

Mesenchymal stem cells (MSCs) are attractive seed cells for immunotherapy, tissue engineering and regenerative medicine due to their self-renewal and multidirectional differentiation abilities, diverse immunoregulatory functions and ease of isolation from a wide range of tissues. MSCs exert their immunoregulatory effect on immune cells via cell-to-cell contact and paracrine mechanisms. In turn, MSCs can also be modulated by immune cells. Macrophages are constantly present in the mucosa of the intestinal tract of mammals and play an important role in the development and progression of inflammatory bowel disease (IBD), a chronic and recurrent inflammatory disease of the gastrointestinal tract characterized by idiopathic mucosal inflammation. The increased morbidity and mortality of IBD have made it a disease hard to cure in the clinic. MSCs have emerged as an important tool for IBD therapy due to their abilities to differentiate into enterocyte-like cells and regulate inflammatory cells, especially macrophages. In this review, we discuss the recent advances in the interaction between MSCs and macrophages in diseases, with an emphasis on IBD. We propose that an optimized MSC-based therapy would provide a novel strategy for the treatment of IBD and the prevention of IBD-associated colorectal cancer (CRC).

Key words: mesenchymal stem cell, inflammatory bowel disease, macrophage, immunoregulatory, colorectal cancer.

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Crosstalk between mesenchymal stem cells and macrophages in inflammatory bowel disease and associated colorectal cancer

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Introduction

In the past decades, stem cell therapies have been emerging as a potential tool to treat diseases. According to the literature, Tavassoli *et al.* first reported that autologous fragments of rodent bone marrow were able to generate heterotopic marrow and bone upon transplantation in 1968 [1]. The group of Friedenstein successfully identified and cultured a subpopulation of stromal cells from bone marrow, which had a high replicative potential and could form colonies of fibroblastic cells *in vitro*, displaying the ability of colony forming unit-fibroblast (CFU-F), which could form ectopic bone marrow comprising trabecular bone, chondrocytes, adipocytes, and hematopoiesis-supporting stroma [2, 3]. These stromal cells were termed osteogenic stem cells or bone marrow stromal stem cells [4, 5]. In 1991, Caplan *et al.* named the CFU-F identified by Friedenstein *et al.* as MSCs based on the fact that they could behave as unique progenitors for all connective tissues of mesodermal origin [6]. In 2006, the International Society for Cellular Therapy (ISCT) established the unified and minimal criteria to define MSCs [7]. To date, great efforts have been made to study the nature, phenotype, function, and regulation of MSC in health and diseases.

Mesenchymal stem cells are a heterogeneous population of fibroblast-like, plastic-adherent cells with the potential to self-renew and differentiate into distinct types of cell lineages such as osteoblasts, chondrocytes, adipocytes, tenocytes, myotubes, neural cells, and hematopoietic-supporting stroma, either *in vitro* or *in vivo* [8–10]. Mesenchymal stem cells can be isolated from various tissues such as bone marrow, umbilical cord, and adipose [11]. In the early 2000s, it was reported that MSCs display an immunomodulatory effect on lymphocytes [12, 13]. Mesenchymal stem cells have also been shown to regulate the proliferation, differentiation and immune function of myeloid cells ranging from monocytes [14], dendritic cells (DCs) [15], macrophages [16, 17], and myeloid-derived suppressor cells (MDSCs) [18], to granulocytes [19]. In recent years, MSCs have been tested in a variety of diseases such as myocardial infarction [20, 21], acute renal failure [22], acute liver injury [23], collagen-induced arthritis (CIA) [24], graft-versus-host disease (GVHD) [25], and IBD [26].

Inflammatory bowel disease, including Crohn's disease (CD) and ulcerative colitis (UC), is a chronic, recurrent inflammatory disease of the gastrointestinal tract and is characterized by idiopathic mucosal inflammation. The incidence and prevalence of IBD are generally higher in the western countries than in Asia, but are rapidly increasing in Asia [27]. Furthermore, IBD is associated with increased mortality risk as IBD is known to be linked

to the development of colorectal cancer (colitis-associated colorectal cancer, CAC) [28]. However, there is still no effective method to cure IBD. Recent studies suggest that MSCs are an important therapeutic tool in IBD. MSCs can migrate into intestinal injured tissue and differentiate into enterocyte-like cells [29, 30]. In addition, MSCs can release growth factors and cytokines to inhibit intestinal inflammation, regulate immune responses and promote enterocyte proliferation to repair the injured tissue [31]. In this review, we discuss the emerging role of MSCs in the treatment of IBD and IBD-associated colorectal cancer.

