase converts ATP to ADP and then to AMP. CD73 further dephosphorylates AMP to adenosine, which exhibits immunosuppressive properties<sup>[69,70]</sup>. Also, the ability of MSC to modify the immune system response can be enhanced by treatment with proinflammatory cytokines, TNF- $\alpha$  and IFN- $\gamma$  in particular<sup>[19-21]</sup>. Under inflammatory conditions, MSC express membrane proteins with an immunological regulatory function, such as PD-L1 and the Fas ligand, through which they direct to the target cells and prevent their activation/function<sup>[6,22,32-34]</sup>.

### **Interaction between MSC and immune cells: Direct cell contact or secretion of molecules?**

Secreted bioactive molecules as well as the membrane proteins of MSC demonstrate an ability to mediate immunosuppression. Nevertheless, there are controversies in the literature about the interaction of MSC with immune cells<sup>[71-73]</sup>. For MSC treatments to reach their full potential, a broader understanding of how cells exert their immunosuppression must be developed. Then it will be possible to define the relevant pathways for improving MSC treatment for specific inflammation or immune disorders.

Factors secreted by MSC have modulated the expression profile of cytokines in macrophages, inducing the polarization of these cells to an anti-inflammatory phenotype (M2)<sup>[74,75]</sup>. However, González *et al.*<sup>[63]</sup> reported a partial dependence of the cell-cell contact mechanism by the induction of secretion of immunosuppressive factors. In their study, different co-culture systems of adipose tissue-derived MSC and macrophages were assessed and high levels of IL-10 were only observed in the co-culture system that promoted cell-cell contact. Furthermore, macrophages that phagocyte MSC acquire regulatory properties<sup>[35]</sup>. In this sense, bioactive factors and/or cell-cell interaction promote distinct types of regulatory macrophages that can change their function in response to the proinflammatory signals of the micro-environment<sup>[76]</sup>. MSC may also affect populations of monocytes, precursors of macrophages and dendritic cells, through the secretion of HGF that induces monocytes to an immunomodulatory phenotype (CD14<sup>+</sup>CD16<sup>-</sup>) with IL-10 production<sup>[27]</sup>.

However, some authors suggest that activation of T cells by MSC is independent of cell contact<sup>[77-79]</sup>. Several soluble factors have been associated with the immunomodulatory ability of MSC to affect the activation or proliferation of T cells, such as the secretion of HGF, TGF- $\beta$ , IDO, and PGE-2<sup>[21,23,68,71,73]</sup>. Saldanha-Araujo *et al.*<sup>[80]</sup> demonstrated an additional mechanism by which MSC suppress T cell proliferation. This study demonstrated that, during the interaction between MSC and T cells, there

is adenosine production by MSC, which reduce T cell proliferation by flagging the adenosine receptor on the membrane surface. Still, other authors suggest that cell-cell contact is essential for an intense immunosuppressive effect<sup>[78]</sup>. In fact, MSC express integrins, intercellular adhesion molecules, and vascular cell adhesion protein on their surface and can bind to T cells with high affinity<sup>[71,81]</sup>. Quaedackers *et al*<sup>[82]</sup> cultivated MSC with peripheral blood mononuclear cells and indicated that such interaction is a specific process, since the subpopulations of lymphocytes that interacted with MSC were distinct from cells that remained in suspension. The T cell fraction that adhered to MSC was regulatory T cells exhibiting an immunosuppressive phenotype. In inflammatory environment, the expression of the molecules PD-L1 and PD-L2 on the MSC surface enhance, restricting the function of T cells through PD-1 ligands<sup>[83]</sup>. The high levels of these inhibitory molecules on the MSC membrane confirm that one of the mechanisms of MSC immunosuppression is also by cell-cell contact-mediated responses.

