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Mesenchymal Stromal Cell Therapy for the Treatment of Intestinal Ischemia: Defining the Optimal Cell Isolate for Maximum Therapeutic Benefit

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Abstract

Intestinal ischemia is a devastating intraabdominal emergency that often necessitates surgical intervention. Mortality rates can be high, and patients who survive often have significant long-term morbidity. The implementation of traditional medical therapies to prevent or treat intestinal ischemia have been sparse over the last decade, and therefore, the use of novel therapies are becoming more prevalent. Cellular therapy using mesenchymal stromal cells is one such treatment modality that is attracting noteworthy attention in the scientific community. Several groups have seen benefit with cellular therapy, but the optimal cell line has not been identified. The purpose of this review is to: 1) Review the mechanism of intestinal ischemia and reperfusion injury, 2) Identify the mechanisms of how cellular therapy may be therapeutic for this disease, and 3) Compare various MSC tissue sources to maximize potential therapeutic efficacy in the treatment of intestinal I/R diseases.

Keywords

Mesenchymal stromal cell; intestinal ischemia; necrotizing enterocolitis; cellular therapy

INTRODUCTION

Intestinal ischemia stems from diverse etiologies and affects patient populations of varying ages and comorbidities. Necrotizing enterocolitis (NEC) and volvulus are two

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manifestations of intestinal ischemia and necrosis in the neonatal population. The mortality rate associated with the most severe cases of NEC is quite high, particularly in the very low birth weight pre-term infants (1). Midgut volvulus from malrotation occurs far less frequently, but carries a significant mortality risk when the bulk of the bowel is affected (2). Acute Mesenteric Ischemia (AMI) is an intraabdominal emergency involving thromboembolic occlusion of mesenteric perfusion that primarily affects the elderly population and those undergoing cardiac bypass surgery. The mortality rate for AMI can be as high as 40% for those necessitating endovascular surgical intervention to lyse the clot and salvage the ischemic tissue (3). Ischemic bowel from incarcerated hernias and bowel obstructions secondary to adhesions also are prevalent in all populations.

Although ischemia from volvulus, AMI, and bowel obstructions can be relieved, ischemia from NEC usually cannot be altered. Regardless of etiology, severe intestinal ischemia can result in bacterial translocation across the damaged epithelium and free radical generation (4). Left untreated, these patients can rapidly decompensate and progress to shock, multi-system organ failure and death. If patients survive the ischemic episode, surgical resection of necrotic tissue often results in short bowel syndrome and the need for long term parenteral nutrition (5).

Few noteworthy advancements in the medical treatment of intestinal ischemia have been made over the last few decades. While anticoagulation therapy initiated after surgical resection of necrotic bowel has been shown to minimize the risk for subsequent infarcts, long-term survival outcomes have not improved (6). Therefore, mesenchymal stromal cell (MSC) therapy offers a novel therapeutic option for the treatment of this disease. Studies have observed the capacity of MSCs to attenuate ischemic intestinal injury through enhanced restitution of intestinal mucosa, reduced bacterial translocation from the lumen into circulation, and attenuation of the inflammatory response (7–9). While stromal cells derived from various tissues present similar basic biological features, disparities in expansion potential and immunomodulatory properties exist (10). Although stromal cell therapy suggests promise in the treatment of intestinal ischemia, identification of the optimal cell isolate must be made prior to widespread therapeutic implementation. The purpose of this review article is to: 1) review the mechanism of intestinal ischemia and reperfusion injury, 2) identify the mechanisms of how cellular therapy may be therapeutic for this disease, and 3) compare various MSC tissue sources to maximize potential therapeutic efficacy in the treatment of intestinal I/R diseases.

MECHANISM FOR INTESTINAL ISCHEMIA-RELATED INJURY

The initial phase of ischemic intestinal injury involves depletion of oxygen and disruption of normal epithelial barrier function. While enterocytes are relatively resistant to transient hypoxic conditions, long term occlusion of blood supply can result in irreversible cell death. Dying enterocytes release cell contents into the extracellular matrix, which bind to immune cells provoking the inflammatory response. These cellular constituents, referred to as damage-associated molecular patterns (DAMPs), include nucleic acids, heat-shock proteins and high-mobility group box chromosomal protein 1 (HMGB1) (11). Hypoxia-induced destruction of enterocytes also results in the disruption of paracellular tight junctions (12).

The failure of the epithelial barrier allows translocation of microbes and their products, referred to as pathogen associated molecular patterns (PAMPs), from the lumen into the lamina propria, thereby triggering inflammation. Ischemia also prompts the activation of transcription factors vital to hypoxia adaptation. One such factor, hypoxia-inducible factor (HIF), is stabilized under hypoxic conditions and upregulates genes for anaerobic metabolism (13, 14), angiogenesis (15), and inflammation attenuation(16).

Reestablishment of blood flow by surgical or endovascular bypass, or by medicinal dissolution of thrombus can further aggravate the ischemic bowel through reperfusion injury and the generation of reactive oxygen species (ROS) (17). During hypoxia, many mitochondrial enzymes, including cytochrome oxidase and manganese superoxide dismutase, decrease in activity due to a lack of a final electron acceptor for oxidative phosphorylation (18, 19). The loss of cytochrome oxidase activity prevents normal oxidative phosphorylation upon reoxygenation, and results in the production of ROS by more proximal mitochondrial complexes (20, 21). ROS generated in ischemia and reperfusion (I/R) injury alter signal transducers, peroxidize membrane lipids, oxidize DNA, and denature enzymes (22, 23). These ROS-mediated cellular alterations trigger apoptosis, resulting in further disruption of the intestinal barrier, endothelial dysfunction and inflammation (24).

