Pulmonary homing of mesenchymal stem cells: From embolism risk to a therapeutic advantage in pneumonia (Review)

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Abstract. Mesenchymal stem cells (MSCs) hold notable therapeutic potential for pneumonia, yet their intravenous administration is limited by pulmonary homing, in which the majority of infused cells become trapped in the lung microvasculature due to their size. Historically considered an embolic hazard and a barrier to systemic delivery, this phenomenon may instead be advantageous when the lung is the intended therapeutic target. The present review reframes pulmonary homing as a potential therapeutic delivery advantage for pneumonia treatment and summarizes the updated consensus criteria for defining MSCs and compares the key features of mesodermal- vs. ectodermal-derived MSC populations. How MSCs temper pneumonia-associated cytokine storms by modulating macrophage pyroptosis, neutrophil extracellular trap formation and natural killer cell activity is also examined. Finally, the mechanisms that drive pulmonary entrapment are reviewed and the balance between therapeutic benefit and embolic risk is considered. Reinterpreting a long-perceived liability as a therapeutic asset relies on a detailed understanding of the biophysical and molecular determinants that govern MSC retention in the lung.

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1. Introduction

Mesenchymal stem cells (MSCs) have garnered notable attention as a cell-based therapeutic strategy for inflammatory lung diseases, including pneumonia, owing to their multifaceted immunomodulatory, anti-apoptotic and tissue-regenerative capacities (1,2). Upon systemic delivery, MSCs exhibit a well-documented phenomenon termed pulmonary homing, in which a notable proportion of infused cells are initially retained within the pulmonary microvasculature rather than entering the systemic circulation (3). This behavior is influenced by both physical and molecular factors. The relatively large size of MSCs compared with pulmonary capillaries can lead to mechanical obstruction within the pulmonary microvasculature, while interactions between MSC integrins, such as β1, α5 and αVβ3 integrins, and their endothelial ligands may further promote cell retention (4,5). This inherent tropism for the lung has historically been framed as a safety liability. The acute mechanical occlusion of pulmonary microvessels by infused MSCs raises concerns regarding microembolic events that may precipitate transient pulmonary hypertension, hypoxemia or focal ischemia (3). These risks are amplified in pneumonia, whereby the lung parenchyma is already vulnerable due to active infection and dysregulated inflammatory cascades. In this compromised microenvironment, superimposed microvascular obstruction may further deteriorate pulmonary

function and, by extension, challenge the clinical viability of systemic MSC delivery. However, a growing body of evidence is now challenging this conventional risk-centric perspective, redefining pulmonary homing as a potentially beneficial trait that could be therapeutically harnessed (6-8). In pneumonia, where pathological injury is confined to the lung, the natural propensity of MSCs to lodge in the pulmonary circulation can be harnessed for targeted *in situ* delivery, directing therapeutic cells precisely to where they are most needed. Once lodged in the pulmonary microvasculature, MSCs activate a broad paracrine response. They secrete anti-inflammatory mediators such as IL-10, epithelial reparative factors including keratinocyte growth factor (KGF) and antimicrobial molecules, including LL-37, β-defensin-2, lipocalin-2 and hepcidin (9). These signals modulate alveolar macrophages (AMs), epithelial cells and endothelial cells, helping to suppress excessive inflammation, strengthen the alveolar-capillary barrier and improve pathogen clearance through increased phagocytic activity and antimicrobial responses (10,11). Collectively, pulmonary homing presents a compelling translational paradox: A phenomenon initially identified as a source of embolic risk is being reconceptualized as a potential precision-delivery mechanism for pneumonia therapy. Whether this shift from liability to therapeutic asset can be fully realized relies on a more granular understanding of the biophysical and molecular determinants of MSC entrapment, to calibrate the risk-benefit balance favorably. The present review summarizes mechanisms underlying MSC pulmonary homing and retention, examines how the pulmonary inflammatory microenvironment may influence these processes and discusses the therapeutic opportunities and safety challenges associated with exploiting pulmonary homing for targeted treatment of pneumonia. Strategies that may help shift pulmonary retention from an inherent limitation toward a controllable therapeutic advantage are further highlighted.

2. Definition, core characteristics and clinically relevant sources of MSCs

Definition and identification criteria of MSCs. The International Society for Cell & Gene Therapy has recently updated the consensus framework for defining mesenchymal stromal cells. This revision emphasizes standardized terminology, transparent reporting of tissue source, species, culture conditions and functional characterization (12). The term mesenchymal stromal cell is recommended as the broader designation, whereas the use of the term MSC requires evidence supporting stemness-associated properties such as clonogenicity, self-renewal and multilineage differentiation. The updated consensus revises MSC identification and clinical quality control. CD45 negativity remains the sole mandatory marker to exclude hematopoietic contamination, whereas CD73, CD90 and CD105 are now recommended reference indicators rather than rigid requirements. Flow cytometry data should be reported in sufficient detail, including the cut-off values used and the proportion of positive cells. Such standardized characterization is particularly important when comparing studies of pulmonary homing, as differences in MSC source, phenotype and manufacturing conditions may influence cell size, adhesion properties and pulmonary retention, thereby contributing to variability in both safety and therapeutic outcomes. The updated criteria also place fewer restrictions on tissue origin. Unlike the 2006 International Society for Cellular Therapy minimal criteria, which mandated two basic requirements (adherent growth and trilineage differentiation), the current framework no longer enforces either (13). This shift reflects a deeper understanding that MSC therapeutic efficacy primarily relies on paracrine secretion rather than multilineage differentiation capacity. For pneumonia-associated research, this paradigm emphasizes core functional evaluations such as anti-inflammatory activity, alveolar repair capacity and bactericidal effects, thereby optimizing preclinical assessment and advancing the clinical translation of MSC-based precision therapy for pulmonary infectious diseases.