MSC can also immunomodulate other cell types of the innate and the adaptive immune system, such as B lymphocytes, dendritic cells, and natural killer (NK) cells<sup>[72,84]</sup>. Luk *et al*<sup>[14]</sup> have demonstrated that MSC, under normal culture conditions, promote B cell survival and induce the formation of regulatory B cells, but negligible interference on B cell proliferation and immunoglobulin G production was observed. However, after pre-treatment with IFN- $\gamma$ , MSC appear to inhibit B cell proliferation and reduce immunoglobulin G production, even though these primed cells lose the ability to induce the formation of regulatory B cells. Moreover, the authors evaluated distinct mechanisms as key factors for MSC-mediated immunomodulation. First, they demonstrated that the effects of MSC on B cells do not depend only on soluble factors, since no production of regulatory B cells or IL-10 was induced when MSC were cultured in a Transwell system with separated chambers. Second, they assessed that the presence of heat-inactivated MSC (dead cells not capable of secreting factors but phenotypically intact) was not sufficient to induce IL-10 producing B cells. These data suggest that B cell modulation by MSC is mediated by an active metabolic process and requires B cell and MSC contact.

Another mechanism of immunosuppression exerted by MSC has been observed in the inhibition of the differentiation and maturation of dendritic cells derived from CD14<sup>+</sup> monocytes<sup>[85]</sup>. Co-culture with Transwell suggests that IL-6 and macrophage colony stimulating factor are partially involved in the inhibition of dendritic cell differentiation by MSC. MSC may also alter the cytokine secretion profile of dendritic cells<sup>[86]</sup>. Co-culture with MSC demonstrates decreased secretion of TNF- $\alpha$  by mature myeloid dendritic cells, while increasing IL-10 secretion by plasmacytoid dendritic cells<sup>[87]</sup>. Moreover, MSC are sensitive to lysis by activated NK cells but are resistant to naive NK cells<sup>[88]</sup>. Spaggiari *et al*<sup>[89]</sup> observed that MSC treated with IFN- $\gamma$  are resistant to lysis by NK cells. In addition, they found that some inhibitory effects of MSC on NK cells demand cell-cell contact, while others are regulated by soluble factors, including PGE-2 and TGF- $\beta$ 1. Therefore, these data together suggest that the mechanism of immunoregulation of MSC depends on the types of cell populations, the inflammatory conditions, and the presence or absence of cell-cell contact.

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## MSC THERAPY IN IBD

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Autologous and allogeneic MSC have been evaluated in clinical trials in two different modalities: Local injection of MSC to treat fistulizing CD and intravenous (IV) infusion of MSC to treat UC or luminal colitis<sup>[42,90-93]</sup>. Published work demonstrates that to date 117 IBD patients with refractory disease or intolerant to standard treatment have received one or more IV infusions of autologous or allogeneic MSC<sup>[94]</sup>. Currently, results of clinical trials are particularly encouraging in terms of safety and efficacy; however, due to different study designs regarding tested groups, short follow-up, and a lack of endoscopic data and unified primary outcomes, no final conclusions can be made. In fact, MSC demonstrated their ability to repair perianal fistulas in CD patients, refractory to conventional or biological therapy in several controlled trials<sup>[95,96]</sup>. Still, MSC need to demonstrate their clear efficacy on luminal CD and UC<sup>[97,98]</sup>.

In this sense, experimental studies in animal models have contributed to a better understanding of cellular, molecular, and immunological mechanisms of IBD associated with cell therapy. Recent studies have demonstrated a clinical and histopathological improvement of colitis after an infusion of MSC, such as decreased inflammation and increased survival<sup>[99,100]</sup>. In addition, much has been researched regarding the homing of exogenous MSC infused by different pathways in response to an inflammatory insult. A comparative study between the IV and intraperitoneal



(IP) routes in a trinitrobenzene sulfonic acid (TNBS)-induced colitis model concluded that, in systemic administration, MSC accumulated preferentially in the lungs, with no evidence of migration to the colon. On the other hand, MSC injected *via* IP were located in the inflamed colon<sup>[101]</sup>. Another study in an experimental model of sodium dextran sulfate (DSS)-induced colitis demonstrated that MSC migrate towards the lung, liver, and spleen, and even a small amount to the inflamed colon after 24 h of IV infusion. In contrast, IP and intracolonic routes showed more cell grafting in the colon and fewer cells trapped in the pulmonary alveoli<sup>[100]</sup>. However, a previous study conducted by our research group also evaluated the effect of MSC administered by different routes, IV and IP, in DSS-induced acute colitis. We demonstrated that infusion of MSC by IV route decreased intestinal inflammation, modulated serum cytokines, and induced apoptosis of T cells of the intestinal mucosa. Meanwhile, the same effect was not found in animals treated by IP route<sup>[102]</sup>.

