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Endogenous and Exogenous Cell-Based Pathways for Recovery from ARDS

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Synopsis

Regenerative medicine has entered a rapid phase of discovery, and much has been learned in recent years about the lung's response to injury. In this review, we first summarize the cellular and molecular mechanisms that damage the alveolar-capillary barrier, producing ARDS. We then turn our attention to the latest understanding of endogenous repair processes, highlighting the diversity of lung epithelial progenitor cell populations and their regulation in health and disease. Finally, we review the past, present and future of exogenous cell-based therapies for ARDS.

Keywords

ARDS; lung progenitor cells; MSCs

ARDS: Disruption of the Alveolar-Capillary Barrier

Acute Respiratory Distress Syndrome (ARDS) develops when the normal capacity of the alveoli to remain dry and participate in gas exchange is overwhelmed by a cascade of insults to the delicate alveolar-capillary barrier resulting in airspace fluid accumulation. In health, pulmonary capillary endothelial cells form a relatively tight membrane resistant to the paracellular movement of proteinacious fluid and inflammatory cells. This barrier depends on adherens junctions held together by VE-cadherin, as shown by studies specifically targeting this molecule with a metalloprotease.[1] Endothelial adherens junctions can be disrupted by TNF-α, VEGF and other cytokines from activated leukocytes,[2] as well as thrombin, complement activation, and toll-like receptor 4 signaling.[3] In addition, lung endothelial cells can be damaged or killed by bacterial products,[4] activated platelets,[5,6] and neutrophils.[7]

Increased permeability of lung endothelium is necessary but not sufficient for the development of pulmonary edema. Clearance of extravasated fluid from the interstitial space

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by lymphatics is normally rapid.[8] Similar to the lung endothelium, alveolar epithelial cells are joined together by tight junctions, but this barrier can be disrupted by toxic mediators from activated neutrophils[9] or macrophages,[10] pathogens including influenza,[11] and excessive mechanical stretch.[12] In addition, the alveolar epithelium is normally capable of actively transporting fluid from the alveolar lumen to the interstitial space as a final defense against alveolar flooding. The rate of alveolar fluid clearance can be increased by mild insults[13] but has been shown to be reduced by high tidal volume mechanical ventilation, inflammatory cytokines, and infection.[14] Not surprisingly, pathologic[15] and clinical studies[16] of patients with ARDS have revealed evidence of combined endothelial and epithelial dysfunction, including impaired alveolar fluid clearance. Furthermore, damage to alveolar type II cells along with extravasated plasma proteins and cellular debris disrupts the normal secretion and function of pulmonary surfactant.[17]

Endogenous Cell-Based Pathways for Recovery

General mechanisms of recovery

Returning the alveolus to a functional state is the obvious imperative for survival and recovery from ARDS. Repair and/or replacement of most damaged alveoli must occur in patients given the relatively mild pulmonary physiologic abnormalities measured in long-term survivors.[18] The processes by which this occur remain largely unknown, but some key insights have been generated over the last several decades. Broadly speaking, there must be resolution of edema fluid, removal of inflammatory cells and debris, and repair of the structural integrity and function of the alveolar epithelium and lung endothelium.

As recovery begins, aided by the resolution of the triggering event and prevention of further mechanical injury with lung-protective ventilation, there is a shift away from pro-inflammatory signaling. Interleukin-10 (IL-10), secreted by CD4 T cells, macrophages, and dendritic cells, is present even early during acute inflammation and acts primarily on macrophages to reduce pro-inflammatory mediator secretion and antigen presentation while enhancing scavenger function and production of other anti-inflammatory molecules, such as IL-1 receptor antagonist (IL-1ra).[19] Thus, IL-10 is thought to be critical in balancing pathogen clearance and tissue homeostasis. Its importance in this regard is highlighted by the existence of pathogen mimics such as Epstein-Barr virus encoded BCRF1.[19] A subset of CD4 T-cells termed regulatory T cells (Tregs), major secretors of IL-10 in a variety of disease states,[20] are present in the airspaces of patients with ARDS, and are critical in the resolution of endotoxin-induced acute lung injury in mice, in part through increasing the anti-inflammatory molecule TGF-β.[21]