Different types and characteristics of MSCs

Mesoderm-associated MSC sources. MSCs are primarily isolated from bone marrow, adipose tissue and umbilical cord. Bone marrow-derived MSCs (BM-MSCs), the earliest and most well-characterized MSC population, demonstrate plastic adherence, colony-forming capacity and osteogenic, chondrogenic and adipogenic differentiation (14,15). They also promote angiogenesis and exert immunomodulatory effects through factors such as VEGF, indoleamine 2,3-dioxygenase (IDO), TGF-β, prostaglandin E2 (PGE2) and IL-10 (16,17). However, the clinical application of BM-MSCs remains challenging for several reasons. Their low frequency in bone marrow (0.001-0.01% of nucleated cells) means that obtaining sufficient numbers for therapeutic use requires extensive *ex vivo* expansion, which increases manufacturing time and may affect cell quality. Bone marrow collection is also invasive and therefore less suitable for repeated cell procurement. In addition, donor-to-donor variation and age-related changes in MSC abundance and biological properties can lead to differences in cell yield, proliferative capacity and therapeutic potency, making the production of a consistent cell product more difficult (18-21). Adipose tissue-derived MSCs (AD-MSCs) are more readily accessible and can be obtained through relatively minimally invasive procedures. They proliferate faster compared with BM-MSCs and secrete VEGF, hepatocyte growth factor and numerous immunomodulatory factors, including VEGF, hepatocyte growth factor, PGE2, TGF-β, IL-10, and IDO, supporting their use in tissue repair and anti-inflammatory applications (22-24). AD-MSCs generally demonstrate stronger adipogenic but weaker osteogenic and chondrogenic differentiation compared with BM-MSCs (25,26). Umbilical cord-derived MSCs (UC-MSCs), mainly isolated from Wharton's jelly, offer non-invasive collection, low immunogenicity and few ethical concerns. They exhibit greater proliferative and expansion capacity compared with both BM-MSCs and AD-MSCs and further demonstrate potent immunomodulatory activity, including T cell suppression mediated partly by TGF-β and IDO (27). However, their colony-forming and isolation efficiencies are relatively low and adipogenic differentiation is limited. Their strong expansion capacity and low immunogenicity make UC-MSCs particularly attractive for allogeneic cell therapy.

Ectodermal lineage of MSCs. Ectoderm-derived MSCs (EMSCs) retain neural crest-related properties; therefore, are more closely associated with neural repair compared with

conventional mesodermal MSCs. EMSCs can be obtained through minimally invasive endoscopic brushing or biopsy, express neural crest markers such as SOX10 and p75 neurotrophin receptor in addition to standard MSC markers and display strong clonogenicity, rapid proliferation, neurogenic potential, dopaminergic neuron-like differentiation capacity and secretion of neurotrophic factors such as brain-derived neurotrophic factor, glial cell line-derived neurotrophic factor, neurotrophin-3 and nerve growth factor (28-35). However, given that their main biological advantages are related to neural differentiation and neurotrophic support rather than lung targeting or pulmonary immunomodulation, EMSCs are less directly relevant to MSC-based pneumonia therapy. In addition, donor age and the local inflammatory environment may influence their biological properties, including proliferative capacity, differentiation potential, and the secretion of immunomodulatory and neurotrophic factors (36).

3. Advances in MSC-based therapy for pneumonia

Current status and unresolved difficulties in pneumonia treatment. Pneumonia remains one of the leading infectious causes of mortality worldwide and continues to impose a notable burden on healthcare systems (37-40). Although antimicrobial therapy, antiviral treatment, oxygen therapy and intensive care have improved patient outcomes, the clinical management of severe pneumonia remains constrained by numerous key bottlenecks. Pathogen identification is often delayed or incomplete. In clinical practice, clinicians often start empirical antibiotics or antivirals before microbiological confirmation, while the causative pathogen remains unidentified in a substantial proportion of hospitalized patients despite standard diagnostic testing (41,42). This uncertainty may lead to inadequate initial coverage, unnecessary broad-spectrum antibiotic exposure, delayed therapeutic adjustment and increased antimicrobial resistance. The global spread of multidrug-resistant pathogens has further weakened the reliability of conventional antibiotic strategies, making lower respiratory tract infection a key contributor to antimicrobial-resistance-associated mortality (43).

A further limitation of conventional pathogen-directed therapy is that antimicrobial treatment alone may not be sufficient to reverse the dysregulated host response once severe lung injury has developed. In severe bacterial pneumonia, viral pneumonia and pneumonia-associated acute respiratory distress syndrome (ARDS), disease progression is driven not only by pathogen burden but also by excessive cytokine release, endothelial and epithelial barrier disruption, alveolar edema, neutrophil and macrophage hyperactivation, pulmonary microvascular injury and impaired resolution of inflammation (44-49). Therefore, even when antimicrobial therapy reduces pathogen replication, patients may continue to deteriorate and develop refractory hypoxemia, ARDS, sepsis or multi-organ dysfunction. Supportive interventions, including high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation, prone positioning and extracorporeal membrane oxygenation, are important for patients who are critically ill; however, these interventions primarily maintain oxygenation and organ function rather than directly restoring alveolar-capillary barrier integrity or repairing the injured pulmonary microenvironment (50,51).

