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Therapeutic Potential of Mesenchymal Stem Cells and MSC-derived Extracellular Vesicles for Bronchopulmonary Dysplasia: From Preclinical Promise to Clinical Trials

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ABSTRACT

Background: Bronchopulmonary dysplasia (BPD) is the most common respiratory complication in infants born extremely preterm. Despite advances in neonatal care, including improved respiratory support, nutrition, and infection control, no definitive cure for BPD has been identified. This study aimed to synthesize contemporary evidence on mesenchymal stem cell (MSC)-based strategies and MSC-derived extracellular vesicles (MSC-EVs) for BPD, and to discuss their* therapeutic therapeutic potential and remaining challenges.

Methods: This study reviews clinical and preclinical data across multiple models to evaluate the therapeutic effects of MSCs and MSC-EVs for the treatment of BPD.

Results: The reviewed literature highlights that both MSCs and MSC-EVs improve alveolar and vascular development, reduce inflammation and fibrosis, and mitigate pulmonary hypertension. MSC-EVs offer cell-free advantages, including reduced immunogenicity, lower tumorigenic risk, enhanced stability, and tunable targeting. Although MSCs and MSC-EVs hold substantial promise, Phase 1 safety data for EV-based therapies in neonates are lacking, underscoring the necessity of early clinical trials to define tolerability and pharmacodynamics.

Conclusion: Transformative advances have been made in the treatment of well-recognized BPD. The field is moving toward standardized EV production, definitive trial design, and exploration of MSC-EV–based therapies as safer, scalable medical countermeasures, with biomarker-guided patient selection and multi-omics integration to refine precision therapy for BPD.

Introduction

Bronchopulmonary dysplasia (BPD) is the most prevalent respiratory disorder in infants born extremely preterm. It was First described by Northway in 1967, during a period when it was considered a frequently fatal condition.[1] Inflammation, oxidative stress, and parenchymal fibrosis play a critical role in the pathogenesis of the disease.[2] The number of secondary septa and alveoli decreases in infants with BPD, resulting in a reduced alveolar surface area, which is essential for effective gas exchange. The muscle layer in the arterioles becomes thickened, leading to increased vascular resistance and contributing to pulmonary hypertension. Angiogenesis is impaired, leading to the formation of abnormal vessels and capillaries. The formation of more fibrotic tissue leads to the widening and thickening of the interstitial spaces. Additionally, an imbalance between reactive oxygen species (ROS) production and the antioxidant Antioxidant system* insufficiency insufficiency leads to oxidative stress, thereby contributing to the development of BPD.[3]

Low gestational age is the primary factor associated with the Development of BPD. In addition to the well-documented deficiency of surfactant, the immature lung exhibits several characteristics that increase the risk of BPD, including underdeveloped airway structural components (such as extracellular matrix, collagen, and elastin), inadequate antioxidant mechanisms, decreased compliance, and insufficient fluid clearance. These characteristics increase the lung's susceptibility to injury and play a key role in the development of BPD in vulnerable tissues.[4] Therefore, the most significant risk factors for BPD are prematurity and low birth weight. Clinical epidemiological studies indicate that the incidence of BPD in very premature infants is approximately 40%, with the rate increasing as gestational age decreases. Almost 80% of infants born between 22 and 24 weeks of gestation are diagnosed with BPD, while only about 20% of infants born at 28 weeks of gestation develop the condition. This data Illustrate how gestational age significantly affects the likelihood of developing BPD.[5] Other perinatal risk factors include intrauterine growth restriction (IUGR), male sex, ethnicity [6], maternal smoking [7], and chorioamnionitis.[8] Genetic risk factors may also play a role in the development of BPD, prompting ongoing research for potential genetic markers associated with the condition.[9] In addition to perinatal risk factors, several postnatal risk factors exist, including hyperoxia, mechanical ventilation, sepsis, symptomatic patent ductus arteriosus (PDA), and extrauterine growth restriction (EUGR). All these risk factors influence the development of BPD by modifying various biological pathways that play a role in lung development and function. These alterations can lead to impaired angiogenesis, disrupted inflammatory responses, and abnormal lung structure, ultimately increasing the vulnerability of the lungs in premature infants.[10]

