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Strategies to enhance paracrine potency of transplanted mesenchymal stem cells in intractable neonatal disorders

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Mesenchymal stem cell (MSC) transplantation represents the next breakthrough in the treatment of currently intractable and devastating neonatal disorders with complex multifactorial etiologies, including bronchopulmonary dysplasia, hypoxic ischemic encephalopathy, and intraventricular hemorrhage. Absent engraftment and direct differentiation of transplanted MSCs, and the "hit-and-run" therapeutic effects of these MSCs suggest that their pleiotropic protection might be attributable to paracrine activity via the secretion of various biologic factors rather than to regenerative activity. The transplanted MSCs, therefore, exert their therapeutic effects not by acting as "stem cells," but rather by acting as "paracrine factors factory." The MSCs sense the microenvironment of the injury site and secrete various paracrine factors that serve several reparative functions, including antiapoptotic, anti-inflammatory, antioxidative, antifibrotic, and/or antibacterial effects in response to environmental cues to enhance regeneration of the damaged tissue. Therefore, the therapeutic efficacy of MSCs might be dependent on their paracrine potency. In this review, we focus on recent investigations that elucidate the specifically regulated paracrine mechanisms of MSCs by injury type and discuss potential strategies to enhance paracrine potency, and thus therapeutic efficacy, of transplanted MSCs, including determining the appropriate source and preconditioning strategy for MSCs and the route and timing of their administration.

Despite recent advances in neonatal intensive care medicine, intractable neonatal disorders, including bronchopulmonary dysplasia (BPD) (1,2), severe intraventricular hemorrhage (IVH) (3), and hypoxic ischemic encephalopathy (HIE) (4), remain major causes of mortality and serious morbidities in survivors. Currently, few effective therapies are available to ameliorate injuries resulting from these disorders. Therefore, the development of new, safe, and effective therapies to improve the outcomes of these devastating neonatal disorders is an urgent issue.

Recently, several preclinical studies have demonstrated the promise of stem cell therapies in attenuating tissue injuries in newborn animal models of BPD (5–10), HIE (11), and IVH (12–15). Furthermore, phase I clinical studies in newborn infants with BPD (16), HIE (17), or severe IVH have shown that stem cell treatments for newborn infants might be safe, feasible, and potentially efficacious. Taken together, these findings suggest that stem cells might represent a paradigm shift in the treatment of currently intractable and devastating neonatal disorders. However, stem cell therapies are still experimental, and the precise mechanisms of action underlying them remain to be elucidated. This review summarizes the therapeutic potential of stem cells for these neonatal disorders. We focus on the paracrine protective mechanism underlying the beneficial effects of stem cell therapies and potential strategies to enhance the paracrine potency, and thus therapeutic efficacy of MSC transplantation to facilitate bench-to-bedside translation of stem cell therapies for these disorders.

PROTECTIVE MECHANISMS UNDERLYING STEM CELL THERAPIES

Pleiotropic Protective Effects of Stem Cell Therapies

Because the pathophysiological mechanisms of tissue injuries after BPD (18–21), severe IVH (22,23), or HIE (24) are complex and multifactorial, modulating only one factor might not be sufficient to ameliorate the disease. Therefore, a multifaceted therapeutic agent might be necessary to improve outcomes of patients with these intractable neonatal disorders. The pleiotropic beneficial effects of stem cell therapy, such as antiapoptotic, anti-inflammatory, antifibrotic, and antioxidative effects, have been observed in various animal models of BPD (5–8,10), severe IVH (13–15), or HIE (11,25,26). Furthermore, in addition to their beneficial anti-inflammatory effects, antibacterial activity of transplanted stem cells were observed in an animal model of *Escherichia coli* pneumonia (27). Considering their manifold therapeutic effects, stem cells, rather than other single therapeutic agents, might be the most promising candidates for therapies aimed at improving the prognosis of certain neonatal disorders.

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Engraftment and Regeneration

Recent insights into the biology of stem cells have ignited the hope of regenerating damaged organs by stem cell transplantation (28–34). Among various stem cell therapies (35,36), mesenchymal stem cells (MSCs) have emerged as the most promising therapeutic candidates in regenerative medicine, as they are more ethically and socially acceptable and show less tumorigenicity than embryonic stem cells. Because of their multilineage differentiation potential, the protective effects of MSC transplantation were initially ascribed to the engraftment of these cells in injured tissues and their subsequent transdifferentiation to repair and replace damaged cells (37,38). However, the very low rate of *in vivo* engraftment and differentiation of transplanted MSCs (8,15,39) suggests that long-term survival of MSCs might not be essential for their beneficial effects (28,40). Therefore, the therapeutic effects of MSC transplantation might not be associated with their differentiation and direct replenishment of damaged tissue parenchymal cells.

