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The Immunomodulatory Properties of Mesenchymal Stem Cells: Implications for Surgical Disease

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Abstract

Mesenchymal stem cells (MSCs) have been used experimentally and clinically in the treatment of a wide variety of pathologies. It is now clear that a number of different mechanisms contribute to the therapeutic effects exerted by these cells. The ability of MSCs to interact with and modulate the functions of a wide variety of immune cells has been recognized as one such mechanism. The implications that the immunomodulatory properties of MSCs may have for the treatment of solid organ rejection, the Systemic Inflammatory Response Syndrome, cancer, and Crohn's disease are reviewed herein.

Keywords

Crohn's disease; transplant; sepsis; SIRS; cancer; tumor; inflammation; immunomodulation; immunoprivilege

INTRODUCTION

Mesenchymal stem cells (MSCs) from the bone marrow of adult humans were first isolated and characterized in the early 1990s [1–2]. These cells were considered remarkable at the time because, prior to their discovery, it had not been considered that such multipotent cells existed in mature, adult tissue. MSCs exhibit a unique plasticity—namely, the ability to differentiate along osteogenic, chondrogenic, and adipogenic lineages. This particular quality quickly generated and continues to generate large amounts of enthusiasm among investigators with an interest in employing these cells for tissue regeneration and replacement purposes. Although originally harvested from bone marrow, MSCs have since

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been isolated from a multitude of sources including adipose tissue, placental tissue, lung, dental pulp, and several others. These cells can be isolated and expanded in culture using straightforward techniques. Furthermore, their lack or paucity of major histocompatibility complex (MHC) class II and other immunoactive co-stimulatory molecules renders these cells “immunoprivileged,” allowing them to evade detection and elimination by foreign immune systems. This raises the attractive possibility for non-autologous, “off-the-shelf” usage and transplantation across MHC barriers [3–4]. Finally, MSCs have been observed to exhibit several interesting properties and functions that extend beyond their multipotency. Work conducted in recent years has established that MSCs interact closely with cells of the immune system and thereby modulate many of their activities and functions. This property has led many to question whether or not MSCs might have a therapeutic role to play for an array of immune-mediated conditions. Within this review, basic concepts regarding the immunomodulatory properties of MSCs and their implications for a variety of conditions treated by surgeons and investigated by surgical scientists will be summarized.

IMMUNOMODULATORY FUNCTIONS OF MSCs AND THEIR THERAPEUTIC IMPLICATIONS

MSCs are easily obtained and can be maintained and expanded in culture for later use. In recent years, much enthusiasm has been generated concerning the use of these previously harvested and expanded cells as a therapeutic modality for a wide range of conditions. MSCs, for example, have been seeded on biologic mesh in an attempt to generate new bone or cartilage and infused directly into the myocardium in an attempt to improve myocardial healing and function following myocardial infarction [5–9]. Interestingly, despite the wealth of information that has been learned about MSCs following *ex vivo* expansion and subsequent transplantation, their true *in vivo* function remains somewhat poorly understood. Although readily obtained from such sources as bone marrow and adipose tissue, these cells comprise only minute proportions of the total population of cells in these tissues and their numbers appear to decline substantially with age [10–11]. Because of their relative scarcity, determining what specific role these cells play under homeostatic and/or pathologic conditions has been difficult.

Nevertheless, evidence has accumulated to suggest that these cells may play a multitude of roles in their hosts. Within the bone marrow, MSCs most likely serve to support and maintain the process of hematopoiesis. However, as discussed, MSCs exist throughout the body and even those typically housed in the bone marrow, by following chemotactic gradients, have the ability to enter the circulation and home to sites of injury and inflammation. Outside of the bone marrow, their physiologic role appears to be in the regeneration and reconstitution of healthy tissue following injury. The notion, however, that these cells simply differentiate into mature cell types in order to repopulate the injured tissue is likely an oversimplification of their true function. When stimulated by injury and inflammation, MSCs release an abundant supply of paracrine growth factors, cytokines, and chemokines [12–14]. Together, these secreted factors exert a net trophic effect on tissue, stimulate neoangiogenesis, limit cellular apoptosis, recruit immune and other cell types to the site of injury, and reduce fibrosis and maladaptive scarring that may develop following organ injury [15–16]. Each of these effects can in fact occur independently of MSC differentiation [17–19].