Host-directed anti-inflammatory therapy, particularly corticosteroid treatment, has provided an additional approach to controlling excessive host inflammation in severe pneumonia. Corticosteroids can improve outcomes in selected patients with severe community-acquired pneumonia or coronavirus disease 2019 (COVID-19)-related respiratory failure by suppressing excessive systemic and pulmonary inflammation and limiting inflammation-associated lung injury. For example, early hydrocortisone treatment reduced 28-day mortality and the need for invasive mechanical ventilation or vasopressor therapy in patients with severe community-acquired pneumonia, while dexamethasone reduced mortality in hospitalized patients with COVID-19 who required supplemental oxygen or invasive mechanical ventilation (52-54). However, these benefits are dependent on disease severity and treatment timing, and excessive immunosuppression may compromise antimicrobial host defense and increase the risk of secondary infection and metabolic complications.

Targeted cytokine blockade offers a more selective approach to host-directed immunomodulation. For example, IL-6 receptor blockade with tocilizumab or sarilumab has shown clinical benefit in critically ill patients with COVID-19 receiving respiratory or cardiovascular organ support, particularly in the setting of systemic inflammation (55). However, the evidence for this strategy is largely derived from selected patients with severe or critical COVID-19, and its efficacy cannot be readily extrapolated to other forms of severe pneumonia. Moreover, inhibition of a single inflammatory pathway does not directly address other important components of severe lung infection, including impaired antimicrobial defense, disruption of the alveolar-capillary barrier and inadequate tissue repair. These limitations underscore the need for an adjunctive therapeutic strategy that can restrain excessive inflammation while preserving antimicrobial host defense and promoting restoration of the alveolar-capillary barrier.

MSC therapy modulates the cytokine storm in pneumonia. Severe pneumonia can be accompanied by an excessive and dysregulated inflammatory response, characterized by sustained activation of immune cells and increased production of pro-inflammatory cytokines, which may contribute to acute lung injury and multiple organ dysfunction (56). MSCs can modulate this pathological response through multiple paracrine and cell-mediated mechanisms, including the secretion of immunoregulatory mediators such as IL-10, PGE2, TGF-β, IDO and nitric oxide, thereby regulating the activity of immune cells and attenuating excessive pulmonary inflammation (57). As summarized in Fig. 1, the anti-cytokine storm effects of MSCs can be organized into three interconnected mechanisms: Inhibition of macrophage pyroptosis, suppression of neutrophil hyperactivation and neutrophil extracellular trap (NET) formation and modulation of natural killer (NK) cell cytotoxicity and IFN-γ secretion. The present review goes on to discuss each mechanism, with an emphasis on how local pulmonary retention may increase the exposure of injured lung tissue to MSC-derived paracrine signals.

Regulating macrophage pyroptosis to alleviate the cytokine storm. Macrophage pyroptosis has been increasingly recognized as a key pathological trigger that fuels the uncontrolled inflammatory cascade characteristic of severe pneumonia,

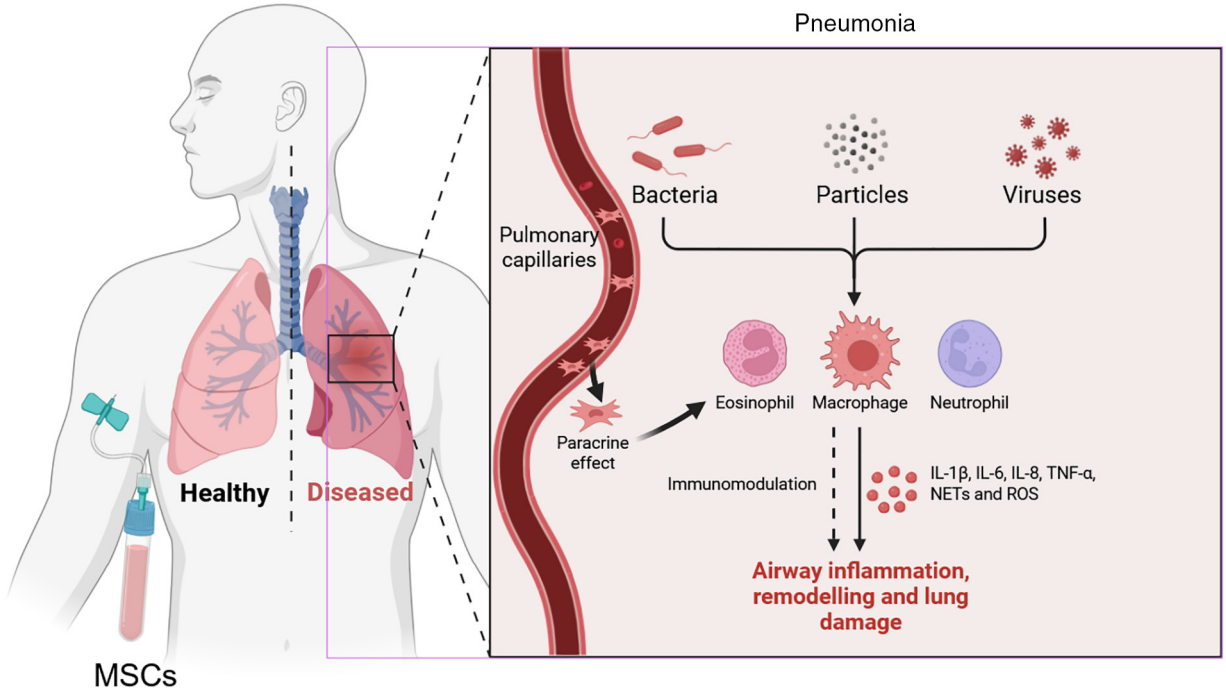


Figure 1. Immunomodulatory effects of MSCs in pneumonia. MSCs, mesenchymal stem cells; NETs, neutrophil extracellular traps; ROS, reactive oxygen species.