The mortality associated with BPD is notably high in the early stages. Moreover, the condition can lead to serious adverse outcomes in the respiratory, circulatory, and even the nervous systems as the infant matures. These complications significantly impact both the survival rate and the quality of life for affected individuals, highlighting the long-term challenges associated with BPD.[11] In recent decades, there have been significant advancements in neonatal intensive care and the development of new treatment strategies, which have resulted in a substantial improvement in the survival rates of preterm newborns. These improvements encompass better respiratory support, improved nutrition, and stronger infection control, contributing to better outcomes and quality of life for these vulnerable infants.[12]

Corticosteroids have long been utilized to improve respiratory function in preterm infants, but their systemic use has decreased due to the side effects, particularly neurological risks such as cerebral palsy.[13] The

majority of the affected infants now survive due to the application of advanced neonatal care techniques, the utilization of effective respiratory support devices, and surfactant treatments.[14] However, regardless of prenatal and postnatal interventions, BPD persists as the most serious chronic respiratory disease in preterm-born infants.

Over the past decade, preclinical and clinical studies have shown that therapies involving mesenchymal stem cells (MSCs) provide a novel treatment strategy for BPD.[15] Furthermore, it has been discovered that stem cells primarily function through extracellular vesicles (EVs) and other forms of paracrine signaling. Currently, EVs are regarded as a novel means of cell-to-cell communication, which plays a role in various physiological and pathological processes.[16] The development of therapeutics utilizing EVs is considered the most hopeful next-generation approach for preterm infants susceptible to BPD. Hence, this review outlines the progress in BPD treatment with MSCs and MSC-EVs in order to offer new possibilities for the management of BPD.

MSC-Based Therapies for BPD

The use of MSCs represents a novel and promising therapeutic approach for multiple diseases, due to their capacity for self-renewal, high proliferative potential, and ability to differentiate into mesodermal lineage Cells. They also exhibit immunomodulatory and anti-inflammatory Effects that facilitate allogeneic transplant procedures.[17] A comprehensive systematic review of all preclinical MSC studies in experimental BPD models confirms that cord- or cord blood–derived MSCs consistently enhance lung structure and function, reduce pulmonary hypertension, decrease inflammation and fibrosis, and improve lung vascular development in BPD models.[18] These outcomes extend into adulthood and have not been associated with any long-term adverse consequences, including tumor formation.[19]

The Mechanisms of MSCs in the Treatment of BPD

MSCs are believed to act through two main mechanisms by which they exert effects: (i) paracrine effects of MSC-derived humoral factors, which have immunomodulatory, anti-inflammatory, angiogenic, and antibacterial actions; and (ii) tissue regeneration via the MSCs' multilineage differentiation capacity at the injury site, although this effect is limited. In hyperoxic neonatal lungs, differentiation appears quantitatively insignificant, with therapeutic benefits primarily attributed to paracrine signaling.

MSCs influence various immune cells—activated T cells, B cells, NK cells, dendritic cells, Monocytes/macrophages, neutrophils, and mast cells—through paracrine mechanisms. MSCs exert their paracrine effects by secreting various bioactive mediators, including cytokines such as IL-6 and IL-8; vascular endothelial growth factor (VEGF); extracellular matrix molecules like collagen and elastin; and exosomes. [20] Indeed, multiple preclinical studies have reported MSC engraftment rates below 1% within 48 Hours post-administration, indicating that differentiation into lung-specific cell types is not a major contributor to repair in BPD models.[18, 19, 21]

Experimental Studies on MSC-Based Treatment of BPD

Several investigations using MSC-derived conditioned medium in experimental BPD indicate that MSCs exert their effects in BPD models mainly via paracrine factors Rather than tissue regeneration. These studies reported protection of pulmonary epithelial and microvascular endothelial cells from oxidative stress, prevention of hyperoxia-induced impairment of alveolar development, and lung repair via stimulation of bronchioalveolar stem cells.[19] In MSC-treated BPD animal models, Increased numbers of bronchioalveolar stem cells and distal epithelial progenitors was observed compared to untreated groups. However, the expanded stem/progenitor pool arises from stimulation of the host's own repair mechanisms via paracrine signaling, not from replacement by exogenous MSCs.[21] Consistently, it has been

confirmed that engraftment rate of human MSCs in hyperoxia-exposed neonatal lungs is very low, decreasing from detectable levels on the first day after administration to nearly zero within four days, as assessed by immunofluorescence and human-specific sequencing.[19] Therefore, the therapeutic impact of MSCs in BPD models likely derives from paracrine-mediated repair, rather than regenerative effects resulting from the engraftment and differentiation of the administered cells. This characteristic may underlie the diverse functions of MSCs, which include not only potent anti-inflammatory effects but also antifibrotic, antiapoptotic, antioxidant, and pro-angiogenic activities.[17]