The immunoregulatory function of mesenchymal stem cells

In 1986, Juneja *et al.* reported that MSCs interacted with the transformed cells UTMB-460 (a monoclonal human B-lymphoblastic cell line) *in vitro* and played a critical role in the establishment of the UTMB-460 cell line, which is the first study about the effect of MSCs on immune cells [32]. Since then, the immunoregulatory functions of MSC have been gradually revealed by the researchers. MSCs are found to inhibit the proliferation of T cells, B cells, and natural killer (NK) cells [33–35]; alter the cytokine secretion profile of dendritic cells (DCs), naive and effector T cells (T helper 1 [T(H)1] and T(H)2), and NK cells [35–37]; suppress the migration, maturation and antigen presentation of DCs [38]; restrain the induction of cytotoxic response of T cells and NK cells to alloantigens [35, 39]; and modulate the M1/M2 balance of macrophages [40]. The mechanisms involved in the immunomodulatory roles of MSC include cell-to-cell contact, secretion of regulatory cytokines and other factors, the expression of inhibitory membrane molecules, and induction of cell anergy and apoptosis [41, 42].

Mesenchymal stem cell-mediated immunoregulation on macrophages via cell-to-cell contact

Cells are known to communicate via secreted molecules and by cell surface molecules, which are deciphered by the target cell upon receptor binding, or by direct cell-to-cell contact, mediated by specialized molecules [43]. Mesenchymal stem cells have an immunoregulatory effect on macrophages through direct cell-to-cell contact. Siniscalco *et al.* demonstrated that MSCs homing to the spinal cord induced the switch of macrophages to an M2 phenotype with anti-inflammatory functions. The intravenously injected MSCs could reduce the protein and mRNA levels of IL-1 β and IL-17 and up-regulated the expression of IL-10 protein, which suppresses the proliferation and activation of T cells in the spinal cord of SNI mice [44]. The mechanism for the modulation of macrophages by MSCs to shift from pro-inflammatory to anti-inflammatory phenotype still remains unknown. The administration of MSCs exerts long-term therapeutic efficacy, suggesting that the immunomodulatory properties of MSCs contribute to tissue repair and regeneration. Gur-Wahnon *et al.* reported that MSCs suppress antigen-presenting cell (APC) maturation by a novel mechanism involving cell-cell interaction rather than the classical mechanism of induction by cytokines [45, 46].

Indeed, although MSCs could home to the site of damaged tissue, they have poor survival ability and transitory persistence in the inflammatory area. MSCs are multipotent stem cells that can modulate immune cells such as regulatory T cells to improve immune dysfunction, so these cells are mainly used for the treatment of immune disorders, such as IBD. Intraperitoneal injections of MSCs can markedly reduce intestinal inflammation [47]. In IBD, the mechanism for the regulation of macrophages by MSCs is complicated and various, and mainly involves cell-to-cell contact and paracrine effects. MSCs have the capacity for migration to colon tissues and inhibition of colitis and the potential for suppression of the development of CAC.

Mesenchymal stem cell-mediated immunoregulation of macrophages via paracrine actions

Mesenchymal stem cells transplantation maintains the survival of monocytes, alters the macrophage phenotype from M1 to M2 in the damaged tissue or organ, such as spleen and bone marrow, and exerts therapeutic effects on inflammatory disease remission via the paracrine effect. Mesenchymal stem cells have poor survival ability and transitory persistence in the inflammatory area. Mesenchymal stem cell transplantation into the injured tissues might be involved in paracrine action by secretion of soluble factors [48]. Paracrine is a kind of cellular communication in which a cell produces a molecule to induce changes in the adjacent cells, altering the behavior or differentiation of those cells. Jin *et al.* found that deregulation of inflammatory soluble factors such as IL-1 α , IL-6, and IL-8 via angiopoietin-1 (Ang-1) could be treated as a potential soluble factor in the co-culture of MSCs with LPS-treated alveolar macrophages. These results indicated that MSCs exerted paracrine actions by increasing the proportion of anti-inflammatory macrophages (M2) and stimulating the production of anti-inflammatory factors in the damaged tissue [49]. The mechanism by which MSCs promote regulatory T cell production is explored as the primary reason for MSC cellular therapy. Induction of MSCs to regulatory T cell generation through TGF- β 1 secreted by MSCs is dependent on the paracrine production of CCL-18 between MSCs and monocytes or macrophages [50].