In this way, there are controversial studies about the location and persistence of MSC in the body after cell transplantation. The efficiency of cellular delivery is dependent on the route of administration<sup>[101,102]</sup>. IV infusion, for example, has been used as a cellular delivery route for preclinical studies<sup>[9,10,102]</sup> and for recent clinical trials<sup>[103]</sup> due to its wide distribution and easy access. However, cell-tracking studies have shown that most MSC are localized in the lungs and have a short-term survival in the body after IV infusion<sup>[9-12]</sup>. The entrapment of MSC in the lungs is occasioned by their size<sup>[24]</sup>, which exceeds the width of the pulmonary micro-capillaries<sup>[25,26]</sup>. In patients, respiratory discomfort has been reported after transfusion of MSC<sup>[10]</sup>; and high and subsequent doses of cells are usually required to observe some effect in animal models<sup>[104]</sup>. Interestingly, in experiments of Lee *et al.*<sup>[105]</sup>, MSC retained in the lungs improved cardiac function after myocardial infarction by releasing the anti-inflammatory protein TSG-6<sup>[105]</sup>.

After 24 h of infusion, MSC tend to disappear from the lungs, and their cellular debris are distributed to other sites, particularly the liver, suggesting that these cells pass their effects to the resident immune cells<sup>[106]</sup>. Then, the resident cells possibly mediate the immunomodulatory effects induced by transplanted MSC<sup>[9]</sup>. Moreover, immune system cells are likely to play a role in the removal of MSC. Activated NK cells, for example, have been shown to be able to lyse autologous MSC *in vitro*<sup>[89]</sup>. Also, apoptosis of infused cells may trigger an immunomodulatory response. Lu *et al.*<sup>[35]</sup> demonstrated that macrophages adapt a new immunoregulatory function after the phagocytosis of dead MSC<sup>[35,107]</sup>. Based on this information, MSC probably interact with resident cells through distinct mechanisms, either by the secretion of paracrine factors or through a direct cell-cell interaction<sup>[13-15,108]</sup>. Intestinal organoids derived from stem cells also provide a system to mimic *ex vivo* interactions between the lamina propria and epithelium intestinal by cell contact-dependent/independent mechanisms<sup>[109]</sup>.

Thus, the application of MSC *in vivo* requires, in addition to the biological knowledge of the cells, a deep understanding of the mechanisms involved in IBD. For this, the immunological properties of the MSC type, the infusion route, and the inflammatory and immunological conditions of the disease should be considered. Therefore, MSC therapy may exert its therapeutic effects mainly by secreting soluble immunomodulating bioactive factors and/or by cell-cell contact and consequently by interaction with immune cells, establishing a favorable environment for regeneration.

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## THERAPY BASED ON THE IMMUNOMODULATORY PROPERTIES OF MSC

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Infused MSC have been demonstrated to promote the intestinal repair processes in both humans<sup>[42]</sup> and animal models<sup>[105,110]</sup>. Nevertheless, the engraftment and the homing mechanism of MSC are not well elucidated and depend on intricate interactions between signaling pathways. Short survival after infusion and poor biodistribution of MSC have proven to be significant technical challenges to overcome before this therapy can be used for clinical purposes. An alteration in the MSC treatment that avoids these issues, but maintains the immunomodulatory properties of MSC, would enhance this therapy. Also, though positive effects of MSC infusion can last longer than the half-life of the cells themselves, they reduce over time. It is thus plausible that successive MSC administrations are necessary as maintenance therapy<sup>[94]</sup>.