commonly referred to as a cytokine storm (58-61). In contrast to the immunologically quiescent nature of classical apoptosis, pyroptosis represents an notably pro-inflammatory mode of regulated cell death (62). This process is initiated upon the detection of cytosolic pathogen-associated molecular patterns or host-derived damage-associated molecular patterns (63). Canonical pyroptosis is characterized by the assembly of inflammasome platforms, with the nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain-containing protein 3 inflammasome as the archetypal sensor, culminating in caspase-1 activation. Alternatively, a non-canonical pathway bypasses this step through the direct engagement of cytosolic lipopolysaccharide (LPS) with caspase-4/5 (in humans) or caspase-11 (in mice) (64). Regardless of the initiating route, a hallmark convergence point is the proteolytic cleavage of gasdermin D (GSDMD). The liberated N-terminal fragment of GSDMD oligomerizes and inserts into the plasma membrane, forming non-selective lytic pores (65). This event induces cell swelling and osmotic lysis, culminating in the release of cytosolic contents and, critically, the mature pro-inflammatory cytokines IL-1β and IL-18 (66). The release of these cytokines recruits additional immune effectors, particularly neutrophils and monocytes, thereby sustains a self-amplifying inflammatory loop, accelerating acute lung injury and systemic cytokine storm progression. Within the pulmonary microenvironment of pneumonia, excessive pyroptotic depletion of the resident AM pool further compromises innate immunity, impairs tissue remodeling and erodes the epithelial barrier integrity (67).

Growing evidence has indicated that MSCs orchestrate a multifaceted regulatory program that tempers macrophage pyroptosis, a key inflammatory cell death pathway (68,69). By modulating this process, MSCs may slow the progression of cytokine storm, particularly in severe pneumonia (70,71). Research further indicates that MSCs primarily execute these immunomodulatory functions by secreting exosomes, which actively intervene in the pyroptotic cascade of macrophages (72). MSC-derived exosomes (MSCs-Exo) directly suppress pyroptosis in AMs with efficacy comparable to Ac-YVAD-CMK, a specific and irreversible inhibitor of caspase-1-dependent pyroptosis (73). Mechanistically, MSCs-Exo are enriched in a diverse array of microRNAs (miRs) with the potential to target genes integral to the caspase-1-mediated pyroptotic pathway. These include, but are not limited to, miR-22-3p, miR-214-3p, miR-221-5p and miR-18a-3p (74). Furthermore, exosomes derived from BM-MSCs have been demonstrated to attenuate macrophage pyroptosis through the miR-125b-5p/STAT3 signaling axis, thereby expanding the known regulatory network of MSC-exosome-mediated immunomodulation (75).

Suppressing excessive neutrophil activation and NETosis to reduce the cytokine storm. Neutrophils are the most abundant innate immune cells recruited to the infected lung and their rapid activation is key in pathogen clearance. However, in severe pneumonia, neutrophils can become hyperactivated, releasing high levels of reactive oxygen species (ROS), proteases and pro-inflammatory cytokines, thereby exacerbating the cytokine storm. A particularly damaging process is NETosis, a type of neutrophil cell death that releases NETs. NETs are web-like structures composed of decondensed chromatin decorated with histones and antimicrobial proteins, including neutrophil elastase and myeloperoxidase (76). While NETs can trap and kill pathogens, excessive NET formation in the alveolar space directly damages epithelial and endothelial cells, promotes thrombosis and stimulates further cytokine release from macrophages and dendritic cells, creating a positive feedback loop that sustains the cytokine storm (77).

MSCs counter this pathological cascade through a coordinated, multi-layered immunomodulatory program targeting neutrophil hyperactivation, NETosis and NET clearance. MSCs suppress neutrophil oxidative burst and degranulation through paracrine release of PGE2 and IL-10, which bind cognate receptors on neutrophils and dampen downstream pro-inflammatory signaling (78). MSCs modulate key upstream intracellular events that drive NETosis, including elevations in cytosolic calcium, activation of protein kinase C and Janus kinase 2 kinase cascades, as well as NADPH oxidase-dependent ROS generation (79). Through this regulatory mechanism, MSCs raise the cellular threshold required for neutrophils to release NETs. Beyond suppressing neutrophils directly, MSCs enhance efferocytosis of apoptotic neutrophils, limiting their downstream consequences including complement activation, endothelial injury and inflammasome priming (80). This multi-tiered strategy disrupts the pathological NETosis-cytokine storm axis and attenuates alveolar injury, thereby promoting the restoration of gas exchange in pneumonia-associated ARDS. MSC-mediated immunomodulation does not impair core neutrophil antimicrobial functions: Phagocytosis and intracellular pathogen killing remain intact even as hyperactivated inflammatory responses are selectively curtailed (81).