Mesenchymal stem cell administration induces B220+CD11b+ monocytes/macrophages and attenuates corneal allograft and experimental autoimmune uveitis (EAU) [51]. Principle mechanisms of tissue repair of MSCs are based primarily on their paracrine effect through expressing soluble factors. Actually, different kinds of MSC paracrine actions are applied to alleviate inflammation such as trophic, immunomodulatory, anti-scarring, and chemoattractant. Recently, Ti *et al.* reported that the therapeutic efficiency of LPS-preprocessing MSC-induced exosomes was valuable to wound healing and chronic inflammation, which indicated that MSCs might secrete an amount of exosomes to enhance the trophic effect through a paracrine action [52]. Almeida *et al.* also showed that MSCs expressed a high level of trophic factors to improve the function of the injured spinal cord [53]. Trans-

plantation of membrane-derived MSCs remarkably deregulated glomerular monocytes/macrophages infiltration and expression of glomerular inflammatory factors such as TNF- α , monocyte chemoattractant protein 1 (MCP-1), type I collagen, and TGF- β , contributing to the acute renal injury healing [54].

Mesenchymal stem cells co-cultured with macrophages secrete more immunomodulatory factors and express fewer pro-inflammatory factors such as prostaglandin E2 (PGE2) and indoleamine 2,3-dioxygenase (IDO), which can be further enhanced by interferon γ (IFN- γ) or tumor necrosis factor α (TNF- α) [55]. The immunomodulatory function of MSCs can also be mediated through several signaling pathways. Activation of Toll-like receptors (TLRs), CSF-2 and CSF-3 could modulate the TLR-2/6-induced MT1-MMP/JAK/STAT3 signaling pathway targeted with neovascularization, resulting in an immunomodulatory effect of MSCs [56]. Mesenchymal stem cells can exert an immunomodulatory effect on macrophages via cell-to-cell contact and paracrine actions, and macrophages also modulate MSCs to a certain extent.

Macrophage-mesenchymal stem cell relations

Cell-to-cell contact and paracrine actions by MSCs are recognized as the primary mechanisms in immunomodulation so plenty of evidence has been obtained in order to review the effects of MSC-mediated immunomodulation on monocytes/macrophages. However, the mutual relation between MSCs and monocytes/macrophages has gradually gained recognition in recent research studies. Monocytes/macrophages also can regulate MSCs to repair damaged tissue and exert their anti-inflammatory function. Gong *et al.* reported that M2 macrophages co-cultured with MSCs could promote the expression of ALP, osteogenic markers, and bone mineralization to sustain bone and expedite bone repair [57]. Macrophages, but not M1 macrophages, can promote MSC osteoblast differen-

tiation [58]. Sesia *et al.* also reported that in the collagen scaffolds, MSCs co-cultured with macrophages (M2 polarization), which stem from monocytes, existed a stronger clonogenic and chondrogenic competence contributing to cartilage formation [59]. Such similar interaction also occurs in cardiac disease. Macrophage depletion destroyed the infarct healing and repair in the early therapy, but M2 macrophages (F4/80(+) CD206(+)) incubated with or without MSCs had a positive effect on infarct size and left ventricular remodeling [60]. LPS-treated macrophages co-cultured with MSCs expressed less TNF- α and IL-1 and more IL-10 in the atherosclerotic plaque [61].

Although the above evidence supports the hypothesis that macrophages have the capacity to regulate MSC immunomodulation, the specific mechanism of macrophages acting on MSCs is still vague. However, the following example may provide some insight. In a mouse asthma model, M2 macrophages devoured MSCs while M1 macrophages did not exhibit the phenomenon, indicating that lung macrophages devoured MSCs to remit the allergic asthma [62]. MSC-derived cell-to-cell contact and paracrine actions are of vital importance to suppress inflammation and protect and repair damaged tissues, but the role of macrophages in MSC action should not be underestimated in research work of the correlativity between MSCs and macrophages.

Mesenchymal stem cells regulate macrophages to treat inflammatory bowel disease

Mesenchymal stem cells-mediated immunoregulation of macrophages via paracrine actions has been demonstrated in various inflammatory diseases, such as bone repair, wound healing, myocardial infarction, acute kidney injury, atherosclerosis, and IBD. We searched the PubMed database using the terms “MSC and macrophage”. There are a total of 530 documents published since 1976 and they have increased rapidly in recent years (Fig. 1). Activated