The most significant component of intestinal I/R injury involves systemic activation of the inflammatory cascade, which in turn can trigger multi-organ failure and death. The I/R injury to the intestinal epithelium allows for the accumulation of PAMPs and DAMPS in the lamina propria (25). Toll-like receptors (TLRs) expressed on cells of the innate immune system bind to these molecules and trigger activation of the local inflammatory response through induction of transcription factors, which include nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), activator protein 1 (AP-1), and mitogen-activated protein kinase (MAPK) (26–28).

These transcription factors activate genes associated with the production of cytokines, interferons (IFNs), chemokines, cell adhesion molecules and chemokine receptors (29). The key mediators of the initial inflammatory response are interleukin-1 (IL-1) (30), tumor necrosis factor-alpha (TNF-α) (12), and platelet activating factor (PAF) (31). These mediators promote complement activation in addition to the chemotaxis, transmigration, and activation of circulating leukocytes. Upon entry to the damaged tissue, these leukocytes trigger the production of multiple other cytokines and inflammatory mediators, including IL-6, IL-8, IL-17, IL-18, thromboxanes, leukotrienes, prostaglandins, nitric oxide (NO), enodothelin-1, and additional ROS (32–36). If counter-regulatory responses are insufficient, accelerated apoptosis of intestinal epithelial cells and disruption of paracellular tight junctions will further facilitate tissue damage ultimately resulting in multi-organ failure and death.

MECHANISM OF STROMAL CELL MEDIATED INTESTINAL PROTECTION

Mesenchymal stromal cell therapy has shown remarkable potential in the treatment of end organ ischemia. Following intestinal injury, these cells promote increased functional recovery and accelerated mucosal restitution, while simultaneously limiting inflammation,

suppressing the host immune system, and promoting free radical scavengers (Figure 1). While the exact mechanism by which MSCs ameliorate I/R injury is multifactorial and not yet defined, three primary mechanisms have been suggested. Once MSCs are activated, they can either differentiate into intestinal cell types, fuse with pre-existing cells, or secrete various bioactive factors that act in an autocrine or paracrine manor to attenuate damage following injury.

CELLULAR DIFFERENTIATION

MSCs can be isolated from almost every type of tissue in the body and possess a multipotent ability to differentiate into various cell lineages. Not only are they able to differentiate into mesodermal lineages, like adipocytes and osteocytes (37), but they have also demonstrated the capacity to differentiate into a multitude of diverse cell lines found throughout the human body, including hepatocytes (38), pancreatic islet-like cells (39), neuron-like cells (40), and epidermal cells (41). This characteristic resulted in the initial hypothesis that upon entry into damaged tissue, transplanted MSCs engraft and differentiate into the phenotype of the injured tissue, restoring the diseased organ with healthy, functioning cells.

Theoretically, cellular differentiation of MSCs within the damaged bowel would result in re-established morphological integrity of the intestinal mucosa and reduced mucosal permeability. While differentiation has been demonstrated in animal models of acute myocardial infarction (42), acute renal failure (43), dermal wound repair (44), gastric perforation (45), and chronic lung injury (46, 47), little evidence suggests that this is the primary mechanism by which MSCs attenuate intestinal I/R injury. In a study by Brittan and colleagues, bone marrow derived MSCs (BM-MSCs) migrated to the intestinal lamina propria and differentiated into myofibroblasts to provide a framework upon which intestinal tissue regeneration following irradiation could take place (48). While this study suggests that native BM-MSCs can home to areas of damage and promote tissue regeneration through cellular differentiation, there is little auxiliary evidence supporting this mechanism of action. As a whole, the notion that MSCs provide therapeutic efficacy via stromal cell differentiation within regenerating tissue has been widely phased out.

HETEROTOPIC CELL FUSION

Heterotopic cell fusion involves the merging of two cells from different lineages. With regards to MSC-mediated tissue repair, it results in the introduction of the nucleus or functional genes from the stromal cell into a degenerating cell, so as to protect and restore the dying cell's activity. Inflammation triggers the migration of BM-MSCs to areas of damage and stimulates an increase in the frequency of heterotopic fusion between the BM-MSCs and differentiated resident cells within the tissue (49). Cell fusion reactions following administration of BM-MSCs have been observed with hepatocytes, Purkinje neurons, and cardiac myocytes. It has been postulated that these newly formed multinucleated cells are preferentially selected for survival, able to withstand a greater degree of stress, and promote tissue homeostasis.

With regards to intestinal regeneration following damage, the data regarding heterotopic cell fusion are conflicting. Multiple studies have observed the fusion of transplanted BM-MSCs

with intestinal epithelial cells and undifferentiated intestinal progenitor cells following radiation induced damage (50, 51). However, de Jong and colleagues observed that BM-MSC and intestinal cell fusion events were extremely rare, if present at all, and irrelevant to the regeneration and homeostasis of damaged intestinal tissue (52). Even if cell fusion between BM-MSCs and intestinal epithelial cells does occur, it is unclear whether this fusion provides significant benefit. More work needs to be done to elucidate the therapeutic efficacy of heterotopic fusion in stromal cell mediated intestinal protection.