### **Bioactive factors of MSC**

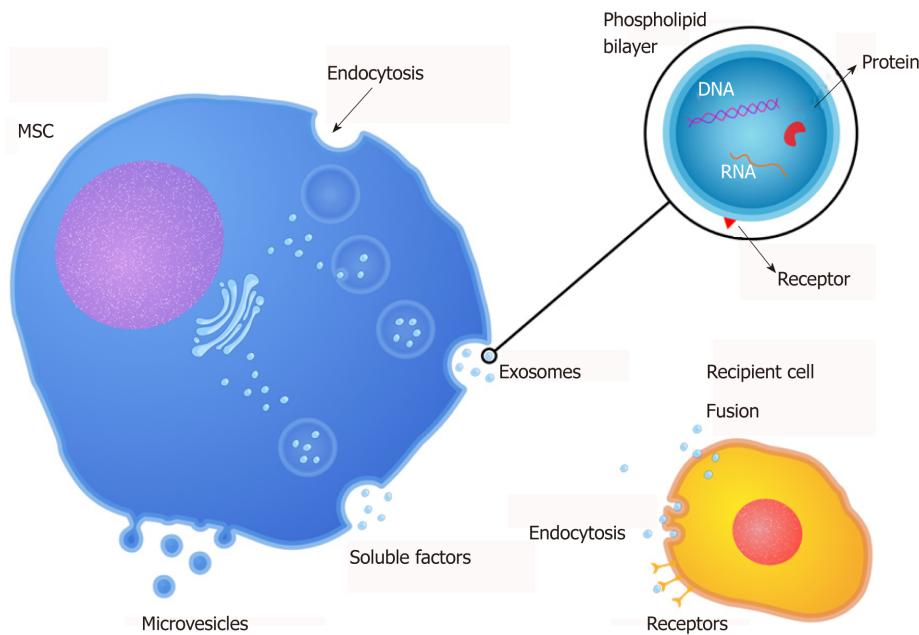
Recent studies have reported that the regenerative potential of MSC therapy has been, at least in part, mediated by paracrine actions<sup>[15,111,112]</sup>. Thus, studies about MSC-

secreted factors have demonstrated that these factors can induce tissue repair in conditions involving tissue/organ damage<sup>[111]</sup>. Furthermore, they are referred to in the literature as “secretome” (soluble factors), and extracellular vesicles and can be found in the MSC culture supernatant; thus, the supernatant of MSC is a denominated conditioned medium (CM). CM is commonly prepared by confluent MSC cultures incubated in serum-free media for 24h without any concentration, selection, or purification of cell products. Therefore, the components of CM are in fact both free soluble factors (cytokines, chemokines, and growth factors) and EVs, which may mediate the therapeutic potential of MSC<sup>[16,113]</sup> (Figure 1).

Few studies have used the MSC-CM as a therapeutic strategy for IBD (Table 1). The paracrine effect of MSC-CM has been observed in experimental models of colitis induced chemically by TNBS and DSS<sup>[15,114,115]</sup>. Heidari *et al.*<sup>[116]</sup> and Pouya *et al.*<sup>[117]</sup> have shown the effects of MSC-CM in DSS-induced colitis by increasing anti-inflammatory responses associated with an increase of regulatory T cells percentage and IL-10 production. Watanabe *et al.*<sup>[15]</sup> demonstrated that MSC-CM was effective for the inductive stage of TNBS-induced colitis and for the recovery stage of DSS-induced colitis independent of the systemic delivery route. Similarly, Robinson *et al.*<sup>[115]</sup> (2014) and (2015)<sup>[118]</sup> showed that MSC and CM treatments prevented damage to the enteric nervous system and alleviated gut dysfunction caused by TNBS-induced colitis. In our previous study, we investigated the paracrine role of MSC in DSS-induced colitis of colon organ culture. Our results have shown that colonic inflammation is alleviated by MSC-CM, and this effect is independent of cell contact<sup>[119]</sup>. Also, CM has been evaluated in several other conditions and diseases, such as myocardial infarction<sup>[120]</sup>, bone defect<sup>[121]</sup>, hepatic insufficiency<sup>[122]</sup>, and spinal cord injury<sup>[123]</sup>. Liu *et al.*<sup>[124]</sup> suggest that MSC-CM administration has the potential to suppress proliferation of artery smooth muscle cells in an experimental model of pulmonary hypertension. Another study reported that the application of MSC-CM in diabetic rats prevented renal disease, primarily by attenuating the expression of TGF- $\beta$ 1<sup>[125]</sup>. Therefore, it may be observed that MSC-CM contains several factors that intervene in different pathophysiological manifestations, such as inflammation, proliferation, angiogenesis, and tissue remodeling<sup>[15]</sup>. Taken together, these results indicate that MSC-secreted factors are able to preserve the intestinal barrier in IBD independent of cell transplantation.