Paracrine Protection

Not only MSCs but also their conditioned media were able to ameliorate hyperoxia-induced (41,42) or lipopolysaccharide-induced (43) acute lung injuries. Moreover, therapeutic efficacy of other cell types, including endothelial progenitor and amniotic epithelial cells, in BPD has also been reported (10,44,45). These findings suggest that the protective mechanisms of MSC transplantation might mainly be related to their ability to stimulate the survival and recovery of damaged tissue by paracrine manners (**Figure 1**).

In various tissue injury models, transplanted MSCs exert anti-inflammatory, antifibrotic, antioxidative, antiapoptotic, antimicrobial, and permeability-decreasing paracrine effects via secretion of soluble factors. These soluble factors include various cytokines such as transforming growth factor-β (46) and interleukin-10 (ref. 47), growth factors such as vascular endothelial growth factor (48), hepatocyte growth factor (49), keratinocyte growth factor (50) brain-derived neutrophic factor (13,51), nerve growth factors (51), and neurotrophin-3 (ref. 51) insulin growth factor-1 (ref. 52), proteins such as angiopietin-1 (ref. 53), tumor necrosis factor-stimulated gene 6 (ref. 54), interleukin-1 receptor antagonist (55), lipocalin-2 (ref. 56) LL-37 (ref. 57), defensin-2 (ref. 58) and others. Recent reports also demonstrated that MSCs ameliorated and resolved inflammation by producing proresolving lipid mediators such as lipoxin A4 in acute lung injury (59) and resolvins in animal models of sepsis (60).

Recently, in addition to the cytokines and other secreted molecules mentioned above, MSC derived-extracellular vesicles (EVs) or exosomes (28,40,61–63) were shown to be key mediators of MSC therapeutic action (62–64). EVs derived from MSCs show therapeutic effects on various tissue injury in preclinical animal models by modulating immune response (65), ameliorating oxidative stress (66), and decreasing apoptosis (67), which is similar to what is achieved using the originating MSCs themselves. In recent studies using newborn animals, MSC-derived EVs protected neonatal lungs after hyperoxic injury (68), fetal brains after hypoxia–ischemia (64), and the intestine from experimental necrotizing enterocolitis (69).

The therapeutic mechanism of MSC-derived EVs or exosomes has been known to be related to the transfer of their vesicular cargo molecules, which mediate cell-to-cell communication. These vesicular molecules are biologically active and include proteins, RNAs such as messenger RNA, microRNA, and transfer RNA, as well as bioactive lipids (70,71). Detailed information regarding MSC-derived EVs or exosomes can be found in other focused reviews (72,73).

However, as a paracrine mechanism of action of MSCs, the importance of the presence of MSCs themselves rather than the MSC secretome for early recovery from ventilator-induced lung injury has been highlighted (74). In addition, attachment of live MSCs to the alveolar epithelium in acute lung injury was shown to be critical for mitochondrial transfer of MSCs (75).

Recently, transfer of mitochondria from MSCs has been demonstrated to be pivotal for the beneficial effects of MSCs (76–78). Recent reports showed that mitochondrial transfer occurred from MSCs to macrophages (78), partly through tunneling nanotubes (77), and the transfer of functional mitochondria in EVs is responsible for the anti-inflammatory effects of MSCs on macrophages in the inflammatory milieu (72,79).

Taken together, these findings suggest that the pleiotropic protective effects of transplanted stem cells might be mediated predominantly by paracrine action via the secretion of various biologic factors—a "hit-and-run" mechanism (80,81)—rather than by direct regenerative action (82–85). The use of a cell-free preparation comprising MSC-derived EVs or exosomes in place of stem cells shows excellent promise as a new therapeutic approach for neonatal disorders, as it circumvents side effects such as tumor formation that are associated with treatments with live stem cells.