IL-10, IL-1ra, and TGF- β notwithstanding, it had generally been thought that resolution of inflammatory injury occurs primarily due to the passive decline of dozens of pro-inflammatory mediators. More recently, however, a number of investigators have defined a new paradigm of active resolution of inflammation. A complex class of highly potent fatty-acid derivatives including lipoxins, resolvins, protectins, and maresins are now known to be generated during resolution. These lipid mediators bind to specific immune and resident cell receptors with high affinity and inhibit granulocyte recruitment and tissue activation, induce phagocytosis of apoptotic cells and bacteria, and aid in clearance of mucosal leukocytes.[22]

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Apoptotic neutrophils and other cells are removed mostly by macrophages in a phagocytic process termed efferocytosis.[23] Interestingly, the act of ingesting apoptotic cells is itself a stimulus to further anti-inflammatory signaling, helping to propel a feed-forward process of resolution.[24]

Endogenous lung progenitors

As the airspaces begin to clear, the damaged alveolar epithelium must replace lost cells and reform tight junctions. How this occurs is an active and controversial area of investigation, but has particular relevance to understanding the potential for stem and progenitor cell therapies in ARDS. As we move from proximal to distal in the lung, settled fact yields progressively to confusion and uncertainty, and so what follows is merely the current state of the evidence (see Table 1).

Based primarily on studies in mice, there is now general agreement that in the large airways basal cells self-renew and produce both ciliated and secretory cell types following epithelial damage incurred by various insults, including acid and naphthalene.[25,26] In the smaller intralobar airways, Clara cells, secretory cells that express secretoglobin 1a1 (Scgb1a1, or CCSP) can self-renew and also produce ciliated cells.[27] The subset of Scgb1a1+ cells at the bronchiolalveolar duct junction (BADJ) that also express surfactant protein C (SPC) has been termed bronchioalveolar stem cells (BASCs). In 2005, Kim et al.[28] reported that BASCs proliferated *in situ* following injury with naphthalene (kills Clara cells) or bleomycin (kills alveolar epithelial cells, AECs) and showed multipotency in clonal assays *in vitro*. Subsequently Rawlins and colleagues performed lineage tracing of cells expressing Scgb1a1 and reported no contribution to the alveolar epithelium following hyperoxia (which damages terminal bronchioles and alveoli).[29] Interestingly, following bleomycin injury, cells expressing Scgb1a1 due indeed produce alveolar epithelial cells as reported by multiple investigators.[30,31] This demonstrates, perhaps not surprisingly, that the injury model itself is crucial in identifying which progenitor populations become active and how repair occurs.

To add to the complexity, there are at least two other cell types that can reportedly produce alveolar epithelial cells:

- Integrin $\alpha 6\beta 4$-expressing alveolar cells (not expressing other known epithelial markers) generate airway and alveolar epithelia *in vitro*[32] and impressively produce alveolar-like structures abutting vascular elements in lung “organoids” when implanted into the kidney capsule of adult mice.[33]
- Kajstura and colleagues[34] reported that c-kit expressing cells derived from adult human lungs and injected into a 2 mm^2 region of mouse lung destroyed by cryo-injury produced airways, alveoli, and blood vessels bearing human lineage tracer; these results await confirmation.

Several other reports add to the theme of progenitor response being dependent upon injury-type. Barkausksas et al.[35] found with lineage tracing that SPC-expressing type II AECs self-renew and produce types I and II AECs slowly during adult life but rapidly following specific ablation of type II AECs with diphtheria toxin. That type II AECs could repopulate alveoli had been suspected since the 1970s[36] but these results provided the best evidence to

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date. Similarly, Desai and collleagues[37] recently reported that type II AECs repopulate alveoli slowly during healthy adulthood but rapidly after hyperoxia-mediated alveolar injury.

In contrast to these relatively mild, mostly alveolar-specific injuries, Kumar et al.[38] reported that H1N1 influenza in mice induced massive areas of lung destruction followed by the appearance of p63+, keratin-5+ (Krt5) pods of cells that appeared to migrate from airways into injured lung parenchyma and potentially give rise to new alveoli, though the ultimate fate of these cells has not yet been determined convincingly by lineage tracing. This phenomenon had not been reported following the comparatively milder injury models in common use and demonstrates that lung progenitor populations may respond in a graded fashion to injury.