MSC also have been displayed to release EVs, which can be implicated in cell-cell interaction by carrying biologically active lipids, proteins, and nucleic acids in and on their membrane (Table 1)<sup>[26,28]</sup>. EVs are cell-derived membranous structures released by cells. They can be originated from multivesicular bodies (exosomes) or directly from the cell membrane (microvesicles - MVs). Both exosomes and MVs are comprised of two regions: The membrane and the natural internal cargo. The outer membrane, composed of lipid layer and proteins, packages bioactive molecules and protects the internal cargo, consisting of lipids, proteins, DNA, mRNA, micro-RNA, and other components from the parental cell. The cargo carried by EVs dictated their function<sup>[126,127]</sup>. The MSC treatment may be mediated by free soluble factors and components contained in EVs, which composition is cell-origin specific<sup>[24,25,114]</sup>. Kim *et al.*<sup>[128]</sup> profiled MSC-derived MVs proteome and identified 730 proteins engaged in processes associated with self-renewal and/or differentiation of MSC. Also, they pointed out that the micro-RNAs (miRNAs) profile of MVs presents a pattern shared with their cells of origin. Nevertheless, selected miRNAs were evident only in the released MVs but absent in the MSC<sup>[128]</sup>. Accordingly, another study has extracted RNA from MSC and their MVs for 365 known mature miRNAs, and they observed that 41 miRNAs were co-expressed in MVs and cells, others were cumulated within MVs and absent in the cells after MVs secretion, and still others were maintained within the cells and not liberated in MVs<sup>[129]</sup>.

Thus, several studies have been focused on MSC-derived EVs as a treatment for IBD (Table 1). Wong *et al.*<sup>[130]</sup> identified in circulating exosomes of DSS-induced colitis mouse 56 differentially expressed proteins that are involved in macrophage activation. Wu *et al.*<sup>[131]</sup> demonstrated the role of miR146-a in attenuating experimental colitis since EVs derived from MSC overexpressing miR146-a significantly inhibited TNF receptor-associated factor 6 and IL-1 receptor associated kinase 1. Yang *et al.*<sup>[132]</sup> demonstrated that EVs protect against TNBS-induced colitis by attenuating oxidative stress and apoptosis. Mao *et al.*<sup>[114]</sup> demonstrated that exosomes released from human umbilical cord-derived MSC homed to colon tissue of IBD mice and relieved the severity of the DSS-induced colitis by altering the expression of inflammatory genes and decreasing the infiltration of macrophages. Interestingly, ubiquitination may play an important role in the anti-inflammatory effect observed in IBD animals treated with MSC-derived exosomes. Ubiquitin is upregulated in IBD mice and promotes activation of the nuclear factor kappa B pathway by increasing the ubiquitination and degradation of inhibitor of kappa B alpha and regulating inflammation through



**Figure 1 Release of bioactive factors by MSC.** MSC can secrete bioactive factors including free soluble factors (cytokines, chemokines, and growth factors) and extracellular vesicles (microvesicles and exosomes) that mediate the therapeutic potential of MSC. MSC: Mesenchymal stromal cells.

mTOR signaling. However, the expression of ubiquitin was inhibited in the colonic mucosa and spleen after the MSC-derived exosomes treatment<sup>[133]</sup>.