Studies on MSC-Based Treatment in Neonates with BPD

The strong preclinical evidence has led to prompt initiation of early-phase clinical investigations. Several clinical trials have evaluated MSC therapy in patients with BPD (Table 1).[22-27] In the first-in-human clinical trial for treatment of BPD using MSC, human umbilical cord blood-derived MSCs (hUC-MSCs) were administered intratracheally. The study demonstrated the safety and feasibility of MSC therapy, with significant reductions in inflammatory marker expression observed in tracheal aspirates both short- and long-term. In this study, umbilical cord tissue is considered a premier source of MSCs due to its easy accessibility, reduced antigenicity, and initial proliferative potential, although these cells may undergo senescence after several passages.[22] Ahn et al. conducted a phase I trial in nine preterm infants (GA 23–29 weeks) requiring ventilation within 5–14 days after birth, administering intratracheal umbilical cord MSCs. The procedure was well tolerated, with no safety concerns reported.[23] Another study demonstrated that MSC delivery by either intratracheal or intravenous routes diminished proinflammatory cytokines in tracheal aspirates, improved alveolarization, and decreased BPD severity.[24] A different clinical trial Investigated intravenous administration of allogeneic hUC-MSCs for severe BPD, with gradually increasing doses to establish safety data. Notably, it is the first trial to examine the therapeutic impact of hUC-MSCs in children with severe BPD, beyond prevention.[25] A more recent phase II trial employing the same proprietary cell product reported its findings.[26] At present, numerous MSC-focused clinical trials are either ongoing or being planned across countries to assess their effectiveness in preventing or treating BPD in premature infants. With results from current trials anticipated by clinicians, MSC therapy may soon be used clinically for human BPD; meanwhile, a study found that a single intravenous dose of hUC-MSCs was tolerated in thirteen patients with severe BPD.[27] Although MSCs derived from umbilical cord tissue exhibit reduced antigenicity compared to adult-derived MSCs, they may still be subject to immune clearance in neonates via maternal IgG and innate immune mechanisms such as NK cells and macrophages.[20, 25]

Table 1. Clinical Trial Studies of MSC-Based Therapies for BPD.

Author (Year)	Type of Study	Key Findings	Ref.
Chang et al. (2014)	Phase I clinical trial	First-in-human intratracheal hUC-MSCs for BPD; demonstrated safety, feasibility, and reduction of inflammatory markers.	22
Ahn et al. (2017)	Phase I follow-up clinical trial	Two-year follow-up confirmed safety and potential benefits of intratracheal MSCs in preterm infants with BPD.	23
Álvarez et al. (2018)	Case series (2 infants)	Off-label MSC therapy reduced proinflammatory cytokines and improved alveolarization in severe BPD.	24
Wu et al. (2020)	Clinical trial protocol	Randomized controlled trial protocol Investigated IV hUC-MSCs in severe pediatric BPD patients.	25
Ahn et al. (2021)	Phase II clinical trial	IV hUC-MSCs in preterm infants with BPD demonstrated safety and promising efficacy in reducing BPD severity.	26
Xia et al. (2023)	Phase I clinical trial	A single IV dose of hUC-MSCs in severe BPD was well tolerated in children, Confirmed safety in a dose-escalation design.	27

Currently, there is no consensus on the best administration parameters for MSC therapy in BPD. Evidence suggests that the optimal dose may vary depending on the location of injury and the route of administration. In preclinical BPD models, MSCs are predominantly delivered via intratracheal instillation, intravenous administration, and intraperitoneal injection.[15] Sung et al.'s preclinical study suggests that intratracheal administration of umbilical cord blood–derived MSCs provides superior therapeutic benefits compared with intravenous infusion in a model of lung injury.[28] The meta-analysis by Augustine et al. indicates a significant therapeutic advantage of MSCs over controls in all routes examined (intraperitoneal, Intratracheal, intravenous), with intravenous administration showing greater efficacy than intratracheal delivery. Bone marrow–derived MSCs were more common than umbilical cord–derived MSCs. No No differences in dose-response were observed among low, middle, and high doses. MSC treatment was beneficial relative to controls, regardless of treatment or assessment timing.18 These reports suggest that, despite diverse management strategies, MSC therapy contributes to improved alveolarization in BPD models.