Modulating NK cell cytotoxicity and IFN-γ secretion to restore cytokine balance. NK cells are well recognized for their role in eliminating virus-infected cells and tumor targets, yet they also contribute markedly to cytokine storm pathology in severe pneumonia (82). Upon stimulation by IL-12, IL-15 and IL-18, activated NK cells become major sources of IFN-γ, which in turn amplifies macrophage and neutrophil activation, sustains further cytokine release and drives progressive immune escalation (83). In parallel, NK cell cytotoxicity mediated by perforin and granzymes directly damages alveolar epithelial cells, compromising barrier integrity and predisposing the lung to secondary bacterial invasion.

MSCs attenuate these pathological responses through a context-dependent, multi-mechanistic strategy. Paracrine mediators including PGE2, IDO and TGF-β suppress NK cell proliferation, curtail IFN-γ secretion and reduce cytotoxic degranulation under hyperinflammatory conditions (84). MSCs also downregulate activating receptors such as NK group 2, member D and NKp30, diminishing NK cell responsiveness to inflammatory stimuli (85,86). MSC-mediated regulation of NK cells appears to be modulatory rather than completely suppressive. MSCs attenuate excessive IFN-γ production to levels that preserve antiviral defense without sustaining pathological immune amplification (87,88). By reducing the broader inflammatory burden, MSCs further prevent secondary NK cell overstimulation driven by other immune effectors, including activated macrophages, neutrophils, monocytes and T cells. Collectively, these mechanisms restore cytokine homeostasis, enabling effective pathogen clearance while limiting NK cell-mediated immunopathology. Consistent with this, MSC treatment in pneumonia models has been associated with reduced pulmonary IFN-γ concentrations, decreased NK cell infiltration and improved clinical outcomes (89,90).

4. Intravenous (IV) administration: The principal route for MSC clinical application and its core drawbacks

The route of MSC administration is a key variable that determines *in vivo* fate, therapeutic time window and safety profile. Among the available delivery routes, intravenous (IV) administration is widely used due to its technical simplicity, minimal invasiveness, reproducibility and compatibility with repeated dosing (91,92). However, a wealth of tracking and functional studies have consistently demonstrated that MSCs face a severe 'pulmonary first-pass effect' immediately after IV infusion: MSCs have a diameter of ~15-19 μm, whereas human pulmonary capillaries average only 5-8 μm in inner diameter (3,93). As a result, the majority of infused cells are initially retained in the lung and only a fraction subsequently redistributes to organs such as the liver, spleen and bone marrow over the following hours and days (94-96).

When the intended target is not the lung, pulmonary first-pass retention becomes a major delivery obstacle. Following intravenous infusion, most MSCs are initially sequestered within the pulmonary microvasculature, limiting the proportion of intact cells reaching distal organs, such as the heart, brain, kidneys and skeletal muscles (75,97,98). This pulmonary sequestration limits the number of cells available for subsequent systemic distribution and distal tissue targeting. Despite engineering strategies being able to enhance cell homing to target organs by several-fold in mouse models, the absolute homing rate in target organs rarely exceeds 5% of the injected dose, as the loss due to pulmonary first-pass entrapment cannot be completely avoided (99-101). This limitation may partly explain why encouraging preclinical observations have not translated into uniformly positive clinical outcomes. In ARDS, for example, early-phase trials such as the Stem Cells for Acute Respiratory Distress Syndrome Treatment trial supported the feasibility and short-term safety of BM-MSC infusion but did not establish definitive efficacy (102,103). Similarly, numerous COVID-19-associated ARDS studies have reported an improvement in inflammatory markers or exploratory clinical outcomes, whereas larger randomized trials have failed to meet key primary endpoints such as oxygenation improvement, survival rate or ventilator-free outcomes. This discrepancy may reflect differences in MSC source, manufacturing, dose, administration timing, patient characteristics and trial design, although the relative contributions of these factors remain uncertain (104-107). Thus, IV delivery may be inefficient for non-pulmonary targets. In pulmonary disease, lung entrapment may offer a pharmacokinetic advantage, but it does not prove clinical benefit.

A key unresolved question is whether MSC products from different tissue sources can be treated as interchangeable for IV use. Despite different MSCs sharing standard minimal defining criteria, these criteria do not establish functional equivalence (13). Comparative studies have demonstrated that MSC source can influence proliferative capacity, senescence, differentiation potential, secretome profile and immunomodulatory activity (108,109). Head-to-head studies also support source-dependent efficacy. In rat *Klebsiella pneumoniae* pneumosepsis, naïve BM- and UC-MSCs were shown to improve lung airspace restoration, whereas naïve AD-MSCs did not, although physiological indices remained unchanged (110). In

LPS-induced murine ARDS, UC-MSCs demonstrated greater benefits in survival rate and barrier protection compared with BM- or AD-MSCs (111). However, these model-specific findings do not establish a universally superior MSC source for infectious pneumonia. This distinction is clinically relevant as hemocompatibility is product-dependent. Adipose- and perinatal tissue-derived MSCs may express higher levels of tissue factor/CD142 and demonstrate stronger procoagulant activity compared with BM-MSCs; this difference may increase the risk of instant blood-mediated inflammatory reaction, thrombin generation and clot formation after systemic infusion (112-114). Therefore, IV MSC products should be evaluated using source- and manufacturing-specific release criteria, including assays for tissue factor expression, complement activation, platelet interaction and coagulation. However, direct human trials comparing MSC sources under the same disease setting, dose, manufacturing process, release criteria and endpoints remain scarce. Thus, claims of source-specific clinical superiority still rely primarily on *in vitro* studies, animal models or indirect cross-trial comparisons. Similarly, pulmonary 'homing' after IV infusion should be interpreted cautiously: Current biodistribution data suggest that early lung accumulation mainly reflects passive pulmonary first-pass trapping rather than active homing or durable engraftment (115,116). Overall, IV infused MSCs may exert transient paracrine or immunomodulatory effects while they are retained in the lung, but active pulmonary targeting, long-term engraftment and the selection of a clinically superior MSC source remain insufficiently proven in humans.