Coordination of endogenous progenitor responses

With such flexibility in the response of lung epithelial progenitors, two recent reports deserve special attention because they illustrate potentially important regulatory mechanisms. In 2011, Ding and colleagues[39] performed pneumonectomies (PTX) on adult mice, and reproduced the finding that the intact lobes of the lung undergo rapid expansion with apparent formation of new alveoli.[40] By flow analysis, proliferating epithelial cells 3 days post-PTX were similar phenotypically to BASCs. Interestingly, disrupting VEGF signaling only within pulmonary endothelium blocked the epithelial progenitor response. In a series of elegant experiments, the authors showed that VEGF signaling in lung endothelium triggers the production of matrix metalloproteinase 14, which in turn releases EGF-receptor ligands that drive epithelial progenitor proliferation and alveologenesis.

Lee et al.[41] cocultured single BASCs with primary lung or liver endothelial cells and found that only lung endothelia supported BASC multilineage differentiation into airway and alveolar epithelial cells. Thrombospondin 1 (Tsp1), an inhibitor of angiogenesis expressed developmentally during alveolization,[42] was found to be central to this supportive role as mice deficient in this molecule had impaired epithelialization of airways (following naphthalene) and of alveoli (following bleomycin). Remarkably, alveolar repair in Tsp1 knockout mice could be rescued by the conditioned media of primary lung endothelial cells. Taken together, these results suggest an important role of the lung vasculature in guiding the expansion and differentiation of epithelial progenitors, similar to what is thought to occur in lung development[43] as well as in other adult tissues harboring multipotent progenitors, including the brain[44] and bone marrow.[45] Given the intricate structural and functional relationships between alveoli and lung capillaries required for effective gas exchange, this interaction during repair is not surprising. Clearly, further insights into how these vascular and epithelial processes are coordinated will be important in optimizing endogenous lung repair and in developing exogenous repair strategies.

Enhancement of epithelial and endothelial barrier function

Once reconstituted as a tight membrane, the alveolar epithelial barrier can resume effective active edema fluid transport and clearance as well as surfactant secretion. Although little is known about endogenous mechanisms controlling epithelial barrier tightening, several key

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signaling pathways are now known to regulate endothelial barrier function. Garcia and colleagues have discovered an important role for the sphingolipid sphingosine-1-phosphate (S1P) in rapidly enhancing lung endothelial barrier function by altering the cytoskeleton to increase cell overlap, and inducing adherens and tight junction assembly.[46] S1P or its synthetic analogs have shown therapeutic efficacy in murine[47] and canine[48] models of endotoxin-induced acute lung injury, ischemia-reperfusion,[49] radiation-induced lung injury,[50] and influenza.[51] Angiopoeitin-1 is produced by a variety of cells and acts on endothelial Tie2 receptors to promote barrier integrity.[52] Adrenomedullin binds calcitonin receptor-like receptor on lung endothelial cells and promotes intercellular adherence.[53] Administration of adrenomedullin improves endothelial barrier function in rodent models of ventilator-induced[54] and endotoxin mediated lung injury.[55] Finally, London and colleagues[56] reported that Slit acts on lung endothelial Robo4 receptors to reduce vascular leakage in response to intratracheal endotoxin and H5N1 influenza, likely by promoting VE-cadherin expression.

Exogenous cell-based pathways for recovery

As many of the mechanisms of lung injury have been worked out over the last several decades, researchers have tested a variety of targeted pharmacologic interventions in patients with ARDS, including anti-oxidants, beta-agonists, surfactant, and IL-10.[57] However, the results have been uniformly disappointing, probably in part because ARDS is heterogeneous and is characterized by multiple injurious cascades operating simultaneously. Mortality has declined as lung protective ventilation and fluid management strategies have been implemented,[58] and additional clinical benefits from paralysis[59] and prone positioning[60] may improve outcomes further. Nevertheless, there remains a compelling need to develop therapies that directly target the complex pathophysiology of ARDS. Exogenous cell-based therapies may hold special promise in this regard, as recent research has shown they are capable of affecting multiple pathways of lung injury and repair.