Environmental Cues Trigger the Secretion of Paracrine Factors

Accumulating evidence indicates that MSCs release cytoprotective paracrine factors strictly in response to environmental cues (86,87). We observed that despite the use of the same human umbilical cord blood (UCB)-derived MSCs, pivotal cytoprotective paracrine factors varied by disease animal model. The protective effects of human UCB-derived MSC transplantation on hyperoxic neonatal lung injuries were associated with significant upregulation of hyperoxia-induced vascular endothelial growth factor (VEGF) and hepatocyte growth factor (11). Furthermore, knockdown of VEGF secreted by MSCs (7) transfected with small interfering RNAs specific for human VEGF abolished the protective effects of MSCs, such as attenuation of impaired alveolarization and angiogenesis, reduction of increased terminal deoxynucleotidyl transferase nick-end labeling - and ED-1-positive cells, and downregulation of proinflammatory cytokine expression, indicating that VEGF secreted by transplanted MSCs (7) and

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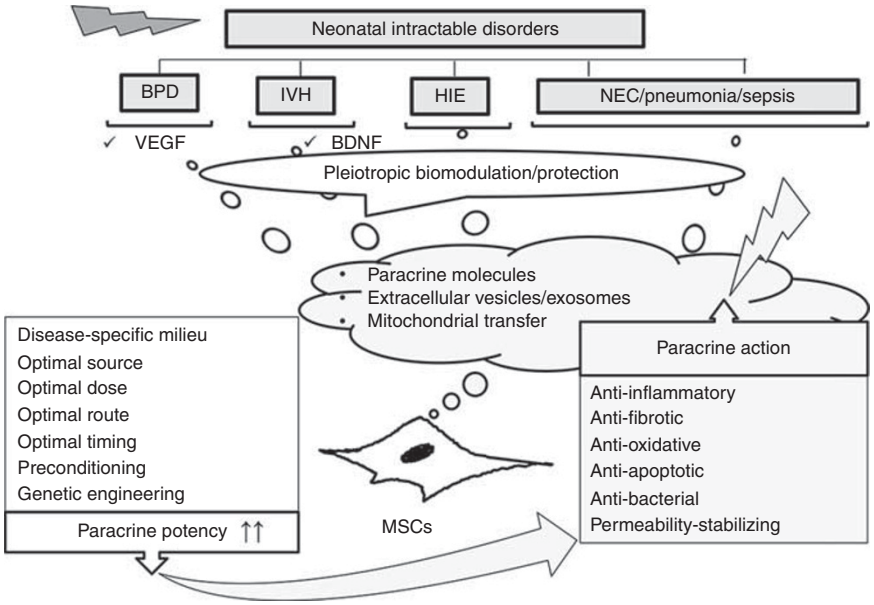

Figure 1. Schematic showing paracrine mechanism of pleiotropic biomodulation and protection provided by mesenchymal stem cells (MSCs) against neonatal intractable disorders such as bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), hypoxic–ischemic encephalopathy (HIE), and others. Phase I clinical trials in newborn infants have shown that stem cell transplantation is safe and feasible in BPD, IVH, and HIE. Several preclinical evidences of protection against other diseases such as necrotizing enterocolitis (NEC), pneumonia, and sepsis post-MSC transplantation or application of MSC-secreted extracellular vesicles or exosomes in animal models are available. MSCs locally or systemically transplanted into various tissue injuries exert anti-inflammatory, antifibrotic, antioxidative, antiapoptotic, antibacterial, and permeability-stabilizing paracrine actions through the secretion of soluble paracrine molecules. Among them, MSC-derived extracellular vesicles or exosomes are known as the key mediators of MSC therapeutic effects. Moreover, transfer of mitochondria from MSCs to host cells is one of the important paracrine mechanisms underlying the beneficial effects of MSCs. The paracrine potency of MSCs are associated with disease-specific environmental milieu, and potential strategies for enhancing the paracrine potency of MSCs include optimal determination of cell source, dose, route, and timing for MSC transplantation. Furthermore, various preconditioning and genetic engineering of MSCs can potentiate the paracrine potency of MSCs. MSC-secreted vascular endothelial growth factor (VEGF) and brain-derived neurotrophic factor (BDNF) are critical paracrine factors mediating protection obtained after MSC transplantation against BPD and severe IVH, respectively.