In this way, the secreted bioactive factors could play an essential role in repairing damaged colon from experimental colitis to regenerative medicine. In relation to cellular therapy, bioactive factors are easier to prepare and store. Then, it is a therapy devoid of cells, and possible risks of rejection between donor and recipient can be minimized. Lastly, pulmonary capillaries are not a barrier for this therapy in IV transplantation, and CM can reach sites beyond the lung<sup>[111]</sup>.

### **MSC membrane**

There is inconclusive evidence that bioactive anti-inflammatory factors alone are responsible for the immunomodulatory effects of transplanted MSC. The short-term survival of MSC in the body after infusion raises the questions of whether MSC have sufficient time to be activated by inflammatory conditions and then secreted factors<sup>[9]</sup>. Hoogduijn *et al*<sup>[106]</sup> found that MSC infusion initiates a mild and immediate systemic inflammatory response, which may be the activator of posterior immunosuppression. In this study, the inflammatory response was found in the lung and characterized by an increased expression of pro-inflammatory monocyte and cytokines. Also, MSC infusion provides inflammatory conditions for their activation and that at least part of the immunomodulatory response mediated by MSC is independent of activation by anti-inflammatory soluble factors. Instead, passive interactions with host cells probably mediate these effects<sup>[14]</sup>. de Witte *et al*<sup>[134]</sup> demonstrated that infused MSC are internalized by monocytes and induce phenotypical and functional changes in these cells, which subsequently migrate from the lungs to other body sites and modulate immune cells response. Other studies also indicated that MSC induced an immunosuppressive phenotype on macrophages after phagocytosis and that the macrophage depletion reduced the therapeutic effect of MSC<sup>[35,135]</sup>.

Based on this analysis, some studies have shown that MSC exert their effects through intermediary cells by contact with the cell membrane<sup>[14,134,136,137]</sup>. MSC express immunomodulatory molecules on their membrane, such as CD90 (Thy-1 membrane glycoprotein) that is involved in MSC differentiation pathways, ATPases, and CD73, which dephosphorylate ATP into AMP and AMP into adenosine, respectively<sup>[136]</sup>. Interestingly, a recent study has determined that heat-inactivated MSC preserve their immunomodulatory capacity after IV infusion in a lipopolysaccharide-induced model, suggesting that cell-membrane-dependent interactions with immune cells are triggering factors of the immunological regulatory effects<sup>[14]</sup>. Song *et al*<sup>[107]</sup> systemically administered MSC extract obtained by cell lysis in experimental colitis, and their results demonstrated that the MSC extract polarized the macrophage functional phenotyping from M1 to M2. This new therapeutic approach could overcome the low homing efficiency of MSC in patients with IBD.