Endothelial progenitor cells (EPCs)

Given the derangement of endothelial barrier function known to characterize ARDS, these cells have intuitive appeal as a potential therapy. EPCs were originally described in the late 1990s as circulating CD34+ cells that differentiated into endothelial cells *in vitro* and localized to sites of angiogenesis in adult animals.[61] In 2005, Yamada et al.[62] found that circulating EPCs were increased in patients with bacterial pneumonia, and that lower EPC counts were associated with persistent lung fibrosis following pneumonia resolution. Burnham and colleagues[63] then isolated EPCs in patients with ARDS, finding that the number of EPC colonies predicted improved survival. In 2008, Lam et al.[64] reported that administering autologous EPCs to rabbits 30 minutes following oleic acid injury improved endothelial barrier function and reduced lung edema, hemorrhage, and inflammation. Mao and colleagues[65] treated rats with autologous EPCs or saline 30 minutes after intravenous endotoxin, finding that EPC-treated rats had improved survival, reduced lung edema, and increased IL-10. Interestingly, there was evidence of modest engraftment into the injured lung endothelium up to 14 days later. Such engraftment may be model-specific, however, as these cells do not appear to contribute to lung endothelial expansion after

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pneumonectomy.[66] Autologous EPCs are now the subject of clinical trials in cirrhosis (NCT01333228), ischemic stroke (NCT01468064), and critical limb ischemia (NCT01595776). However, given that EPCs circulate at low levels, autologous transplantation is unlikely to be an option in the acute phase of ARDS, and the safety of allogeneic EPC transplantation remains unknown.

Mesenchymal stem/stromal cells (MSCs)

In contrast to EPCs, MSCs are relatively immunopriveleged and known to be well-tolerated after allogeneic transplantation.[67] These cells were first described in the 1960s as plastic-adherent, spindlelike cells, that can be isolated from bone marrow, fat, umbilical cord blood, placenta, and connective tissues.[68] Although defined in part by the capacity to differentiate into osteoblasts, chondroblasts, and adipocytes, the overwhelming balance of evidence is that they rarely integrate and survive long-term in adult tissues after allogeneic transplantation.[69] They have been studied extensively in models of acute inflammation in many different organ systems, and have been found to have remarkable therapeutic effects across a range of murine models of acute lung injury, including bleomycin,[70] intratracheal[71–73] or intraperitoneal[74] endotoxin, cecal ligation and puncture,[75,76] pseudomonal abdominal sepsis,[77] and *E-coli* pneumonia.[78] Recently, human bone marrow derived MSCs were shown to reduce inflammation and improve alveolar fluid clearance in *ex vivo* human lungs injured with live *E-coli*.[79] At least some of their therapeutic properties can be recapitulated by the microvesicles they actively secrete in culture.[80–82]

MSCs are thought to work by multiple mechanisms in these models (Fig. 2), including (a) reducing alveolar-capillary barrier permeability,[72,75,76,83] in part by secretion of angiopoietin-1,[84] (b) increasing alveolar fluid clearance, at least in part by secretion of keratinocyte growth factor,[79,85] (c) shifting cytokines and resident macrophages from pro- to anti-inflammatory,[86] (d) improving bacterial clearance by enhancing phagocytosis and secreting antibacterial peptides,[77,78,83] and remarkably (e) transferring mitochondria to alveolar epithelial cells, rescuing ATP generation.[73]

Another intriguing possible mechanism has come to light recently. When postnatal rodents are exposed to high oxygen concentrations, they develop pulmonary hypertension due to a dramatic simplification of lung architecture, modeling human bronchopulmonary dysplasia (BPD). In 2009, MSCs were shown to largely normalize lung capillary and alveolar growth when given by airway or blood in mouse and rat BPD models, but without any evidence of significant engraftment.[87,88] Interestingly, Tropea and colleagues[30] reported in 2012 that MSCs increased BASCs in the BPD model by a paracrine mechanism. This work suggests that MSCs, like lung endothelium, may help orchestrate epithelial progenitor responses to injury. Indeed, in other experimental systems, MSCs have been shown to interact with endothelial cells to establish a hematopoietic microenvironment after heterotopic transplantation,[89] to increase the proliferation and survival of hippocampal neural progenitors,[90] and to increase c-kit+ cardiac stem cells in a porcine model of myocardial infarction.[91]