Challenges for Clinical Application of MSCs

As neonates with BPD enter these early-phase investigations, numerous methodological and translational challenges must still be addressed. MSCs can be isolated from various adult tissues (bone marrow, adipose tissue, and umbilical cord), but Adult-tissue-derived MSCs exhibit substantial heterogeneity, with observed differences in proliferation, senescence, immunomodulation, and cytokine secretion profiles. This heterogeneity underscores the need to select MSCs according to specific indications and to monitor their functional traits, since exposure to whole blood can trigger immediate inflammatory responses that vary by donor and increase with higher doses. In contrast, MSCs derived from pluripotent stem cells (PSCs) tend to be more homogeneous, with higher proliferative potential and stronger immunomodulation, potentially mitigating some drawbacks of adult MSCs. Therefore, PSC-MSCs may offer an alternative cellular source that overcomes many of the limitations associated with adult MSCs.[15] Safety is a central issue in MSC transplantation for researchers and clinicians. MSCs exert therapeutic effects, including immunosuppression, antifibrotic activity, angiogenesis, and tissue repair; however, concerns persist regarding genomic instability, chromosomal aberrations, and potential tumor-promoting effects.[15] Ahn et al. found intratracheal MSC therapy to be safe, with no obvious adverse reactions during follow-up to the age of 2 years.23 In a study of 12 extremely low birth weight (ELBW) infants with BPD, it was reported that intratracheal administration of a single dose of hUCB-MSCs was well tolerated, demonstrating safety and feasibility.[29] This finding influences considerations for clinical use of MSCs, including storage, handling, and timing of administration.

Despite early trials suggesting safety and preliminary efficacy, there is currently no standardized clinical protocol for BPD regarding dosage, timing, or predictive models, underscoring the need for larger, well-designed studies. Moreover, MSC-derived products (exosomes, microRNAs, and secreted factors) indicate potential therapeutic value. These derivatives may offer safer and more practical alternatives to direct MSC transplantation by reducing the risks associated with cell-based therapies.[15]

In summary, clinical investigations of MSCs for the treatment of BPD have demonstrated benefits, including anti-inflammatory effects, mitigation of lung injury, and antifibrotic potential. Nevertheless, widespread clinical adoption of BPD requires further multicenter, large-scale, prospective randomized trials.

MSC-EV-Based Therapies for BPD

MSC-EVs are heterogeneous vesicles, ranging from nanometer to micrometer in size, secreted by MSCs. They play a key role in

repairing tissue and organ damage, serving as the primary medium for communication between MSCs and damaged tissues. In particular, MSC-derived EVs (e.g., exosomes, microvesicles, microparticles, ectosomes, and endosomes) function as essential mediators of intercellular communication, reprogramming damaged cells via transfer of bioactive cargo.[30]

In recent years, the focus in regenerative medicine has shifted from MSC engraftment and differentiation toward their therapeutic effects mediated by paracrine secretion. As mentioned above, current data suggest that paracrine signaling is the primary mechanism of action for MSC-based therapies in BPD. MSCs communicate with injured lung tissue primarily via EVs that deliver anti-apoptotic, anti-inflammatory, and pro-angiogenic bioactive substances, highlighting paracrine signaling as the primary mechanism.[31]

MSC-EVs, with MSC-exosomes in particular, may offer advantages over whole-cell therapies, given their reduced membrane-bound protein expression (including MHC) and the absence of inherent tumorigenic potential. They tend to be less immunogenic than parent cells and can be modified to enhance bioavailability and targeting.[32] Their stability during cryopreservation and ease of drug formulation further support their use as targeted therapy delivery vehicles.[33] Therefore, MSC-EVs represent a rapidly expanding area of research for BPD treatment, though their evaluation remains largely limited to preclinical animal studies.[34]

The Mechanisms of MSC-EV-Based Therapies in the Treatment of BPD

Several studies indicate that EVs mediate tissue regeneration and therapeutic effects primarily through the biomolecules they carry. EV surface proteins and the Cargo molecules, including mRNA and miRNA, can trigger signaling in target cells and influence their behavior after binding and internalization.[34]