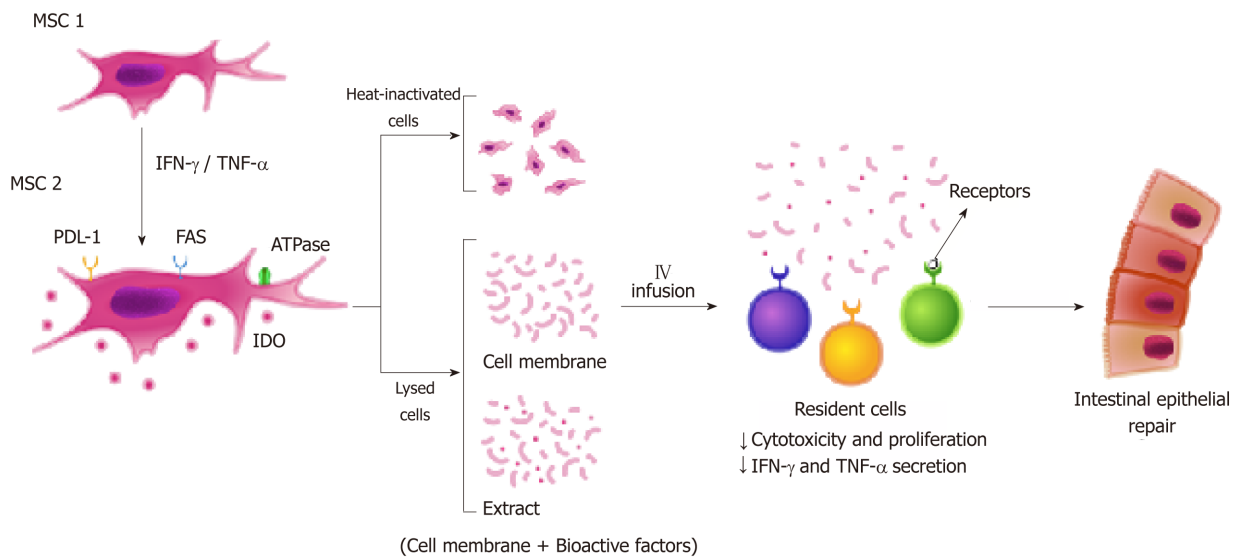
**Table 1 Studies using bioactive factors derived from mesenchymal stromal cells as a therapeutic strategy for inflammatory bowel diseases**

Bioactive factors	MSC origin	IBD model	Pathway	Results	Ref.
CM	Rat bone-marrow	DSS and TNBS-induced colitis in rats	IP, IV, and enema	Effective for the inductive phase of TNBS-induced colitis and for recovery phase of DSS-induced colitis.	Watanabe <i>et al</i> <sup>[115]</sup> , 2014
CM	Human bone-marrow	TNBS-induced colitis in pigs	Enema	Prevent loss of myenteric neurons and damage of nerve process.	Robinson <i>et al</i> <sup>[115]</sup> , 2014
EVs	Rat bone-marrow	TNBS-induced colitis in rats	IV	Inhibit NF- $\kappa$ Bp65 pathways, modulate anti-oxidant/oxidant balance, and apoptosis.	Yang <i>et al</i> <sup>[132]</sup> , 2015
Exosomes	Human umbilical cord	DSS-induced colitis in mice	IV	Increase IL-10 and decrease TNF- $\alpha$ , IL-1 $\beta$ , IL-6, iNOS, and IL-17.	Mao <i>et al</i> <sup>[114]</sup> , 2017
Extract	Human umbilical cord	DSS-induced colitis in mice	IP	Inhibit inflammatory cytokines and alter macrophage functional phenotype from M1 to M2	Song <i>et al</i> <sup>[107]</sup> , 2017
CM	Mouse adipose tissue	DSS-induced colitis in mice	IP	Increase Treg, IL-10, and TGF- $\beta$ , and decreased IL-17.	Heidari <i>et al</i> <sup>[116]</sup> , 2018
CM	Mouse adipose tissue	DSS-induced colitis in mice	IP	Increase Treg, IL-10, and TGF- $\beta$ , and decreased IL-17.	Pouya <i>et al</i> <sup>[117]</sup> , 2018
CM	Human umbilical cord	DSS-induced colitis in mice	Culture medium (organ culture)	Decrease IL-6 and increase Ki-67.	DA Costa Gonçalves <i>et al</i> <sup>[119]</sup> , 2018
Exosomes	Human umbilical cord	DSS-induced colitis in mice	IV	Downregulated ubiquitin inhibiting NF- $\kappa$ B and mTOR activation.	Wu <i>et al</i> <sup>[133]</sup> , 2018
EVs	Mouse bone-marrow overexpressing miR-146a	TNBS-induced colitis in rats	IV	Suppress the activation of NF- $\kappa$ B pathway, decrease TNF- $\alpha$ , IL-6, and IL-1 $\beta$ .	Wu <i>et al</i> <sup>[131]</sup> , 2019

MSC: Mesenchymal stromal cells; IBD: Inflammatory bowel diseases; DSS: Sodium dextran sulfate; CM: Conditioned medium; EVs: Extracellular vehicles; TNBS: Trinitrobenzene sulfonic acid; IP: Intraperitoneal; IV: Intravenous; TGF: transforming growth factor; Treg: Regulator T cell; NF- $\kappa$ B: Nuclear factor kappa B; IL, Interleukin; TNF- $\alpha$ : Tumor necrosis factor-alpha.