contained within MSC-derived exosomes (not yet published) is a critical paracrine factor that plays seminal roles in attenuating hyperoxic neonatal lung injuries. Although the same human UCB-derived MSCs as those used to treat neonatal hyperoxic lung injuries were transplanted into a newborn animal model of severe IVH, we observed significant upregulation of brain-derived neurotrophic factor (BDNF) both in DNA and antibody microarray analyses (13). Furthermore, in newborn rats with severe IVH, knockdown of BDNF secreted by MSCs abolished the neuroprotective effects of MSCs, such as significantly reduced posthemorrhagic hydrocephalus and impaired behavior, increased apoptosis, inflammation, and astrogliosis, and reduced myelination, indicating that BDNF secreted by transplanted MSCs is a critical paracrine factor that plays critical roles in attenuating severe IVH-induced brain injuries in neonatal rats. Additionally, Toll-like receptor-4 (TLR-4) signaling in transplanted MSCs and the subsequent secretion of β-defensin 2 was essential in mediating the antibacterial and anti-inflammatory protective effects of MSCs in acute lung injuries following *E. coli*-induced pneumonia (27). Our conflicting data on the critical role of the proinflammatory phenotype of TLR-4-primed MSCs (88), which exerted anti-inflammatory properties in *E. coli*-induced acute lung injuries, suggest that MSCs sense and control host inflammation by switching between their roles as proinflammatory or anti-inflammatory mediators (89). In addition, TLR-4 in MSCs plays pivotal roles in eliminating pathogens by augmenting antibacterial effects and reducing host tissue injuries by attenuating the inflammatory response (90,91). Collectively, these studies suggest that key paracrine factors secreted by MSCs from the same source play important roles in mediating the therapeutic effects of MSCs in different preclinical disease models (11,13,48), suggesting that there is a crosstalk and interplay between the host tissue and transplanted MSCs (61,92). Therefore, unlike drug treatments that deliver a single agent at a specific dose, transplanted MSCs act as a "paracrine factors factory" that sense the microenvironment of the injury site and secrete various paracrine factors that exert several reparative functions, including antiapoptotic, anti-inflammatory, antioxidative, antifibrotic, and/or antibacterial effects in response to local microenvironmental cues to enhance the regeneration of damaged tissue (86).

Moreover, recently, the change of the name of MSCs into "medicinal signaling cells" were proposed instead of calling as "stem cells" because transplanted MSCs to treat the diseases act their primary beneficial and medicinal function at the injury sites of the body through their secretory action (93).

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POTENTIAL STRATEGIES TO ENHANCE PARACRINE POTENCY OF STEM CELL THERAPIES

As the therapeutic efficacy of MSCs seems to be dependent on the paracrine potency of MSCs, the following potential strategies to enhance the paracrine potency of MSCs, including determining the best source, route, timing, and preconditioning approach for MSCs, might improve the therapeutic efficacy of transplanted MSCs (9,35,82,84,94,95).

Paracrine Potency Assay

As implied by the relatively loose minimal criteria for defining MSCs, including their fibroblast-like morphology, plastic adherence in culture, defined cell surface marker expression profiles (CD 73-, 90-, and 105-positive and CD 45-, 34-, 14-, and 11b-negative), and capacity for differentiation into cell types such as adipocytes, chondrocytes, and osteoblasts (96), MSCs might represent a heterogeneous cell population (83,96). Therefore, their paracrine potency and therapeutic efficacy might vary with source (97–99) and batch (100) of MSCs. Therefore, identifying a specific marker or feature to predict the *in vivo* therapeutic potential of transplanted MSCs is the Holy Grail in clinical translation of MSCs transplantation for use in neonatal disorders (101,102).

The close association of the therapeutic efficacy of MSCs with their paracrine potency suggests that measuring paracrine potency of MSCs might be a surrogate measure of their *in vivo* therapeutic efficacy. The expression of soluble tumor necrosis factor receptor-1 in MSCs was quantitatively assayed as a surrogate measure of potency for the treatment of steroid-resistant acute graft-vs-host disease (103). However, as the clinical trial failed to meet the primary criterion of therapeutic efficacy, it remains unknown whether soluble tumor necrosis factor receptor-1 by MSC expression levels are predictive of the *in vivo* therapeutic efficacy of MSCs. An *in vitro* assay measuring IL-10 released from blood cells might be useful in analyzing the potency of MSC-conditioned media and MSC lysates (104). Our data indicating a critical role for VEGF secreted by MSCs in BPD (7) and in BDNF and severe IVH (13) suggests that quantification of these factors might be used as a potency biomarker assay to select MSCs with the best predicted *in vivo* therapeutic efficacy for application in neonatal disorders. Further studies will be necessary to identify robust and predictive markers of therapeutic efficacy and develop quantitative assays that measure the paracrine potency of transplanted MSCs and predict their *in vivo* efficacy.