PARACRINE MEDIATORS

Growing evidence favors the paracrine mechanism of MSC-mediated organ protection (Figure 2). While cellular differentiation and heterotopic cell fusion events have been observed, the secretion of anti-inflammatory and pro-regenerative factors by MSCs results in the greatest modification of tissues following I/R insult. Numerous studies have suggested that applying cell free media that has been conditioned by stromal cells provides equivalent protection as the cells themselves (53–57), suggesting that the paracrine factors produced by the cells in the conditioned media are what drive the therapeutic efficacy of MSCs within damaged tissue. Additionally, the rate of transplanted stromal cell engraftment and survival is so low that cellular differentiation and fusion events are likely too few to directly influence recovery of tissue function (58). Furthermore, multiple studies have appreciated post-injury improvements in tissues located elsewhere from where MSCs engrafted, suggesting that MSC homing to the actual site of I/R damage is not mandatory for therapeutic efficacy (59–61). Therefore, the primary mechanism by which MSCs appear to combat the progression of intestinal I/R damage is via a multifactorial paracrine-mediated process, in which immunomodulation, tissue restoration, and ROS scavenging occurs.

IMMUNOMODULATION—MSC paracrine mediators appear to play a role in the attenuation of the inflammatory response generated by intestinal I/R injury. The induction of transcription factor NF-kB following insult regulates the production of pro-inflammatory cytokines by activated macrophages and other cells of the innate immune system. Various studies have observed the capacity of MSCs to decrease the activation of NF-kB in animal models of intestinal I/R injury (8, 62). Subsequently, MSC therapy has been associated with decreased levels of proinflammatory cytokines, particularly TNF-α (8, 63), IL-1β (63), and IFN-γ (64). These changes favor T cell differentiation into Th2 and T regulatory cell types, minimize inflammatory mediated intestinal destruction, and decrease the risk of systemic sepsis. Additionally, reduced TNF-α levels were seen to enhance expression of intestinal tight junction proteins, thereby resulting in decreased intestinal permeability and preserved mechanical barrier function (65).

Studies have also observed increased production of anti-inflammatory cytokines in I/R injured tissues treated with MSCs. One of the anti-inflammatory cytokines, IL-10, was observed to block NF-kB signaling, downregulate the expression of Th-1 inflammatory cytokines, and moderate COX-2 activation. While elevated IL-10 levels were initially believed to be made from the MSCs (66–68), studies now suggest that IL-10 may be produced by monocytes that were stimulated to differentiate by MSCs (69). Melief and colleagues observed that an elevation in MSC derived IL-6 triggered the differentiation of

monocytes to IL-10 secreting macrophages (70). MSC immunomodulation in intestinal I/R injury through increased production of anti-inflammatory cytokines and decreased synthesis of inflammatory mediators minimizes intestinal damage and reduces the risk for multi-organ failure and death.

TISSUE RESTORATION—Through the release of various bioactive factors, MSCs facilitate angiogenesis, inhibit apoptosis, alter the coagulation cascade (71), and stimulate resident intestinal stromal cells to proliferate and restore necrotic tissue. Upon entering hypoxic environments, MSCs upregulate mRNA expression of numerous growth factors, including vascular endothelial growth factor (VEGF), fibroblast growth factor-2 (FGF2), and transforming growth factor-β (TGF-β), resulting in enhanced tissue restoration (72). The upregulation in growth factor expression is believed to be mediated by a p38 mitogen-activated protein kinase (MAPK)-dependent mechanism (73).

Each growth factor modulates various parts of the healing process and their beneficial effects are multifactorial. VEGF and FGF2 are key promoters of angiogenesis following acute ischemia and inflammation (74–76), and appear to enhance MSC survival upon transplantation (77, 78). TGF-β appears to be a key mediator of tissue remodeling, and enhances the expression of tight junction proteins to restore the intestinal barrier (79). IL-6, traditionally thought of as an acute phase reactant, may actually be protective to the gut during the inflammatory response. Several studies have suggested that it promotes intestinal hyperplasia and prevents cell death (80, 81). While other paracrine mediators have been observed in other models of I/R injury, these growth factors have been the most extensively demonstrated in models of intestinal insult.

In addition to growth factor production, MSCs have been shown to secrete growth factor-containing exosomes into the extracellular milieu. The exosomes bind to target cells in the extracellular space and either alter target cell signaling or unload their vesicular contents into the target cell cytoplasm (82). Studies analyzing the alterations generated by MSC exosomal contents have observed enhanced angiogenesis and epithelial and endothelial wound healing in target tissues (83, 84). With regards to intestinal injury, Rager and colleagues appreciated improved functional recovery of the bowel wall in a murine model of NEC conferred by MSC-derived exosomes administered intraperitoneally in a cell-free medium (85). These studies further support the paracrine model of MSC restitution of ischemia-damaged tissues.