With this in mind, there is considerable optimism following the recently completed Korean phase 1 clinical trial of MSCs in neonates at high risk of BPD.[92] In this dose-escalation

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study, 9 patients with mean gestational age of 25 weeks (mean birth weight 790 g) received either 1×10^7 or 2×10^7 allogeneic umbilical cord blood-derived MSCs/kg by airway at an average of 10 days after birth. There were no adverse events, and although the study was not designed to test efficacy, BPD severity appeared lower in treated patients than in a matched comparison group. A two year follow-up study of these patients is planned (NCT01632475).

Given the encouraging preclinical results from MSCs in rodent, sheep (Asmussen et al., in revision at *Thorax*) and *ex vivo* perfused human lung models of acute lung injury, an NHLBI-supported phase 1/2 (NCT01775774/NCT02097641) clinical trial of bone-marrow derived allogeneic MSCs in patients with moderate to severe ARDS is now underway. START (STem cells for ARDS Treatment) targets a total enrollment of 69 patients, 9 in phase 1, and 60 in phase 2. In phase 1, three cohorts of patients received 1, 5, or 10×10^6 cells/kg intravenously, and there were no significant adverse events at the highest dose. In phase 2, patients will be randomized 2:1 to receive 10×10^6 MSCs/kg or plasmalyte control. The primary endpoint of Phase 2 will be safety, but secondary endpoints will include the lung injury score, PaO_2/FiO_2, oxygenation index, SOFA score at day 3, ventilator-free days, 60 day mortality, plasma biomarkers of lung epithelial injury, endothelial injury, and inflammation, and protein in a mini-bronchoalveolar lavage at 48 hours.

Barriers to developing cell-based therapies in patients with ARDS

As with all trials in critical care, the complex nature of the patients and the importance of logistical speed pose formidable hurdles in the design and implementation of exogenous cell-based therapies for ARDS. Beyond these difficulties, additional challenges, many summarized in a recent report from an NIH-NHLBI workshop,[93] include:

- Ensuring consistent cell therapy product. This involves strict screening of donors and Good Manufacturing Practice for sterility, use of animal derived products, and passage number.
- Quality control. Standard testing for cultured cell products includes screening for bloodborne pathogens, post-thaw cell viability, bacterial endotoxin, and cytogenetics.
- Assessing potency. Ideally a rapid, simple, reliable assay that can be run at multiple sites and correlates well with observed therapeutic effects. This is a challenging but critical barrier to up-scaling any new promising cell-based therapy for widespread use (as for phase 3 trials and beyond); an effective potency assay is essential in fine-tuning donor selection, manufacturing processes, and final preparation of the product.
- Developing pre-clinical (animal) data that adequately mirror the phase 1 safety studies required by the FDA. This might require a shift in mindset for basic science investigators, as it requires careful attention to logistics including cell storage, shipment, packaging, freezing and thawing procedures (including method of cryoprotection), dilution, washing, and method and speed of administration. In addition, supportive animal studies must follow Good Laboratory Practice (GLP) guidelines.

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- Determining the optimal dosage, route, and timing of cell delivery. Intratracheal administration bypasses the vasculature and theoretically offers more direct access to injured lung tissue,[92] though may pose additional hazards to gas exchange in the acute and often dynamic respiratory failure that characterizes ARDS.
- Careful consideration should be given to employing large animal models given that such studies may (a) provide important additional information on efficacy, (b) permit monitoring of salient physiological safety endpoints, especially during and immediately after cell administration.
- Filing an Investigational New Drug application (IND). For this challenging process, it is helpful to elicit initial feedback from the FDA[94] during the planning stages of the animal experiments, and to obtain institutional support for the writing and submission of this highly technical document.

Remaining questions and research priorities

Regenerative medicine has entered an era of intense discovery, as evidenced by exponential growth in clinical trials targeting a wide range of human diseases with cellular therapies; this promise holds true for those of us engaged in developing better therapies for ARDS. However, key questions remain, and many obstacles may yet prevent effective cell-based therapies from becoming a reality.