An additional manner in which MSCs may participate in the process of tissue healing and regeneration is via their ability to influence the activation, proliferation, and function of immune cells. Original observations concerning the immunomodulatory capacity of MSCs were made in association with *in vitro* studies in which the presence of MSCs was found to suppress T lymphocyte activation and proliferation following introduction of alloantigens

[20–21]. Since these initial observations, it has been determined that MSCs can influence a wide variety of both adaptive and innate immune functions (Figure 1). Although an oversimplification of the complete breadth of their actions, the effect that MSCs have on the immune system is generally suppressive in nature. Specifically, MSCs can suppress the activity of CD8⁺ cytotoxic T lymphocytes directly by inhibiting their proliferation following antigen stimulation and indirectly by increasing the relative proportion of CD4⁺ T helper 2 (T_H2) lymphocytes and CD4⁺ regulatory T lymphocytes. The net effect is an increase in interleukin (IL)-4 production by CD4⁺ T_H2 lymphocytes and a reduction in interferon (IFN)- γ production by CD8⁺ T lymphocytes, favoring an overall anti-inflammatory state and suppression of T lymphocyte mediated immunity [22–23]. To the degree that B lymphocyte activation is largely T lymphocyte dependent, the influence of MSCs on T lymphocyte activity may also indirectly suppress B lymphocyte functions [24]. Additionally, MSCs appear to exert a direct influence on B lymphocytes via cell-cell contact and through secretion of paracrine molecules [25–26]. Some *in vitro* studies indicate that this effect may serve to suppress their proliferation and function, while others suggest, seemingly to the contrary, that MSCs may actually enhance the survival and function of B lymphocytes [27–28]. The majority of these observations have been made in the context of *in vitro* cell culture studies and, as such, the true effect that MSCs may have on B lymphocytes *in vivo* remains to be determined.

MSCs also exert significant effects on cells of the innate immune system including monocytes, monocyte-derived dendritic cells (DCs) and macrophages, natural killer (NK) cells, and neutrophils. *In vitro* work has revealed that MSCs can suppress the maturation of monocytes into dendritic cells, thereby inhibiting the antigen-presentation function of these cells [29–30]. Additionally, when cultured in the presence of MSCs, cytokine production by macrophages and monocytes is substantially altered and characterized by reduced secretion of the pro-inflammatory cytokines, tumor necrosis factor (TNF)- α and IL-1 β , with concurrent increase in the production of the anti-inflammatory cytokine, IL-10 [23,31–32]. MSCs also appear to exert a suppressive influence on NK cells. NK cells are cytotoxic effector cells of the innate immune whose primary role appears to be in tumor surveillance and clearance of virally infected cells. MSCs have been observed to inhibit the activation and cytotoxic functions of resting NK cells although these cells appear to be uninfluenced by MSCs once they have already been activated [33–34]. Lastly, in regard to cells of the innate immune system, MSCs can also reduce the intensity of the respiratory burst that is a critical component of the phagocytotic function of neutrophils [35]. This may be a critical method whereby MSCs can limit the severity of tissue damage following ischemic and ischemia/reperfusion injury.

Taken together, it is clear that MSCs exert a potent and multi-faceted immunomodulatory, and primarily immunosuppressive effect. They exert this effect both via direct cell-cell interactions and, as discussed, via secretion of soluble paracrine factors. Again, the significance of these effects under physiologic conditions *in vivo* remains unknown. It has been proposed that the immunomodulatory functions of MSCs may play a role in establishing and maintaining self tolerance by the host immune system [36]. Regardless of their natural function, many investigators have begun questioning whether these properties of MSCs may hold therapeutic potential. To evaluate their therapeutic role, investigators have employed either autologous or allogeneically-derived MSCs, expanded them in culture, and introduced these cells either systemically (i.e., intravenously) or directly into the tissue of interest. To date, infusion of MSCs has shown early promise in the treatment of several immune and inflammatory-mediated conditions including graft-versus-host disease, diabetes, and rheumatoid arthritis. Additionally, pre-clinical and in some cases clinical studies are underway to evaluate the therapeutic potential of these cells for several immune-mediated conditions commonly encountered and treated by surgeons. These conditions and

the implications that MSC-mediated immunomodulation may entail for each are summarized below (Table 1).