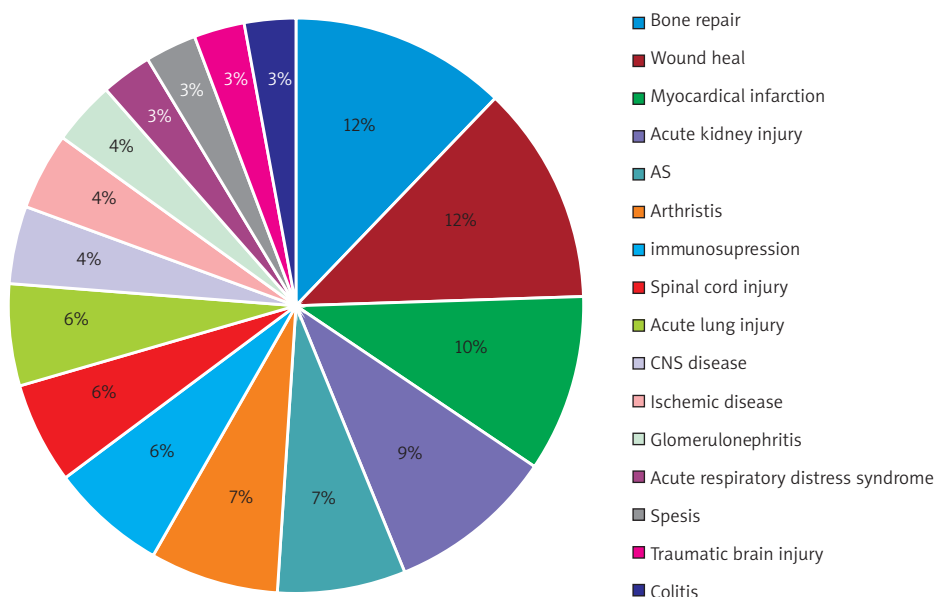


Fig. 1. Distribution of MSC regulation on macrophages in different diseases

MSCs stimulate alternatively macrophage activity to boost wound tensile strength in senior mice [63]. In the infarction location, pro-inflammatory macrophages were gradually transformed to anti-inflammatory macrophages via the increased expression of IL-10 mediated by MSCs to ameliorate acute myocardial infarction [64]. Fernandes *et al.* reported that osteoclasts and macrophages can promote the process of bone formation whereby MSCs stimulate macrophages (M2) dependent on gp130 or oncostatin M [58].

Inflammatory bowel disease is a type of idiopathic intestinal tract disease involving the ileum, rectum and colon, while various anti-inflammatory and immunosuppressive therapy, such as corticosteroids, immunosuppressive agents and biological agents, do not have a long-term clinical curative effect on IBD, especially refractory IBD [65]. Cell therapy research on MSCs associated with IBD has emerged continuously in recent years because of MSC immunosuppressive capability [66]. Although MSCs can home to the damaged intestinal mucosa, the short duration in the resting place requires repeated treatment during each phase of clinical treatment [67]. More functions of MSCs for the treatment of IBD are obtained through paracrine soluble molecules and regulating T cell number and function [68-70]. MSCs can also boost the production of Treg cells in the intestinal inflammatory region, thereby reducing the antigenic effect of the antigen and debasing the inflammatory factor and enhancing immune cell apoptosis [71].

The salutary effect of MSC on IBD is also dependent on the dose and the mode of MSC infusion. In *in vivo* experiments, the dose of MSC administration is usually 10^5 – 10^6 MSCs/mouse [72] and in pre-clinical trials, the amount of administration is usually about 10^6 – 10^7 /KG, and the therapeutic effect may increase with the dose to some extent, but the side effects caused by different doses are still not fully described [73]. For perianal fistulizing CD, in both *in vivo* and pre-clinical trials, the curative effect of perianal injection and intraperitoneal injection of MSC is better than intravenous MSC, as judged through the colon length, weight loss control and clinical pathology score. In contrast, for luminal IBD, the efficacy of intravenous injection is also weaker than local MSC injection. Ko *et al.* demonstrated that MSCs coated with antibodies and delivered to the colon, which modified the survival rates, therapeutic scores and body weight in the IBD mice [74]. Also researchers have detected that MSCs not only have the efficiency to upgrade the length of the colon and size of the spleen but also depress the risk of colorectal cancer via reducing the production of TNF- α , IL-1 β and IL-6 and stimulation of the STAT3 signaling pathway [75]. The therapeutic effects of MSCs with intraperitoneal injection and IBD drugs are mutually compatible [76]. The gene expression level in IBD mice treated with MSCs is also discrepant compared to IBD rats and the normal group. Xing *et al.* established IBD rat models to verify such a hypothesis. The results demonstrated that in the MSC-treated group, the expression of the genes *Olfm4* and *Wnt3a* was deregulated while GSK-3 β was upregulated, which contrasts with the IBD group [77]. Wang *et al.* also discovered that MSC administration decreased the expression of IL-31b [78]. Although such

benefits derived from MSC treatment are able to relieve the pain of patients with IBD, there are numerous difficulties involved in the application of MSCs. For example, the IBD animal model cannot completely replace and reflect the actual condition of IBD patients. Different sources of MSCs can also differentially influence the MSC action [79].