ANTI-OXIDANT PROPERTIES—While the reestablishment of blood flow to ischemic bowel is vital to salvaging the tissue, the generation of reactive oxygen species adds insult to injury. Stromal cells have been observed to produce various antioxidant enzymes that work to fight the accumulation of these oxygen free radicals. Superoxide dismutase, catalase, and glutathione peroxidase are highly expressed by stromal cells and work collectively to convert oxygen free radicals to water and oxygen (86, 87). In scavenging ROSs and converting them to innocuous particles, stromal cells prevent further disruption of the intestinal barrier, decrease endothelial dysfunction and minimize inflammation.

FINDING THE OPTIMAL STROMAL CELL ISOLATE FOR THERAPY

Adult MSCs are believed to reside in all tissues and organs (88), and show unique promise with regards to autologous and allogeneic transplant in various models of ischemia. While MSCs isolated from bone marrow (BM-MSC), adipose (AT-MSC), umbilical cords (UC-MSC), and placentas (PT-MSC) have been the most well-studied and are more easily sequestered, human MSCs have also been isolated from the intestines, skin, kidney, heart, spleen, dental pulp, nasal mucosa, trachea, prostate stroma, limbal stroma, and synovial fluid in the knee joint (89, 90).

According to the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy, MSC classification necessitates the expression of CD73, CD90, CD105 surface molecules, and lack of expression of CD34, CD45, CD11b or CD14, CD19 or CD79α and HLA-DR (91). Additionally, the cell must be adherent to plastic when cultured in standard conditions and able to differentiate into osteoblasts, adipocytes, and chondroblasts in vitro.

Compared to embryonic stem cells (ESCs), which present significant ethical limitations, and induced pluripotent stem cells (iPSCs), which possess significant safety concerns for malignant trasnformation, adult and birth-associated tissue MSCs have shown the most promise with regards to translational stem cell therapy over the last decade. MSCs isolated from each tissue type display unique properties with regards to immunogenicity and differentiation potential (Table 1), so an understanding of each tissue-specific MSC isolate is vital to studying their effect in various models of I/R injury.

BONE MARROW MSCs

Bone marrow derived MSCs (BM-MSCs) have been the most widely studied source of mesenchymal stromal cells to date. Clinical transplantation of BM-MSCs appear to be well tolerated and play a significant role in immunosuppression (92–94). Although no clinical trials to date have studied the use of BM-MSCs in intestinal ischemic injury, many studies have observed improved functional recovery outcomes following autologous BM-MSC transplantation in patients with myocardial infarction (95–98). Additionally, a commercial allogeneic BM-MSCs product, Prochymal, has shown improved functional recovery following MI, suggesting the potential use of BM-MSCs as a commercial, off-the shelf product for intestinal ischemic injury (99).

While no clinical data exists yet supporting BM-MSC treatment in patients with intestinal ischemia, many studies using animal models have shown great promise. Markel and colleagues observed that administration of human BM-MSCs after sixty minutes of ischemia in mouse models of intestinal I/R injury improved survival outcomes and resulted in the production of high levels of growth factors and lower levels of proinflammatory chemokines (7). Other groups have also shown benefit to BM-MSCs in mouse models of intestinal ischemia (100, 101). Studies using rat-derived BM-MSCs in a rat model of intestinal I/R injury observed improved integrity of the intestinal mucosa, reduced translocation of bacteria from the lumen into circulation, and a decreased inflammatory response (8, 9).

While extensive data and experience favor BM-MSCs as the optimal cell isolate to use in the progression towards clinical trials, there are significant disadvantages to consider. First, bone marrow aspirations to isolate BM-MSCs are invasive and painful, making the process less desirable for allogeneic donors and autologous transplant patients. Bone marrow isolates would also not be feasible in the most premature of patients with intestinal ischemia. Additionally, the yield of BM-MSCs from the aspirate is relatively low compared to all other nucleated cells, and the frequency declines even more so with age (102). Furthermore, the proliferative potential of BM-MSCs pales in comparison to other MSC isolates (103). These attributes of BM-MSCs are the primary reason alternative tissue MSCs are now under investigation.

ADIPOSE TISSUE MSCs

Since Zuk and colleagues first isolated MSCs from lipoaspirates in 2001 (104, 105), the use of adipose tissue-derived MSCs (AT-MSCs) in regenerative medicine studies has grown more than any other tissue type over the last decade. Numerous attributes make AT-MSCs favorable in comparison to other MSCs. AT-MSCs show greater proliferative potential than other MSC isolates, and with the incidence of obesity steadily rising, their ease of accessibility and limitless supply via liposuction of subcutaneous adipose tissue make them an ideal candidate for widespread therapeutic use (106–109).

Studies using AT-MSCs in conjunction with animal models of intestinal I/R injury have shown great promise. Allogeneic rat AT-MSC transplantation appears to attenuate intestinal I/R injury through the suppression of inflammation and ROS generation (110). Additionally, improved survival outcomes have been observed in murine models that were administered human AT-MSCs following I/R injury. These improved outcomes were associated with enhanced mesenteric perfusion, preservation of intestinal tight junctions and decreased systemic inflammation (111).