IMPLICATIONS FOR SOLID ORGAN TRANSPLANTATION

Developing the ability to successfully transplant allogeneic organs has undoubtedly been among the most remarkable achievements in modern surgery. Despite drastic improvements in immunosuppression regimens that have made long term patient and organ survival possible, organ rejection and adverse reactions associated with chronic immunosuppression remain significant barriers in the field of transplantation. Guided by reports suggesting that MSCs possess an ability to modulate the immune system and amidst efforts to further improve upon immunosuppressive regimens, significant effort has recently been devoted to examining whether MSCs may have a role to play in the prevention of allograft rejection. The basic hypothesis among interested investigators is that infusion of MSCs in conjunction with solid organ allograft transplantation may enhance the host immune system's tolerance of the transplanted organ and may reduce the requirement for chronic immunosuppressive medications.

In 2008, an international study group adopting the title, MISOT (Mesenchymal Stem Cells In Solid Organ Transplantation) was formed to explore what is known about the use of MSCs in the context of solid organ transplantation and how to best proceed with future clinical trials in humans [37]. Although no clinical studies to date have examined the effectiveness of MSCs in the prevention of solid organ allograft rejection, an abundant and expanding amount of evidence from animal models suggests that this approach may have merit. Based on observations made in laboratory models, a potential role for these cells in the prevention of acute heart, liver, kidney, and skin allograft rejection has been suggested [38–41]. In the majority of these studies, allogeneic MSCs are co-infused at the time of organ transplantation. Improved allograft survival and/or a reduction or elimination in the need for concurrent pharmacological immunosuppression have been the most commonly reported findings. Despite the lack of clinical studies, MSCs remain attractive therapeutic candidates in the prevention of organ rejection not only because of their ability to modulate the host immune system in a manner that may promote tolerance of the transplanted organ, but their healing capacity and trophic functions may also help to minimize ischemic, ischemia/reperfusion, and inflammatory injury to the allograft.

Inhibition of the T lymphocyte response against foreign antigen has long been the primary goal of clinical immunosuppression following solid organ allograft transplantation. Not surprisingly, the potent immunomodulatory effect exerted by MSCs on T lymphocyte response appears to be of primary importance in their ability to prevent allograft rejection. As previously discussed, MSCs suppress the proliferation and function of cytotoxic T lymphocytes while promoting the activities of helper and regulatory T lymphocytes. Several studies have suggested that this property of MSCs may be important for their ability to prevent the alloimmune response *in vivo* [42]. The precise mechanisms responsible for this effect and whether or not it persists long-term remain to be determined. Regardless, further research will continue because the potential for less toxicity and, perhaps, a more lasting response make MSCs a potentially attractive therapeutic candidate when compared to traditional pharmacological T-cell regulatory agents.

An additional benefit to the use of MSCs for the prevention of solid organ allograft immunorejection is that infusion of these cells at the time of organ transplantation may have the potential to promote a state of immunologic chimerism and long-term tolerance of the transplanted organ by the host immune system. Establishment of immunologic chimerism with respect to donor organ and host has been achieved by simultaneous solid organ

transplantation and transplantation of bone marrow from the same donor and, in a few notable cases, this technique carries with it the advantage of long-term graft survival in the absence of immunosuppression [43–44]. Investigators in the field of hematopoietic stem cell transplantation seeking to further increase the rates of immunologic chimerism establishment have utilized co-infusion of MSCs at the time of hematopoietic stem cell transplantation in an attempt to do so. In many cases, enhancement of cellular engraftment and rates of immunologic chimerism have been observed with co-infusion of MSCs [45–47]. Whether MSCs' ability to promote immune tolerance via establishment of immunologic chimerism holds any therapeutic value in the context of solid organ transplantation has yet to be studied. Nevertheless, should MSCs prove useful in helping to promote a state of immunologic chimerism, it may be another clear benefit to their use in organ transplantation.

IMPLICATIONS FOR SEPSIS AND THE SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

The Systemic Inflammatory Response Syndrome (SIRS) is believed to develop secondary to a dysregulated and overzealous activation of the immune system in response to severe sepsis, surgery, or trauma. The disorder is frequently responsible for causing multiple organ dysfunction, long stays in the intensive care unit, and carries with it a mortality rate between 20 – 40% [48]. Therapies that can effectively prevent or reverse this phenomenon have long been sought but, with only a few exceptions, have remained largely elusive. Because SIRS is an immune-mediated phenomenon, investigators have begun to question whether or not the immunomodulatory functions of MSCs could be useful in the treatment of this condition.