5. Pneumonia-induced injury: A natural exception to the limitations of IV administration

From a delivery limitation to a potential therapeutic advantage. Pneumonia, especially when it progresses to acute lung injury or ARDS, illustrates a potential reversal of the defect-to-advantage paradigm. In non-pulmonary diseases, pulmonary retention of MSCs is usually regarded as off-target loss and a possible source of embolic risk (117). When the lung itself is the therapeutic target; however, the criteria for evaluation shift. The rapid accumulation of MSCs in the pulmonary microvasculature may increase local exposure of the injured lung to anti-inflammatory, barrier-protective and reparative mediators (118). Therefore, the core logic is not that retention is always beneficial, but that controlled pulmonary retention may become useful when local lung action is desired.

Enhanced pulmonary homing of MSCs mediated by the pneumonia microenvironment. The inflammatory microenvironment of pneumonia may further enhance MSC homing and retention through both physical and biological mechanisms. In physiologically normal pulmonary circulation, a notable proportion of intravenously infused MSCs can be retained due to size mismatch (94). During pneumonia, endothelial swelling, interstitial edema, neutrophil infiltration and microthrombosis may further narrow the functional microvascular lumen (119,120). These changes may increase the risk of excessive obstruction, underscoring the need to distinguish potentially useful pulmonary retention from unsafe vascular plugging. Clinically reported embolic events remain uncommon, although their true incidence is uncertain. In the SEPCELL trial of IV adipose-derived MSCs for severe community-acquired bacterial pneumonia, pulmonary embolism was reported in 1 of 41 patients treated with MSC (2.4%) and 2 of 41 patients treated with a placebo (4.9%) (121). Thus, this trial did not indicate an increased frequency of pulmonary embolism following MSC administration. Consistently, a previous systematic review and meta-analysis encompassing 55 randomized controlled trials and 2,696 participants, revealed no marked increase in thrombotic or thromboembolic events with intravascular MSC administration compared with controls, based on 24 trials reporting this outcome (risk ratio: 1.14; 95% CI: 0.67-1.95) (102). Despite this, the available studies were not sufficiently powered to detect rare events and generally lacked systematic screening for asymptomatic pulmonary microvascular obstruction. Therefore, the incidence of embolic complications directly attributable to MSC infusion remains undetermined.

Physical entrapment represents only the first step in the pulmonary sequestration and subsequent fate of intravenously infused MSCs (Fig. 2A). As presented in Fig. 2B, inflammatory chemokines and adhesion molecules can then promote more selective localization. Alveolar epithelial cells, microvascular endothelial cells and infiltrating macrophages secrete stromal cell-derived factor-1a, monocyte chemoattractant protein-1, macrophage inflammatory protein-1α and adhesion molecules such as intercellular adhesion molecule 1 and vascular cell adhesion molecule 1 (VCAM-1) (122). MSCs express or upregulate corresponding receptors and adhesion partners, including C-X-C chemokine receptor type 4, C-C chemokine receptor (CCR)-2, CCR5 and very late antigen-4, in response to inflammatory stimulation (123). Intravital microscopy has demonstrated enhanced MSC retention in the inflamed pulmonary vasculature of LPS-induced acute lung injury models, partly associated with endothelial VCAM-1 upregulation (124). This cascade-like synergy of 'passive entrapment followed by active migration' constitutes the core dynamics underlying a potential delivery advantage for MSC therapy. Notably, unlike cumbersome genetic engineering strategies, such as viral vector-mediated overexpression of chemokine receptors or adhesion molecules, which may introduce risks associated with insertional mutagenesis and unintended gene expression, the pulmonary homing of MSCs during pneumonia relies largely on their endogenous characteristics. This reliance on endogenous homing mechanisms may help mitigate risks associated with genetic modification, including insertional mutagenesis, unintended disruption of host gene expression, and undesirable alterations in MSC proliferation, differentiation or immunomodulatory function, potentially simplifying clinical translation. This dual-targeting mechanism ensures that MSCs undergo physical retention within the pulmonary microvasculature and migrate along chemotactic gradients, shifting the therapeutic window from dose-dependent to targeting-efficiency-dependent, such that effective local concentrations can be achieved even with relatively low-dose infusion.