Clinical trials utilizing autologous or allogeneic AT-MSCs have shown improved outcomes in patients with various forms of end organ ischemia, including myocardial infarction (112), critical limb ischemia (113) and ischemic stroke (114). Clinical trials utilizing AT-MSCs for the treatment of intestinal ischemia have not yet been offered. However, human clinical trials utilizing AT-MSCs in Crohn's and non-Crohn's disease patients with perianal fistulas have shown both safety and efficacy. Although Crohn's disease is not specifically an ischemic injury, it does involve full thickness inflammation of the intestinal wall and possible bowel perforations. Phase I and phase II trials using autologous AT-MSCs in combination with fibrin glue was both safe and effective in the treatment of complex perianal fistulas, and resulted in higher rates of healing than glue alone (115–117). While a phase III trial did not show statistically significant improvements, further studies are underway to better define ideal AT-MSC therapy candidates (118). It is also important to note that the intralesional injection of autologous AT-MSCs for perianal or rectovaginal fistulas associated with Crohn's disease did not alter the ability to conceive, the course or outcome of pregnancy, or the newborn's health in female patients (119). These observations add weight to the notion that AT-MSCs are safe for clinical use, and suggest that AT-MSCs could show great promise in clinical trials of intestinal ischemic injury.

A notable primary benefit of using AT-MSCs as the cell of choice for clinical therapy is the high yield of cells from liposuction in adult patients undergoing autologous transplant. Nevertheless, limitations still exist, particularly with regards to neonates and underweight adult patients. The extraction of AT-MSCs necessitates a large enough storage of adipose tissue to prevent potential morbidity. Although this limits the potential use of autologous AT-MSCs in these patient populations, it does not eliminate the potential use of allogeneic AT-MSCs as an "off the shelf" source for therapy. The frequency of liposuction procedures in the general population provides for a potentially large cell bank for allogeneic transplant, thereby favoring AT-MSCs for widespread clinical use.

BIRTH-ASSOCIATED TISSUE MSCs

MSCs isolated from birth associated tissues, also referred to as perinatal tissues, primarily involve cells from the umbilical cord blood (UCB-MSCs), Warton's Jelly (WJ-MSCs), amniotic fluid (AF-MSCs), and placenta (PL-MSCs). MSCs can also be found in the amnion and chorion; however, these cells have been studied less than their counterparts (120–122). Birth associated tissue MSCs present a unique MSC source in that these cells possess more primitive properties than MSCs isolated from adult tissues, and they can be obtained unobtrusively posing no risk to mother or baby. Studies using birth-associated MSCs in the treatment of animal models of intestinal ischemia are limited, but existing studies of these cells do show promise in limiting ischemic injury (101). These cells have shown promise in the treatment of other animal models of ischemic injury, including cerebral infarction (123) and hind limb ischemia (124). The potential value of these cells with regards to ease of accessibility and differentiation potential mandate consideration as a possible cell isolate for therapy for intestinal ischemia.

With regards to intestinal ischemia and necrosis, the use of autologous birth associated tissue MSCs appears to be most applicable in neonates with necrotizing enterocolitis. Since NEC primarily affects low birthweight pre-term infants, harvesting these tissues during delivery of high risk infants provides a practical, systematic designation for autologous MSC harvesting and transplant. Birth-associated tissue MSCs also present a unique tissue source for allogeneic transplantation because the majority of these tissues are discarded after delivery and their procurement is non-invasive (125). Therefore, an "off-the-shelf" product could more readily be developed for this particular cell isolate.

While MSCs can be isolated from most all birth associated tissues, UCB-MSCs, WJ-MSCs, AF-MSCs and placental-MSCs are the most studied. The primary disparity among these four cell isolates is MSC isolation efficacy from tissue harvest, with WJ-MSCs having 100% efficacy, AF-MSCs having approximately 90% efficacy, placental-MSCs having 62.5–100% efficacy, and UCB-MSCs having the least isolation efficacy of 60% at best (125). In addition to having the greatest isolation efficacy, WJ-MSCs also have the greatest expansion potential, suggesting that they may be the optimal birth-associated tissue MSC isolate with regards to ease of clinical translation (126). Placental MSCs may also have a slightly higher procoagulation effect (127), which may not be useful in the setting of an already ischemic intestine. Aside from differences in isolation efficacy, expansion potential, and coagulation profiles, all birth-associated tissue MSCs appear to have similar properties with regards to

differentiation potential and immunosuppressive capabilities, suggesting that all of these cell isolates have the potential to attenuate intestinal ischemia and reperfusion injuries.

COMPARATIVE ANALYSIS OF STROMAL CELL ISOLATES

IMMUNOMODULATORY PROPERTIES

The capacity of MSCs to exert anti-inflammatory and immunosuppressive effects in damaged tissues provides clinical value for patients with intestinal ischemic injuries. Through the release of various paracrine mediators and direct interaction with immune cells, MSCs suppress both the innate and adaptive immune responses to favor recovery and regeneration of tissue architecture (128, 129). The anti-inflammatory properties of MSCs minimize cytokine mediated damage to the intestinal epithelial barrier; thus, minimizing the risk for bacterial translocation and subsequent sepsis.

While all MSC isolates demonstrate some degree of immunomodulatory capabilities, differences with regards to the extent to which they subdue the immune response should be considered when assessing the optimal cell isolate to use for intestinal ischemia and necrosis injuries. Careful comparison of MSC alteration in T, B and NK cell activity is vital to understanding subsequent effects on cytokine production within the inflammatory milieu (130). Ribeiro and colleagues appreciated greater inhibition of B and NK cell activation by AT-MSCs compared to BM-MSCs, with minimal NK cell inhibition and no B cell inhibition by WJ-MSCs (131). They also observed AT-MSCs to have the strongest suppressive effects on T cell activation and proliferation.