MSC-EVs contain several proteins associated with angiogenesis, including FGF, PDGF, and VEGF. VEGF acts as a key regulator of pulmonary vessel growth, development, and repair across embryonic, fetal, and postnatal periods, and is also involved in neonatal hyperoxia–induced lung injury. Therefore, VEGF-related angiogenesis is thought to be one mechanism by which MSC-exosomes help treat BPD, by reducing endothelial cell apoptosis, increasing endothelial proliferation, lowering vascular permeability, and promoting new vessel formation.[35]

Emerging evidence shows that MSC-EVs harbor multiple anti-apoptotic proteins and can influence the apoptosis cascade, thereby mitigating conditions closely linked to programmed cell death.[36] Alveolar epithelial type II cells (AEC-II), as progenitors of the lung epithelium, are the primary target cells in BPD-related lung epithelial injury. Excessive apoptosis of AEC-II cells has been reported as a primary driver of BPD.[37] An in vitro study showed that in hyperoxic environments, treatment with human umbilical cord MSC-EVs improved tube-like formation and cell proliferation in HUVECs and decreased apoptosis in MLE-12 cells.[36] However, additional experimental studies are required to elucidate the underlying mechanism.

Additionally, it has been shown in hyperoxic neonatal mice that treatment with exosomes from MSC modulated multiple inflammation and immune-response genes.[38] In BPD, alveolar macrophages play a central role in pulmonary immune response, participating in both the initiation and resolution of inflammation. MSC-exosomes change how macrophages behave: they lower the proinflammatory M1 state and enhance an anti-inflammatory M2 state, evident in both in vitro assays and in vivo models. It has been suggested that tumor necrosis factor alpha-stimulated gene-6 (TSG-6) is an essential therapeutic molecule that protects rats from pulmonary inflammation and injury. Hence, modulation of inflammation and immunoregulatory pathways may constitute important mechanisms underlying MSC-EV–mediated protection against lung injury in BPD models.[39]

MSC-EVs can mitigate mitochondrial dysfunction and oxidative stress–related damage through the transfer of mitochondria, microRNAs, and proteins to macrophages.[34] In fact, MSC-EV–mediated protection against lung injury may be driven by mitochondrial transfer to alveolar macrophages, leading to increased cellular bioenergetics and improved macrophage function.[38] In preterm infants, oxidative stress results from extended exposure to hyperoxia during artificial ventilation as well as from the lung's inflammatory reaction. In particular, oxidative stress induces excessive AEC-II apoptosis and suppresses their proliferative capacity, which is vital for repairing alveolar epithelial injury.[40] Mitochondria are recognized both as major sources of ROS and as intracellular buffers that protect cells from oxidative stress. Emerging data indicate that MS-EVs can contain mitochondria and mediate their transfer to macrophages, linking mitochondrial presence to intercellular communication in the context of oxidative stress.[41] Therefore, MSC-EVs might partially reduce lung injury in BPD animal studies by mitochondrial transfer.

Studies on MSC-EV-Based Treatment of BPD

Several studies have investigated the clinical application of MSC-EVs in BPD treatment (Table 2). In BPD, MSC-EVs support the growth of pulmonary vasculature and alveolar structures, alleviate pulmonary hypertension, and promote repair of lung injury.[34] Therefore, MSC-EV-Based therapies have the potential to alleviate the structural and vascular abnormalities associated with arrested alveolarization and abnormal vascular development in BPD, by mediating restorative effects in the damaged neonatal lung. In preclinical studies of BPD and additional lung injury models, MSC-EV therapy has shown favorable effects. In a hyperoxia-induced rat model of BPD, the impact of intratracheal administration of MSCs and MSC-EVs has been compared. Both treatments mitigated lung injury, but MSC-EVs yielded greater improvements in alveolar development and lung vasculature, supporting intratracheal-delivered EVs as a promising BPD intervention.[42] It has also been reported that the therapeutic potential of MSCs resides in their

Table 2. Clinical Trial Studies of MSC-EV-Based Therapies for BPD.