Optimal Cell Source

MSCs obtained from gestational tissues such as UCB (105), Wharton's jelly, or umbilical cords (106) showed increased secretion of chemokines, proinflammatory proteins, and growth factors, as well as higher rate of cell proliferation, than MSCs obtained from adult adipose tissue or bone marrow. Furthermore, in our recent study comparing the *in vivo* therapeutic efficacy of adipose tissue- and UCB-derived MSCs and UCB-derived mononuclear cells in protecting against hyperoxic lung injuries in newborn rats, UCB-derived MSCs exhibited better therapeutic efficacy in attenuating hyperoxic lung injuries, with effects such as impaired alveolarization and angiogenesis, increased cell death, alveolar macrophages, and proinflammatory cytokines, and increased secretion of VEGF and hepatocyte growth factor, compared with that of adipose tissue MSCs or UCB-derived mononuclear cells (10). Collectively, as donor age negatively impacts the paracrine potency of stem cells and thus the therapeutic efficacy of stem cell therapies, birth-associated tissues such as UCB or Wharton's jelly might be the optimal source for MSCs in future clinical applications to protect against intractable neonatal disorders (107).

Preconditioning of Stem Cells

There is growing evidence that *in vitro* preconditioning of MSCs can optimize their paracrine potency and thus their therapeutic potential (82,108–110). Preconditioning of MSCs includes exposure of *in vitro* MSCs to hypoxic or anoxic conditions (111–114); e.g., the addition of growth factors such as epidermal growth factor (115), glial cell-derived neurotrophic factor (116), insulin-like growth factor-1 (ref. 117); cytokines such as tumor necrosis factor-α (118), or stromal cell-derived factor-1 (ref. 119); hormones such as angiotensin-II (ref. 116), melatonin (120), or lipopolysaccharides (121); and pharmacologic or chemical agents such as hydrogen peroxide (122), deferoxamine (123), or diazoxide (124). Although manifold mechanisms, including improved *in vivo* survival and engraftment after transplantation (125), might be involved, enhancement of the therapeutic potential of MSCs by preconditioning seems to be mediated primarily by stimulating the secretion of growth factors, cytokines, and other proteins, as well as the release of exosomes and EVs from MSCs (114). Enhanced secretion of paracrine factors by preconditioned MSCs has various trophic, immunomodulatory, antiapoptotic, and proangiogenic effects (82). However, the paracrine profiles of the secretomes obtained from preconditioned MSCs are known to vary according to the preconditioning regimen used. Therefore, although encouraging preclinical data increases the hope that preconditioning can enhance the reparative and regenerative capacities of MSCs, additional comprehensive studies will be necessary to decipher the whole secretomes of MSCs, including exosomes secreted after different preconditioning regimens (125), and, based on these data, to establish the optimal preconditioning regimen and schedule to ensure maximal paracrine potency and therapeutic efficacy of transplanted MSCs.

Genetic Engineering of Stem Cells

One promising therapeutic strategy is enhancing the release of a specific paracrine regenerative factor from stem cells by overexpressing it through genetic engineering (108). In agreement with this hypothesis, overexpression of VEGF in MSCs enhanced stem cell-mediated therapeutic efficacy in neural and cardiac repair (126), and intracerebral transplantation of BDNF gene-modified MSCs 1 day after middle

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cerebral artery occlusion promoted functional recovery and reduced infarct sizes in rats (127). In contrast, intranasal transplantation of BDNF-overexpressing MSCs 3 days after neonatal stroke failed to promote recovery from middle cerebral artery occlusion-induced brain injuries (128). Overall, these findings suggest that several details, including route, timing, and dose, might be confounding variables that determine the success or failure of transplanting genetically engineered MSCs. Further studies will be necessary to confirm this. Apart from therapeutic efficacy, safety issues are major limitations to future clinical therapeutic applications of genetically engineered MSCs, as viral integration in the host genome increases tumorigenicity (129). Although the risk of tumorigenicity can be reduced by using an adenovirus vector that does not integrate into the host genome instead of lenti- or retroviruses, further studies that closely monitor the fate of transplanted gene-modified MSCs will be necessary to address these safety concerns.