Indeed recent evidence from the laboratory suggests that MSCs may possess the capacity to alter the immune response that characterizes SIRS and thereby improve the course of this condition [49]. To date, investigations conducted in animal models of endotoxemia, acute respiratory distress syndrome (ARDS), and intra-abdominal sepsis have suggested a possible benefit to the systemic administration of MSCs for treatment of the systemic derangements characteristic of SIRS. Improved hemodynamics, reduction in systemic and local inflammation, reduced organ injury, improved organ function, and improved survival have all been reported [31,50–51]. Although MSCs have not yet been studied clinically for this purpose, human MSCs have been observed to reduce endotoxemia-induced pulmonary injury in an *ex vivo* perfused human lung [52]. These observations have spawned a growing interest in evaluating the immunomodulatory properties of MSCs and their potential utility in the treatment of sepsis and SIRS.

Early work has revealed that MSCs, following systemic infusion, may interact with the host immune system in several ways that may be effective in curtailing the course of SIRS. Their influence on macrophage function appears to be of central importance in their ability to exert this effect. Macrophages serve as the primary effector cells early in the course of SIRS by elaborating large amounts of pro-inflammatory cytokines such as TNF- α and IL-6 in response to invading pathogens or host-derived danger-signaling molecules. MSCs have been observed to interact with macrophages in SIRS models and reduce the levels of pro-inflammatory cytokines that these cells produce. This appears to be directly related to MSCs' ability to increase the expression of the anti-inflammatory cytokine, IL-10, by macrophages and other antigen-presenting cells [31,53]. IL-10 is an important regulator of the inflammatory response and acts to inhibit further pro-inflammatory cytokine release by immune cells while promoting B cell survival and antibody production. The ability of MSCs to influence macrophage IL-10 production appears to be dependent on the expression on the toll-like receptor (TLR)-4 molecule, the tumor necrosis factor receptor 1 molecule, and the secretion of prostaglandin E₂ by MSCs [31]. In addition to their effects on macrophages, MSCs may also exhibit a direct influence on T and B lymphocyte as well as neutrophils

functions, although the importance of this effect on SIRS outcomes is not yet clear [23,35]. As in the prevention of solid organ allograft rejection, MSCs' trophic properties and capacity to prevent tissue injury and influence tissue healing are likely also important mechanisms behind these cells' ability to combat SIRS. Because of their potentially multifactorial and lasting benefits in the setting of SIRS and sepsis, MSCs may represent unique and important agents in the treatment of this condition. Nevertheless, future research will need to assess these therapeutic properties while simultaneously considering important factors such as timing of administration and the heterogeneities stemming from host and etiologic factors that characterize clinical SIRS and have been largely responsible for the failure of clinical therapies despite initial promise in the laboratory setting.

IMPLICATIONS FOR CANCER

It has been well-established that events associated with the growth and spread of cancer are highly influenced by the immune system. The relationship between cancer and the immune system is complex. On one end of the spectrum, inflammatory cells may become activated by a tumor and thereby facilitate its ability to grow and invade surrounding tissue. Conversely, immune cells including T lymphocytes and NK cells play an important preventative role in the development of cancer via their ability to recognize and facilitate the removal of tumor cells. As the relationship between cancer and the immune system is complex, so too is the influence exerted by MSCs on this relationship.

Accumulated evidence suggests that the immunomodulatory properties of MSCs may in fact both deter or promote tumor growth. As discussed, certain immune cells, particularly T and NK cells, play critical roles in tumor recognition and prevention. Since MSCs appear to inhibit the activation and function of both T and NK cells, there exists a theoretical concern supported by some preliminary evidence from the laboratory that these cells may interfere with the body's natural tumor immunosurveillance mechanisms and either promote tumor growth or perhaps even contribute to *de novo* tumor formation [54–55]. Additional properties of MSCs including their ability to promote angiogenesis and provide a stromal support network for tumors have led several investigators to question whether or not these cells may in fact enhance tumor development [56].

To the contrary, there is evidence to indicate that the immunomodulatory properties of MSCs may play an inhibitory role in the development of cancer under some circumstances. In laboratory models, MSCs have been observed to inhibit several types of cancer including lung, colon, pancreas, and Kaposi's sarcoma [57–59]. The mechanisms behind the tumor suppressive effects of MSCs are not yet entirely clear, but appear to be related to their capacity to modulate the inflammatory environment that characterizes many tumors. Additionally, MSCs may exert effects by nonimmune mechanisms, such as their ability to interact with some cancer cells and inhibit intracellular signaling pathways associated with cell growth and division [59]. At this time there is no single answer to describe the role of MSC-mediated immunomodulation and its effect on cancer. Further research will be necessary to clarify what role, if any, the functions of MSCs may have in cancer therapy. Of interest, it has been observed that MSCs possess the ability to selectively home to sites of tumors. As such, many investigators are taking advantage of this property and attempting to systemically administer MSCs that have been modified to act as vectors for gene therapy [61–63].