Therapeutic advantages and limitations of IV administration in pneumonia. Direct comparison of IV administration with other common routes in preclinical pneumonia models

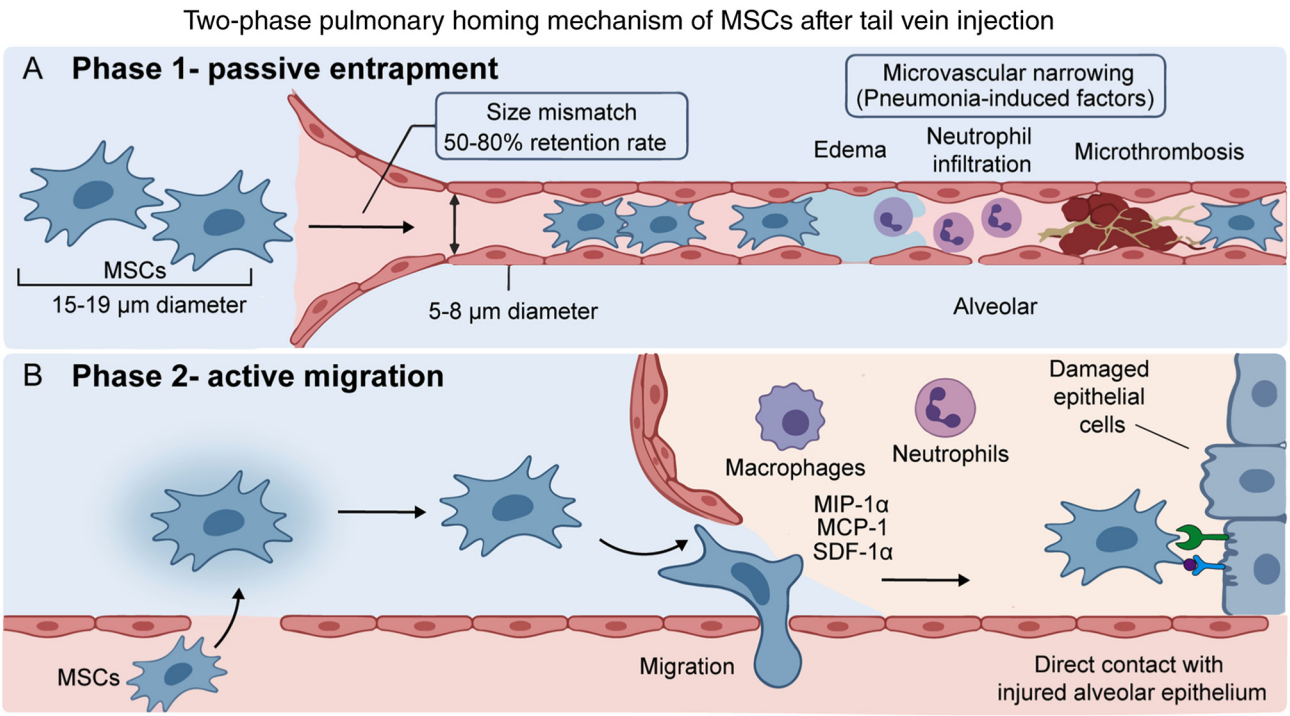


Figure 2. The two-phases of MSC pulmonary homing following intravenous administration. (A) Passive entrapment: MSCs are mechanically retained in pulmonary capillaries due to size mismatch, exacerbated by pneumonia-induced microvascular narrowing. (B) Active migration: Inflammatory chemokines (MIP-1α, MCP-1 and SDF-1α) promote MSC migration toward injured alveolar epithelium. MSCs, mesenchymal stem cells; MIP-1α, macrophage inflammatory protein-1α; MCP-1, monocyte chemoattractant protein-1; SDF-1α, stromal cell-derived factor-1α.

demonstrates its distinct superiority for the treatment of ARDS (125-127). Compared with intratracheal (IT) delivery, the advantages of the IV route become apparent. While the IT route delivers MSCs directly to the alveolar surface, the cells largely remain within the airway lumen and mucosal lining, struggling to traverse the epithelial barrier into the pulmonary interstitium. Researchers have demonstrated that intratracheally administered UC-MSCs in an ovalbumin-induced murine model of asthma exert their therapeutic effects primarily through paracrine signaling rather than through engraftment or integration into the airway epithelium. Histological and flow cytometric analyses revealed that the UC-MSCs localized within the airway compartment without appreciable migration across the epithelial barrier into the underlying parenchyma (128). In addition, IT-delivered MSCs are rapidly cleared by the mucociliary apparatus, markedly diminishing their therapeutic persistence (129). By contrast, IV administration positions MSCs precisely within the interstitial compartment lying between the microvascular endothelium and the alveolar epithelium, which is the site where the alveolar-capillary barrier collapses during ARDS. This strategic localization enables MSCs to more effectively secrete barrier-protective factors such as angiopoietin-1 and KGF, thereby alleviating pulmonary edema (130,131). Beyond their local effects at the alveolar-capillary barrier, MSCs retained within the pulmonary vasculature serve as a source of anti-inflammatory mediators that enter the systemic circulation. This systemic release enables modulation of the systemic inflammatory response syndrome by attenuating the production of pro-inflammatory cytokines, modulating immune cell activation and limiting inflammation-associated tissue injury, a capability that is largely absent following IT administration due to the confinement of MSCs to the airway lumen. The superiority of the IV route has been demonstrated in preclinical models of sepsis-associated ARDS. Specifically, in a cecal ligation and puncture model, IV delivery of MSCs at equivalent doses was consistently demonstrated to outperform IT delivery across numerous clinically relevant endpoints, including enhanced lung compliance, reduced bronchoalveolar lavage fluid protein content (reflecting preserved alveolar-capillary barrier integrity) and improved 24-h survival (132-134).