Alternative studies assessing the relative effects of different MSC isolates on T cell proliferation have been less consonant. While Najar et al. corroborated the conclusion that AT-MSCs provided the greatest suppression of T cell proliferation (132), Li and colleagues observed the greatest decrease in T cell proliferation when these cells were cultured with WJ-MSCs, followed by PL-MSCs, AT-MSCs, and lastly BM-MSCs (133). They also appreciated that WJ-MSCs expressed the lowest level of HLA class II genes, compared to the other 3 populations of MSCs, with BM-MSCs expressing the highest level of HLA class II genes. These results suggest that WJ-MSCs may have the greatest T cell immunosuppressive potential, while simultaneously generating the least immunogenicity.

With regards to alterations in specific inflammatory cytokine levels, LPS-activated macrophages co-cultured with BM-, AT-, and UCB-MSCs exhibited decreased levels of inflammatory cytokines IL-1α, IL-6, and IL-8; however, only UCB-MSCs reached statistical significance (134). These results suggest that UCB-MSCs may exert a greater anti-inflammatory effect than both AT and BM-MSCs.

EASE OF ISOLATION AND AMPLIFICATION FOR WIDESPREAD THERPEUTIC USE

The ultimate goal with MSC therapy in intestinal I/R injury is widespread autologous or allogeneic use. In order to accomplish prevalent implementation, one must consider the ease of MSC isolation from the donor tissue, and the ability of the cells isolated to amplify to large enough numbers to employ therapeutic benefit.

For autologous MSC transplant, the isolation procedure that is least invasive and most tolerated by the patient would be preferred. This would favor the use of AT-MSCs in adults with acute mesenteric ischemia and birth-associated tissue MSCs in neonates with NEC or midgut volvulus. Pertaining to allogeneic transplant, birth-associated MSCs and AT-MSCs are the only MSC isolates that can be extracted from patient tissues that are normally discarded as medical waste, with birth-associated tissue being discarded following delivery and adipose tissue being discarded following routine liposuction. Additionally, cell yields from liposuction procedures generate significantly more MSCs than any other tissue specific MSC isolation procedure, making these cells the most widely available MSC isolate (135).

Prior to autologous transplant, MSCs must first be expanded ex vivo to sufficient numbers to provide maximal therapeutic benefit. The proliferation capacity of each tissue specific MSC varies and is evaluated using a colony forming unit-fibroblast assay or by doubling time. Li and colleagues observed WJ-MSCs had the shortest doubling time, followed by AT-MSCS, PL-MSCs, and lastly BM-MSCs (103). Since a shorter doubling time corresponds to a more rapid growth rate, this study suggests that WJ-MSCs and AT-MSCs have greater amplification potentials compared to PL-MSCs and BM-MSCs. Kern and colleagues appreciated the greatest expansion potential in UCB-MSCs with successful passages past P 10, compared to BM-MSCs (P 7) and AT-MSCs (P 8) (10). Additional studies have confirmed that UCB-MSCs have the most rapid expansion potential with the lowest senescence profile of the MSCs (134). This allows for longer culture lifespans with UCB-MSCs, thus generating a greater number of cells relative to initial MSC yields. While enhanced amplification and expansion potentials can compensate for lower initial cell yields, all three factors must be considered.

ATTENUATION OF INTESTINAL ISCHEMIA REPERFUSION INJURY

Although in vitro studies of immune suppression, growth factor production, and expansion and senescence are important in our understanding of MSCs for intestinal ischemia, what is most important is their efficacy in diminishing the effects of intestinal ischemia. A previous study by Watkins, et. al. compared the effectiveness of BM-MSCs and AF-MSCs in a model of intestinal I/R. They noted a significant decrease in histological injury score and intestinal permeability with cellular therapy, but noted no significant difference between these cells in terms of their effectiveness. Additionally, studies by our group examined BM-, AT-, and UCB-MSCs in a model of intestinal I/R injury. All MSCs improved survival, mesenteric perfusion, and histological architecture following injury as compared to differentiated cellular controls, but no difference was seen in these parameters between MSC cell isolates. These combined studies might suggest that differences in cellular niches may impact certain aspects of cellular function, but that ultimately, differences in harvest tissue source may not have a significant impact on overall outcomes following injury (Jensen, et al., in press, JSR).

CURRENT LIMITATIONS

SAFETY AND EFFICACY

Concerns regarding the tumorigenicity and malignant transformation potential of MSCs have plagued the progression of MSC treatment toward clinical trials. Studies first suggested

MSCs possess the potential to increase tumor burden due to their immunosuppressive effects (136). Additional concerns surround the immunsuppressive effects of MSCs and the potential for systemic infections. However, recent position papers on these topics have suggested a low probability for these concerns (137). A recent systematic review looking at 36 clinical trials found no association between MSC administration and de novo tumor formation or increased susceptibility to infection (138). This meta-analysis suggests the potential benefit of MSC therapy outweighs the potential risk, and that these theoretical risks may be more insignificant than credited.