IMPLICATIONS FOR INFLAMMATORY BOWEL DISEASE

A discussion regarding the use of MSCs in the treatment of inflammatory bowel disease, and particularly Crohn's disease (CD), is especially warranted insofar as clinical trials examining their use in the treatment of this condition are already underway. Although the

etiology and pathogenesis of CD remains incompletely understood, the condition is attributed primarily to an autoimmune phenomenon in which the intestines and other parts of the body are targeted by the individual's own immune system. A current understanding of CD recognizes that a set of heterogeneous, over-active, and sustained responses by cells of both the innate and adaptive immune systems cause excessive inflammation and resultant tissue injury leading to the clinical spectrum that characterizes CD. As such, immunomodulatory and immunosuppressant medications have been the mainstay of therapy in conjunction with surgery for severe and complicated disease. Although these treatments can be effective, they are limited by their complications and frequently offer only partial and non-sustained benefit. Because this is so, improvements in therapy for patients with CD continue to be needed.

The same tissue-healing and immunomodulatory properties of MSCs that have led investigators to explore their therapeutic utility for a variety of conditions are the same properties that may offer benefit for CD. Administration of MSCs in experimental models of inflammatory bowel disease revealed that these cells possess the ability to home to sites of injury and inflammation in the bowel, alter the inflammatory milieu by inhibiting T_H1 lymphocyte activity and favoring a regulatory T lymphocyte response, and ultimately promote healing of inflammatory ulcers and improved nutritional status [64]. Clinical interest in the use of MSCs for treatment of CD developed further following reports suggesting that these cells were able to heal intestinal ulcerations that developed in patients with graft-versus-host disease following hematopoietic stem cell transplantation [65]. Additionally, it had been previously reported that patients with CD who also underwent bone marrow ablation and hematopoietic stem cell transplantation for hematologic malignancies experienced resolution of their intestinal pathology [66]. The effectiveness of marrow ablation followed by stem cell transplantation for the treatment of refractory CD was subsequently verified with prospective clinical trials demonstrating, in total, a greater than 90% remission rate of disease symptoms [67–68]. The available evidence suggested a favorable role for the immunomodulatory capacities of MSCs in the treatment of CD and subsequent clinical trials have begun to examine their utility.

To date, trials examining the safety and effectiveness of MSCs for the treatment of fistulizing and active luminal CD are currently underway. The majority of these trials have employed autologously-derived cells harvested and expanded from adipose tissue or bone marrow. A Phase I trial in which eight patients with Crohn's perianal fistulizing disease were treated with local injection of autologous, *ex vivo* expanded MSCs revealed a 75% fistula-closure rate at 8 weeks follow-up along with an excellent safety profile [69]. In a follow-up Phase II trial, the same investigators compared the effectiveness local injection of fibrin glue alone versus injection of fibrin glue plus adipose-derived MSCs in patients with Crohn's perianal fistulizing disease. With seven patients in each arm, the investigators reported a significant improvement in fistula-closure in the cell-therapy group (71%) vs. the fibrin glue-only group (14%) [70]. Systemic delivery of *ex vivo* expanded MSCs has also been examined for the treatment of severe, medically refractory CD. Phase I and II trials have been conducted with results suggesting that intravenous infusion of autologous or donor-derived bone marrow MSCs effectively lessens disease severity in approximately one-third of patients with severe, medically refractory CD [71]. Currently, a Phase III randomized, double-blinded trial comparing infusion of *ex vivo* expanded, donor-derived Prochymal MSCs (Osiris, Columbia, MD) versus placebo is underway and recent interim analysis suggests that patients receiving cell-treatment experience improved disease remission rates than those receiving placebo (ClinicalTrials.gov identifier NCT00482092). The results of this trial will be important in continuing to assess and clarify the safety, effectiveness, and durability of MSC-based therapies for CD.