Author (Year)	Type of Study	Key Findings	Ref.
Braun et al. (2018)	Preclinical	Daily intraperitoneal MSC-derived exosomes enhance pulmonary vascularization and provided anti-inflammatory and pro-angiogenic effects.	35
Willis et al. (2018)	Preclinical (mouse)	MSC-derived exosomes ameliorate experimental BPD and restore lung function via macrophage immunomodulation.	38
Chaubey et al. (2018)	Preclinical (mouse)	Early gestational MSC secretome attenuates experimental BPD partially through exosome-associated TSG-6.	39
Porzionato et al. (2019)	Preclinical	Intratracheal MSC-EVs reduce lung injury and improve alveolar development in hyperoxia-induced BPD.	42
You et al. (2020)	Preclinical	hUC-MSC-EVs delivered intratracheally promote alveolar and vascular growth via PTEN/Akt-mediated mechanisms.	36
Willis et al. (2020)	Preclinical (mouse)	Early postnatal MSC-EV delivery improve alveolarization, fibrosis, and vascular integrity; may offer potential clinical benefit in established BPD.	43
Porzionato et al. (2021)	Preclinical (rat, chronic BPD)	Long-term intratracheal MSC-EVs improve alveolar development and pulmonary vascular remodeling.	44
Zhou et al. (2022)	Preclinical	hUCMSC-derived EVs enhance AT2 cell proliferation and attenuate lung inflammation in antenatal LPS-induced BPD.	45
Ai et al. (2022)	Preclinical	Dose-dependent MSC-EV therapy suppresses AT2 cell transdifferentiation, alleviating alveolar simplification and fibrosis.	46
Bisaccia et al. (2024)	Preclinical	MSC-EVs mitigate oxidative stress in the lung and brain, enhance alveolar epithelial function, and reduce fibrosis, showing pleiotropic effects.	41

secretome, with MSC-derived exosomes identified as the active therapeutic vectors. These vectors potentially exert their effects by altering the phenotype of pulmonary macrophages.[38] Chaubey et al. indicate that MSC-derived exosomes serve as a significant therapeutic vector in mouse models of chronic lung disease of prematurity, such as BPD.[39] Another study has shown that daily intraperitoneal administration of MSC-derived exosomes in a neonatal rat model of BPD enhances pulmonary vascularization. This study confers both anti-inflammatory and pro-angiogenic effects to protect against hyperoxia-induced pulmonary and cardiac injury associated with BPD.[35] You et al. indicate that human umbilical cord MSC-EVs can be absorbed by lung tissue after intratracheal administration and promote alveolar and vascular growth, potentially via PTEN/Akt–mediated mechanisms.[36] Concurrently, Willis et al. have reported that early postnatal delivery of MSC-EVs may prevent BPD through improvements in alveolarization, fibrosis, and vascular integrity. In addition, MSC-EV therapy could offer clinical benefits for the management—and potentially reversal—of cardiorespiratory complications in infants with established BPD.[43]

The study by Porzionato et al. investigates the long-term protective effects of MSC-EV therapy in experimental models of BPD. Their findings further support the potential of intratracheal-delivered EVs to prevent or treat BPD, demonstrating improvements in alveolar development and pulmonary vascular remodeling in extended-duration studies.[44] In an antenatal LPS-induced rat model of BPD, EVs from hUCMSCs were associated with enhanced lung morphology and function, potentially via stimulated AT2 cell proliferation and reduced inflammatory responses, supporting MSC-EVs as a viable therapeutic platform for BPD.[45] Likewise, Ai et al. have proposed that the effects of MSC-EV–based therapy for BPD may involve suppression of AT2 cell transdifferentiation. They have reported that intraperitoneal MSC-EVs administration at different doses reduces lung injury in a dose-dependent manner, with high-dose EVs alleviating alveolar simplification and fibrosis.[46] A recent study demonstrated that administration of human MSC-EVs in a rat model of BPD mitigates oxidative stress in both the lungs and the brain, two organs critically involved in BPD pathogenesis. The observed protection correlated with enhanced alveolar epithelial performance and decreased fibrosis, suggesting pleiotropic effects of MSC-EVs.[41] These reports provide preclinical evidence supporting MSC-EV–based therapy for BPD.