Macrophages play a crucial role in the pathogenesis of IBD stimulated by intestinal microorganism [80, 81]. CD68+ macrophages accumulated in the lamina of the intestinal inflammatory lesions reduce the expression of tight junction proteins, and damage epithelial cell barrier function and integrity, thereby accelerating disease progression via stimulating iNOS and TNF- α expression [82]. MSCs influence the balance between M1 and M2 macrophages to exert a therapeutic effect. Wang *et al.* reported that in the acute colitis mouse model, the clinical pathological score was significantly decreased in the MSC group compared with the control group. M2 macrophage polarization was enhanced significantly in DSS-colitis with MSC administration and the TGF- β signaling pathway was stimulated mainly by anti-inflammatory macrophages, while the therapeutic effect of MSCs on IBD would fade away if the TGF- β signaling pathway was inhibited [83]. In the peritoneal cavity of mice with acute colitis, the amount of CD206+ M2 macrophages was significantly increased by MSCs with IL-1 pretreatment, which inhibited the number of CD11c+ M1 macrophages, thus alleviating inflammatory responses in the intestinal mucosa [84]. Semitic *et al.* also demonstrated that MSCs mediated the alternative activation of macrophages through the inhibition of galectin-3 [85]. We have demonstrated that hucMSCs could repair DSS-induced IBD through the regulation of 15-LOX-1 expression and the modulation of inflammatory responses in macrophages [86]. The mechanism of MSC regulation of macrophages to treat IBD remains vague, and more intensive and pervasive investigations are needed to better understand it.

Mesenchymal stem cells regulate macrophages to treat inflammatory bowel disease-associated colorectal cancer

Ulcerative colitis (UC) and Crohn's disease (CD) are associated with an increased rate of colorectal cancer (CRC) [87, 88]. The estimated risk of CRC varies among studies, although it is accepted that the risk for malignancy increases with duration of diagnosis [89, 90]. CRC is the third most commonly diagnosed cancer worldwide, which develops slowly and begins with adenoma and progresses over several years to carcinoma [91, 92]. The present studies indicate that MSCs have an effect on the treatment of CRC. The stromal cell niche in the intestine is comprised of numerous, heterogeneous subsets of stromal cells, which include CD45-EpCAM-cells, fibroblasts, myofibroblast, and MSCs [93]. Chen *et al.* reported that MSCs not only could increase the length of the colon and the size of the spleen but also could reduce the risk of colorectal cancer via reducing the production of TNF- α , IL-1 β and IL-6 and inhibiting activation of the STAT3 signaling pathway [75].

Evidence shows that macrophages in the tumor microenvironment display M2 phenotype, which dampens the anti-tumor immune responses [94–96]. MSCs can exert their tumor protecting effects by interacting with macrophages in the tumor microenvironment [94, 95]. Mesenchymal stem cells can polarize macrophages towards the “anti-inflammatory” M2 phenotype, characterized by increased IL-10 production and decreased iNOS and IL-12 expression [94, 95, 97, 98]. However, Sala *et al.* reported that MSCs transplanted into mice with CRC by intraperitoneal injection did not completely home to the damaged inflammatory intestinal mucosa lesion, but rather accumulated in the abdominal cavity and were accompanied by T cells and macrophages. Macrophages treated with MSCs show M2 phenotype with increased production of IL-10 and iNOS and decreased expression of IFN- γ , IL-6 and TNF[47].

Conclusions

In this review, we elaborate the immunoregulatory effect of MSCs on macrophages via cell-to-cell contact and paracrine actions, which inhibits the secretion of pro-inflammatory factors in macrophages to alleviate the severity of IBD. Macrophages also have the capacity to regulate MSCs, which still needs more in-depth analyses to determine the specific mechanism. It seems that MSCs from different sources may have distinct therapeutic efficacy according to the disease. It is necessary to choose the proper approach for MSC transplantation for different types of IBD. The dose of injected MSC also needs to be optimized, which is critical to the repair of damaged intestinal mucosa. Finally, the mechanism for the potential modulation of macrophages by MSCs in IBD needs to be further explored. If these problems were satisfactorily solved, MSC-based therapy would provide a novel strategy for the treatment of IBD and the prevention of IBD-associated CRC.

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