FUTURE DIRECTIONS AND CHALLENGES

The immunomodulatory properties of MSCs may render these cells useful as a therapeutic modality for a variety of conditions. Investigators examining the properties of these cells in the laboratory have observed that MSCs are capable of altering immune cell function in a multitude of ways that may have implications for the treatment of several pathologic conditions. At this time, with the exception of CD, relatively little information exists regarding the effectiveness of MSCs for the treatment of the conditions discussed herein. In order to fully understand their therapeutic capacity and limitations in this regard, ongoing research will need to address and clarify several key issues. First, efforts must be made to understand the true immunomodulatory effect of MSCs *in vivo*. Although significant strides have been made in determining how MSCs affect cells of the immune system under cell culture conditions, it is not clear in all cases if these affects will also occur *in vivo* and, if so, what significance they may entail. As the *in vivo* immunomodulatory actions are further explored, the intensity and duration of these effects must also be evaluated. These factors remain largely unaddressed, but could have clear implications for all conditions discussed and affect timing, dose, and route of MSC-administration. Concurrently, the safety profile of MSC administration must continue to be scrutinized. Fortunately, initial experiences with the clinical use of MSCs indicate a high level of safety associated with these cells. Nevertheless, the theoretic possibility that the immunosuppressive properties of MSCs could entail negative consequences with regard to tumor immunosurveillance and infection must continue to be considered and evaluated. Finally, the feasibility of using allogeneic MSCs must continue to be evaluated. As discussed, most reports indicate that MSCs, by virtue of their low to absent levels of MHC II as well as other co-stimulatory molecules on their surfaces, are relatively “immunoprivileged” and may avoid detection and destruction by foreign immune systems. Despite these assertions, this issue has not been well addressed clinically in the absence of concurrent bone marrow ablative strategies or systemic, pharmacologic immunosuppression. It is important to consider that some reports suggest that there may be some heterogeneity among cultured MSC cell lines and on occasion significant proportions of these cells may express MHC and other immune co-stimulatory peptides, rendering them vulnerable to elimination by foreign immune cells [21,72]. In this regard, efforts designed to determine how culture conditions may affect the immunogenicity of MSCs and how these conditions might be optimized to promote maximum functionality while maintaining these cells’ ability to survive in an allogeneic host are needed.

CONCLUSION

The immunomodulatory properties of MSCs have already shown promise when used as therapy for otherwise medically refractory CD. Accumulating evidence suggests that these properties may also be exploited in the treatment of several other conditions frequently encountered by surgeons. Ongoing efforts focused on evaluating *in vivo* effectiveness, shortcomings, and adverse effects of MSCs are needed to determine if their immunomodulatory properties will evolve from theoretical interest to clinical benefit.

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FIG. 1.

Mesenchymal stem cells (MSCs, center of figure) exert effects on a variety of cells of the immune system. In general, these effects promote an overall anti-inflammatory and immunosuppressive state. Mechanisms governing these interactions include secretion of soluble paracrine factors by MSCs and direct cell-cell contact between MSCs and immune cells. IFN, interferon; IL, interleukin; NK, natural killer; APCs, antigen presenting cells; TNF, tumor necrosis factor

TABLE 1

Possible Therapeutic Effects and Mechanisms associated with MSC-mediated Immunomodulation

	Therapeutic Effect	Possible Mechanism	Clinical Trials
Solid Organ Transplantation	Prevention of allograft rejection	Prevention of T cell response to foreign antigen Promotion of immunotolerance and possibly immunologic chimerism	None to date
SIRS	Reduced systemic and local inflammation Reduced organ injury Reduced organ dysfunction Improved survival	Reduced pro-inflammatory cytokine secretion by monocytes and macrophages Inhibition of cytotoxic T lymphocyte response Inhibition of respiratory burst by neutrophils	None to date
Cancer	Inhibition of cancer cell proliferation and tumor growth*	Reduction of tumor-associated inflammation and tumor spread	None to date
Inflammatory Bowel Disease	Improved healing rates of Crohn's-related perianal fistulas Improved rates and sustainability of disease remission for patients with medically refractory Crohn's disease	Inhibition of T lymphocyte response Promotion of immunotolerance	<u>Crohn's perianal fistula:</u> Phase I and II trials suggest improved healing rates <u>Medically refractory intraluminal Crohn's disease:</u> Phase I and II trials as well as interim analysis of ongoing Phase III trial suggest improved symptomatic relief and disease remission rates

* There exists a theoretical concern supported by preliminary evidence from laboratory models that MSCs may promote the growth of some tumors. This is likely related to MSCs' capacity to suppress the body's natural immunosurveillance mechanisms provided by T lymphocytes and NK cells.