Challenges for Clinical Application of MSC-EVs

MSC-EVs offer several advantages compared with MSCs. First, being cell-free, MSC-EVs are less immunogenic and potentially less likely to induce tumorigenesis or immune activation compared to cell-based therapies; however, long-term safety remains to be fully established, as most preclinical studies have limited follow-up durations. Second, as a cell-free modality, their small size enables deeper tissue penetration. Third, they exhibit good biological stability and can be engineered to carry therapeutic agents. Fourth, MSC-EVs maintain high biocompatibility and can transport a broad range of biomolecules. Fifth, their surface receptors or antibodies can be customized to target specific cell types and deliver therapeutic cargo.[34]

However, despite promising preclinical data, substantial challenges remain to advance MSC-EV therapies into clinical application. So far, most evidence that MSC-EVs could help BPD comes from animal or lab studies. Furthermore, the mechanisms by which MSC-EVs exert therapeutic effects in BPD remain unclear. Additionally, there is no unified standard for MSC-EV preparation, including the source of MSCs, purification methods, composition, and purity of MSC-EVs.[47] The other problem is the route of administration. Current delivery methods for EVs for BPD include intratracheal, nasal inhalation, and intravenous routes.[35, 42] However, which route is best and what the ideal dose should be are

still topics for future research. Moreover, the origin of EVs can impact their biodistribution[48], which is an area requiring discussion and investigation. The heterogeneity of EVs in origin, size, content, and function can affect their performance and therapeutic potential. These heterogeneities influence EV function and pose challenges for standardization and interpretation.[49]

Moving forward, comprehensive cross-disciplinary collaboration and large-scale, well-powered studies are required to generate more data, check safety and effectiveness, and establish a strong theoretical basis to support clinical trial design.[34]

In summary, preclinical evidence supports MSC-EVs as a versatile and potentially more effective alternative to cell-based therapies for BPD. Their ability to promote alveolarization and vascular development, reduce inflammation and fibrosis, and exert protective effects in distant organs (e.g., brain) underscores their pleiotropic mechanism of action. However, promising, translation to the clinic requires careful consideration of dosing, timing (perinatal vs. postnatal), delivery route, and long-term safety. Future work should aim to standardize EV preparations, identify active cargo and target cells (e.g., AT2 cells, pulmonary macrophages), and define robust clinical endpoints to evaluate efficacy in human infants with established BPD. While MSC-EVs demonstrate a favorable safety profile in short-term preclinical studies, further long-term investigations are necessary to fully exclude risks such as tumorigenicity and to validate their clinical applicability.

Future Directions and Prospects for BPD

Two of the most transformative therapeutic approaches in the treatment of BPD, MSCs and MSC-EVs, remain in the preclinical and experimental stages and must progress further before any translational or clinical use can be pursued.[50] Although the results achieved so far are impressive, translational work is necessary to bridge animal findings to human applicability, including the optimization of dosing, delivery methods, and safety profiles. Consequently, while MSCs and EVs show strong potential for treating conditions like BPD, robust preclinical studies in larger or more clinically relevant models are essential to establish efficacy and inform the design of human trials. It is reasonable to anticipate that EVs will be safe, given their status as components of MSC-based therapies, yet this safety profile has not been fully evaluated in a phase-1 clinical trial.[10] Moreover, the optimal route of administration (intravenous vs. intratracheal), timing, and dosage remains to be determined. Therefore, a standardized method for producing and isolating EVs will also be required to generate a product suitable for human translational applications.

A significant future challenge is to identify biomarkers for BPD that can predict the need for therapeutic intervention. Such biomarkers would enable novel therapies to be targeted only to infants who truly require them. In BPD research, a range of -omics approaches—including genomics, transcriptomics, proteomics, metabolomics, nutritional status, and maternal antenatal medications—are central to ongoing international discussions about the syndrome.[10]

Conclusion

In conclusion, there are transformative advances in the treatment of a well-recognized BPD that already benefits from numerous evidence-based strategies for prevention and symptom relief. While such novel therapies have the potential to markedly improve both short- and long-term lung development in affected infants and could alter the disease's natural history, to date, no definitive cure exists. Overall, MSCs and MSC-EVs constitute a compelling therapeutic platform for preventing and treating BPD, with the promise of alleviating structural and vascular lung abnormalities and enhancing long-term cardiopulmonary health.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Author's Contribution

Conducting the research and writing the manuscript, H.S.; reviewing the manuscript, Fs. A, E.Z.
All authors contributed to the manuscript writing and final approval of the manuscript.

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