Optimal Route of Administration

Determining the optimal route for stem cell transplantation might be a critical issue for clinical translation of this therapy. Systemically or intravenously administered MSCs are known to migrate and localize chemotactically to injury sites in host tissue (34,130). Furthermore, systemically injected MSCs are usually retained mainly in the lungs and other organs such as liver, spleen, and kidneys (42,131). In addition, systemic intravenous or intraperitoneal routes of MSC transplantation are less invasive and might be more suitable for use in unstable newborn infants than the more invasive local route of administration such as intratracheal or intracerebroventricular injection. However, systemically transplanted MSCs have the disadvantage of nonspecific targeting because of their broad dissemination and ability to cross an intact blood–brain barrier. In our previous studies, although four- to fivefold higher doses of MSCs were administered intravenously or intraperitoneally (systemically) than administered intratracheally or intraventricularly (locally), significantly higher numbers of donor MSCs were correctly localized in the lungs or brains of a newborn rat model of hyperoxia (5) or severe IVH (14), respectively. Moreover, local, rather than systemic, transplantation of MSCs was associated with greater paracrine potency in the production of trophic factors such as VEGF and hepatocyte growth factor (11), and thus better therapeutic efficacy against newborn BPD (5) and severe IVH (14) in animal models. Paracrine signals are transmitted only over short distances via factors that exert local effects (82). The cross-talk between the microenvironment of injured host tissues and MSCs activates MSCs to produce cytoprotective paracrine factors. Therefore, proximity of the donor cells to the injury site is essential for their paracrine-protective effects. Collectively, these findings support the assumption that local, rather than systemic, administration of MSCs might be the optimal route for MSC transplantation to enhance tissue repair.

Determining the Optimal Timing

Determining the optimal timing for MSC transplantation is another important factor in clinical translation of this therapy. Although the therapeutic windows for MSC transplantation to address neonatal disorders vary widely according to the animal model used and the severity of tissues injury, early rather than late transplantation of MSCs better attenuated hyperoxic lung injuries (6), severe IVH (132), neonatal stroke (133), and hypoxic–ischemic encephalopathy (11). Moreover, our data on upregulation of growth factors such as VEGF and hepatocyte growth factor with early but not with late transplantation of MSCs, despite higher donor cell localization in neonatal hyperoxic lung injuries (6), suggest that the protective effects of MSCs, including proangiogenic, antioxidative, anti-inflammatory, antifibrotic, and antiapoptotic effects, might be associated with or mediated by enhanced secretion of these paracrine growth factors (134). In contrast, prolonged survival and engraftment of donor cells might not be essential for their paracrine potency (28,40). Moreover, as inflammation might affect the secretion of these growth factors by MSCs (135), MSC transplantation soon after injury might be essential for their paracrine potency and the resultant therapeutic efficacy. Overall, the therapeutic time window for stem cell therapy might be narrow, and MSC transplantation as close as possible to the time of brain insult might be optimal for increased paracrine potency and therapeutic outcomes. Further studies will be necessary to confirm this.

Determining the Optimal Dose

Considering various preclinical data showing wide variations in the paracrine potency and therapeutic efficacy of transplanted MSCs according to the timing and route of stem cell administration in different animal models of BPD (6,11), HIE (136), and IVH (14), optimal doses need to be determined at the specific injury site and with the specific timing and route of MSC transplantation.

CONCLUSION

Recent preclinical and clinical studies suggest that MSC transplantation could be a game changer for treating currently intractable neonatal disorders with complex multifactorial etiologies, including BPD, HIE, and IVH. MSCs act as "paracrine factors factory" by secreting various paracrine factors are responsible for their pleiotropic effects in response to microenvironmental cues in the injured host tissues. Therefore, MSC transplantation might open a new chapter in tailor-made neonatal medicine. However, further meticulous studies to delineate the paracrine-protective mechanisms of MSCs with specific injuries and to determine strategies, including the best source, preconditioning regimen, route, timing, and dose of transplanted MSCs, to enhance the paracrine potency and, thus, the therapeutic efficacy of MSCs will be necessary for successful clinical translation of these therapies.

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