It is known that MSC-mediated immunosuppression is induced by inflammatory cytokines. Treatment with IFN- $\gamma$ , TNF- $\alpha$ , and IL-1 $\beta$  causes MSC to express immunomodulatory molecules that mediate the suppression *via* cell-contact dependent mechanisms, including TLRs, PD-L1/PD-1 pathway, and FAS-L/FAS interaction<sup>[73,138-140]</sup> (Figure 2). Duijvestein *et al*<sup>[141]</sup> showed that MSC stimulated with IFN- $\gamma$  enhance their immunosuppressive capacities, resulting in diminished mucosal damage in experimental colitis. Kang *et al*<sup>[142]</sup> found that IFN- $\gamma$  primed MSC secrete tryptophanyl-tRNA synthetase and alleviate the experimental colitis by inducing apoptosis of immune cells. In our previous study, we have shown that MSC stimulated with IFN- $\gamma$  decreased lymphocyte population in colonic organ culture of DSS-treated mice, but no effect of CM treatment was observed. That could be explained by the fact that T cell immunosuppression has a partial dependence on the cell-cell contact mechanism<sup>[119]</sup>. Furthermore, Fan *et al*<sup>[143]</sup> showed that IL-1 $\beta$  primed MSC have enhanced immunosuppressive capacities and migration ability, and Cheng *et al*<sup>[144]</sup> demonstrated that IL-25 primed MSC inhibited Th17 immune response and induced regulatory T cell phenotyping in DSS-induced colitis<sup>[143,144]</sup>.

In another previous study conducted by our research group, we developed a cell-free therapy based on small particles from the membranes of MSC stimulated and unstimulated with IFN- $\gamma$ . These particles contain the membrane-bound proteins of MSC, several of which have an immunomodulatory function and may also overcome the low homing efficiency of MSC. We have demonstrated that membrane particles keep immune regulatory properties of MSC and are potentially capable of passing the



**Figure 2 Enhanced immunosuppressive properties of MSC in cell contact-dependent mechanism.** Treatment with IFN- $\gamma$  and TNF- $\alpha$  induce MSC1 to express immunomodulatory molecules (MSC2) that mediate the suppression via cell contact-dependent mechanisms including PD-L1/PD-1 pathway and FAS-L/FAS interaction. To improve MSC homing, new therapeutic approaches are being developed: Heat-inactivated cells and lysed cells (extract or cell membrane). MSC-based therapy may exert its therapeutic effects mainly by cell-cell contact and consequently by interaction with immune cells, establishing a favorable environment for the regeneration of intestinal tissue. MSC: Mesenchymal stromal cells; IFN: Interferon; TNF: Tumor necrosis factor; PD-L1: Programmed death ligand 1; IDO: Indoleamine 2,3 dioxigenase.

lung barrier and exerting their effects at sites beyond the lungs<sup>[136]</sup>. Most importantly, we also found that the immunomodulation induced by membrane particles stimulated and unstimulated with IFN- $\gamma$  is different. According to this information, the surface phenotype of MSC (protein molecules present on their membrane) is determinants for the therapeutic effect of MSC in patients with IBD.

## CONCLUSION

Taken together, these findings highlight that bioactive factors, cell surface proteins, and metabolic pathways derived from MSC offer unique opportunities for the development of promising cell-free therapies for IBD that associate the potential of MSC with the reduction of the practical complexities arising from the use of living cells. Recent experimental studies have suggested that not only the secretion of bioactive factors but also the surface proteins of MSC have great therapeutic potential that can overcome the deficiencies of current therapy for IBD and could open new frontiers in gastrointestinal medicine.

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