BARRIERS TO CLINICAL IMPLEMENTATION

Prior to 2008, MSC-based Investigational New Drug Submissions and MSC treatment in clinical trials solely involved allogeneic MSCs derived from the bone marrow. Since then, MSC tissue source has greatly diversified with growing emphasis on the use of adipose tissue and birth-associated tissue MSCs (139). The primary limitation to the progression of clinical trials using MSCs in the treatment of patients with intestinal I/R injury is a lack of complete understanding of the behavior and activity of the cells following administration in vivo. The majority of what is known about MSCs has been gathered by observing the cells ex vivo, and studies have appreciated significant microenvironment impact on MSC activity and therapeutic efficacy (140–143). Studies further elucidating the in vivo actions of MSCs in the microenvironment of intestinal ischemia are pivotal to the progression of MSC therapy in patients with these diseases.

Additionally, identification of the optimal mode of MSC administration must also be assessed prior to clinical implementation. Since the exact mechanism by which MSCs exert their effect has not be defined, variation in therapeutic efficacy based on route of administration is probable. Intravascular administration has been associated with lung trapping and the formation of possibly lethal microemboli (144). Additionally, intravascular administration may promote activation of the coagulation cascade, which can be alleviated with the simultaneous application of heparin (127, 145). If paracrine factors predominately mediate the therapeutic effects of MSCs, then differentiation between intravenous, intra-arterial, intraperitoneal, and enema administration would favor the mode of administration that fostered the most conducive environment for MSC survival and proliferation. Further studies are still needed at this time to assess for variation in the ability of MSCs to attenuate intestinal ischemic injury based on the mode of administration so as to optimize stromal cell therapy moving forward.

Another key limitation to clinical use of MSCs in the treatment of intestinal ischemia and necrosis is the current lack of standardization for MSC isolation and preparation prior to administration. Srijaya and colleagues suggest one possible way to accommodate for these variables is by approaching MSC therapy in a way similar to conventional drug therapy, in which allogeneic MSC transplants could be an off the shelf product that can be optimally modulated to minimize these discrepancies (146). Even in patients receiving an autologous transplant, standardization of cell characteristics is vital to preserving consistency in patient treatment. Protocols must be established prior to clinical implementation to maximize MSC therapy effectiveness while minimizing treatment variability.

Clinical trials studying MSC therapy for intestinal ischemia will be invaluable in answering many of the questions that still pervade treatment specificities. Identifying the optimal cell number needed for maximal therapeutic efficacy and the most effective route of administration should be assessed prior to widespread clinical implementation. Additionally, clinical trials involving the administration of the acellular MSC secretome should be evaluated concurrently since the release of paracrine mediators is likely the primary mechanism by which the cells exert their therapeutic effect.

CONCLUSION

Mesenchymal stromal cell therapy in patients with varying etiologies of intestinal ischemia and necrosis presents a novel medical treatment option that could potentially minimize intestinal injury and improve patient outcomes. Through immunomodulation and tissue restoration, MSCs enhance the functional recovery of the intestinal epithelial barrier, minimize bacterial translocation, decrease the inflammatory cascade, and reduce the risk of systemic shock, multi-organ failure, and death. With a growing body of literature supporting a multitude of MSC isolates in the attenuation of intestinal injury, careful analysis of the benefits and pitfalls of each tissue specific cell isolate is vital. Differences among BM-MSCs, AT-MSCs, and birth-associated tissue MSCs with regards to their ability to attenuate intestinal injury, alter the immunomodulatory profile, and obtain and amplify quickly and effectively should be considered when selecting the optimal MSC isolate to use for therapeutic use.