Compared with intraperitoneal injection, IV delivery provides faster access to the pulmonary circulation; therefore, may be more suited to the early hyperinflammatory phase of severe pneumonia (91,135). In rodent models, tail vein injection has been shown to deliver MSCs to the lung within minutes, allowing rapid paracrine signaling by mediators such as TNF-α-stimulated gene/protein-6, IL-10 and TGF-β (6,136). These effects may reduce IL-6, TNF-α and IL-1β, suppress neutrophil infiltration and NETosis, supporting epithelial repair through extracellular vesicles or mitochondrial transfer (137,138). Despite this, the most effective route remains incompletely established in humans. Differences among animal models, timing of administration, cell source, dose, passage number and endpoints limit direct comparison and clinical trials in pneumonia or ARDS have not yet proven a consistent efficacy advantage of IV MSC infusion.

Safety boundary and clinical translation. The potential targeting advantage of IV MSC retention in the lung should be interpreted within a clear safety boundary. Pulmonary first-pass retention may increase local cell exposure in lung injury, but

excessive retention can also represent microvascular obstruction rather than therapeutic targeting. This risk is shaped by product-, infusion- and host-related factors, including total cell dose, cell diameter and deformability, cell aggregation, tissue factor/CD142 expression, infusion concentration and rate, suspension quality, pulmonary vascular reserve and the interval among repeated doses (139-141). Large or aggregated cells, rapid infusion and high cumulative dosing may increase pulmonary vascular resistance, impair oxygenation and amplify coagulation activation, particularly in patients with ARDS or COVID-19-associated endothelial injury and coagulopathy (142,143). Therefore, pulmonary retention should not be treated as inherently beneficial; it represents a pharmacokinetic opportunity only when cell quality, hemocompatibility and patient risk are tightly controlled.

Clinical translation should build these risks into trial design rather than manage them retrospectively. Practical safeguards include: i) Standardized release criteria for cell size, viability and aggregate burden; ii) product-specific testing for tissue factor expression, platelet interaction and coagulation; iii) cautious dose escalation; iv) slow peripheral IV infusion; v) predefined intervals for repeated dosing; and vi) monitoring of oxygenation, hemodynamics, platelet count, fibrinogen, D-dimer and other coagulation parameters (140-142). Existing ARDS and severe pulmonary inflammation trials have generally supported the feasibility and short-term tolerability of IV MSC infusion; however, efficacy remains inconsistent across studies (106,107,144). Neutral or negative results may reflect patient heterogeneity, late administration, variable MSC source and manufacturing quality, weak potency assays, limited biodistribution information or endpoints that do not directly measure lung-specific biological activity (91,142). Therefore, future trials should aim to combine biodistribution-informed dosing, source-specific potency and hemocompatibility testing, early safety stopping rules and mechanistically aligned endpoints that capture both pulmonary safety and target engagement.

The clinical presentation of pulmonary embolic complications is variable and non-specific. Acute pulmonary embolism may present with new or worsening dyspnea, chest pain, hypoxemia, tachycardia or, occasionally, hemoptysis or syncope. Severe cases may involve hypotension, shock and acute right ventricular dysfunction (145). In severe pneumonia, recognition of acute pulmonary embolism is challenging as its clinical manifestations may overlap with deterioration caused by the underlying infection or ARDS. Despite this, acute-onset chest pain, otherwise unexplained hypoxemia, hypotension or evidence of acute right ventricular dysfunction developing during or shortly after MSC infusion should prompt interruption of the infusion and assessment for pulmonary embolism. The diagnostic approach should be determined by the condition of the patient. CT pulmonary angiography can determine pulmonary embolism in stable patients, whereas bedside echocardiography may be more practical when hemodynamic instability prevents immediate transport. Confirmed thrombotic pulmonary embolism should be treated according to established guidelines, with anticoagulation in eligible patients and reperfusion therapy reserved for high-risk disease (146). These recommendations cannot be directly extended to microscopic cellular entrapment without demonstrable thrombus, for which no specific treatment has been established. Therefore, future trials should aim to prespecify the definition, diagnostic evaluation and reporting period for suspected embolic events.

6. Conclusions

IV administration of MSCs has long been approached with caution given that numerous infused cells become retained in the pulmonary microvasculature. This 'pulmonary first-pass effect' has typically been framed as both a delivery defect and an embolic hazard. In pneumonia, the lung itself is the primary site of injury. Therefore, controlled pulmonary retention may enhance local exposure to MSC-derived immunomodulatory and barrier-protective factors. MSCs may suppress macrophage pyroptosis, reduce excessive neutrophil activation and NETosis and calibrate NK cell activity, thereby limiting cytokine storm progression while supporting tissue repair. This proposed benefit does not eliminate safety concerns. Excessive cell dose, large or aggregated cells, rapid infusion, procoagulant activity and repeated administration may shift retention toward harmful microvascular obstruction. Therefore, future studies should aim to define source-specific potency, hemocompatibility, dose-response relationships, infusion protocols, biodistribution and patient-selection criteria. Well-designed human studies with rigorous safety monitoring and clinically meaningful endpoints must test whether pulmonary homing provides a clinical advantage.

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Author contributions

XS and HL contributed to conceptualization and writing the draft. WS, TX, ML and RZ contributed to literature searches, reference collection, evidence summaries, and manuscript drafting and revision. DR and MY supervised and critically revised the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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