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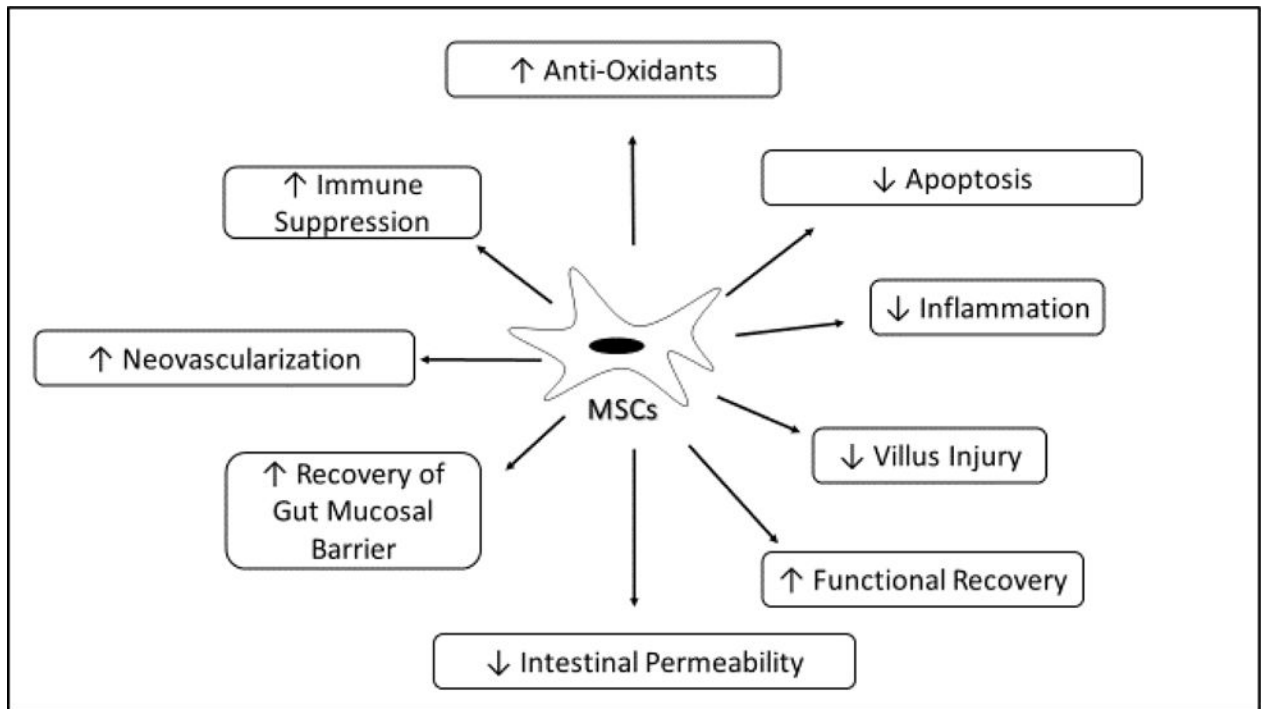
Figure 1.
MSCs are thought to afford protection to ischemic bowel in a number of ways. Ultimately, they work to decrease inflammation, enhance gut restitution, and promote recovery of the injured bowel.
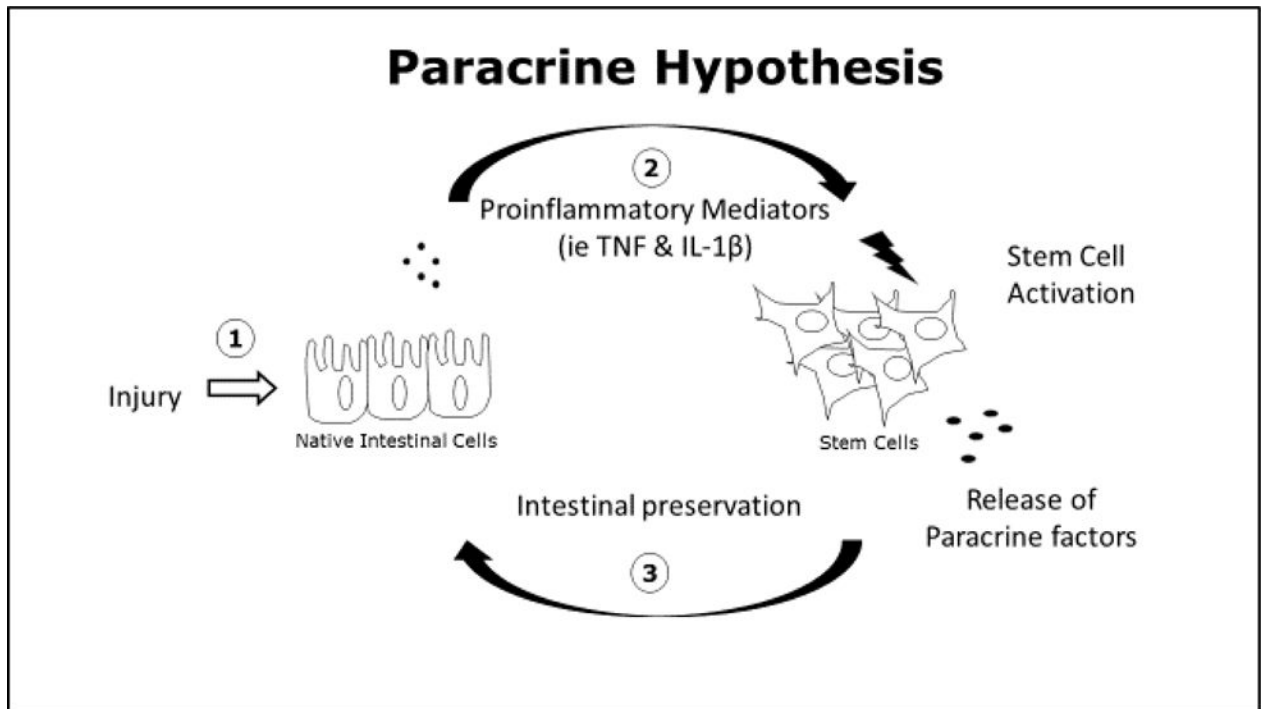
Figure 2.
MSCs are primarily thought to provide protection via the release of paracrine mediators. Injured intestines release proinflammatory signals which activate MSCs to release beneficial factors that can act in a paracrine fashion to facilitate recovery of the ischemic bowel.

Table 1

Comparative Analysis Of Most Optimal MSC Isolate to Use for Therapy of Intestinal Ischemia ("X" denotes best isolate for the given category)

	BM-MSCs	AT-MSCs	Birth Associated MSCs
Easily Isolated from Adults		X	
Easily isolated from Neonates			X
Obtained from Discarded Tissue		X	X
Most Widely Studied	X		
Rapidly Expandable			X
Least Senescent			X
Highest Yield of Cells Obtained		X	
Lowest MHC II			X
Most Immune Suppressive		X	X
Anti-Inflammatory Properties			X
Greatest Protection in an In-Vivo I/R Model	X	X	X