Understanding the endogenous response

The importance of the type of injury in determining the endogenous progenitor cell response (highlighted in detail above) cannot be overstated. Going forward, it will be increasingly important to utilize clinically relevant models of lung injury, including bacterial and viral pneumonia, which together account for the majority of cases of ARDS.[95] These models are challenged by a tendency to be variable in the severity of lung injury, to cause severe systemic illness, and to produce a robust immune response with a complex cellular infiltrate, all of which complicate the kinds of lineage tracing studies that are now the accepted scientific standard.

Looking forward, we must advance the level of evidence of endogenous repair from a simple qualitative demonstration of expression of mature epithelial markers to a richer anatomical and temporal understanding of how newly formed epithelial-lined structures interface with lung capillaries and become (or fail to become) functional alveolar units. It may well be that simultaneous mechanisms are at work, including the diffuse growth of uninjured lung (as occurs following pneumonectomy[39]) and the more dramatic progenitor migratory events reported after influenza.[38] Insights generated from this research have obvious relevance for ARDS but also hold promise for improving our understanding of endogenous repair processes in diseases as diverse as COPD and interstitial lung disease.

Safety of exogenous cell-based therapies

The perils of developing new classes of therapies for patients are well-known from gene therapy trials in the 1990s.[96] Potential complications of allogeneic cell therapy include infections (due to contaminated product, immunomodulation, or even zoonoses, as prions

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can theoretically be carried by cell culture reagents), worsened inflammation from immune rejection of transplanted cells, and for intravenous administration, embolic load on the right ventricle (since most cells deposit at least temporarily in the lung[97]). A recent review[98] reported that MSC therapy in children and adults with left heart failure, myocardial infarction, spinal cord injury, stroke, hematologic malignancies, and Crohn's disease appears to be safe with only transient fever being occasionally noted. Given the concern for possible embolic insult to a pulmonary vasculature and right heart already stressed from the acute hypoxemia of ARDS, it is reassuring that a recent placebocontrolled RCT of MSCs in moderate to severe COPD[99] showed no acute changes in hemodynamics or oxygenation, and no measurable difference in diffusing capacity, ambulatory oxygenation saturation, or echocardiographic estimate of right-sided pressures through two-years of follow-up. The recent phase 1 data from MSC administration by airway to neonates at risk for BPD[92] and intravenously to patients with moderate to severe ARDS (NCT01775774) are similarly reassuring.

Neoplasia is another significant safety concern. In the MSC literature, there is some evidence that murine bone marrow-derived MSCs have genetic instability even at low passage number, with reports of tumor formation following intravenous administration in models of myocardial infarction and diabetic neuropathy.[100] Fortunately, this appears to be unique to murine MSCs, as human MSCs cultured for prolonged periods do not appear to transform.[101] A review of over 500 large animals treated with MSCs for therapy of myocardial infarction failed to reveal any evidence of malignancy out to 3 months.[102] Finally, autopsy material from heavily immunosuppressed patients who had previously received allogeneic MSCs revealed minimal long-term engraftment and no evidence of ectopic tissue formation.[103]

"Off-target" effects

Given that ARDS is frequently associated with multiorgan failure, might exogenous cell therapies prove to have favorable effects outside the lung, for example in acute kidney injury[104] or sepsis?[105] Ideally, trial design for cell therapy in critical illness will incorporate clinical and biological endpoints that can help inform both efficacy and mechanism of action across related organ systems and scientific disciplines. Could cell therapies that effectively dampen the acute inflammatory response in ARDS unexpectedly impair the endogenous lung repair processes highlighted above? Or might they accelerate them? These and other questions should become more tractable in coming years as more data from clinical trials become available, and as the basic science research toolkit continues to expand.

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Key Points

- ARDS occurs when protein-rich fluid accumulates in the airspaces due to a breakdown of the alveolar capillary barrier following endothelial and epithelial damage and dysfunction.
- Endogenous lung progenitor populations are mobilized differentially in various animal models of lung injury.
- Exogenous cell therapies for ARDS hold substantial promise for improving upon the endogenous response, and clinical trials are ongoing.

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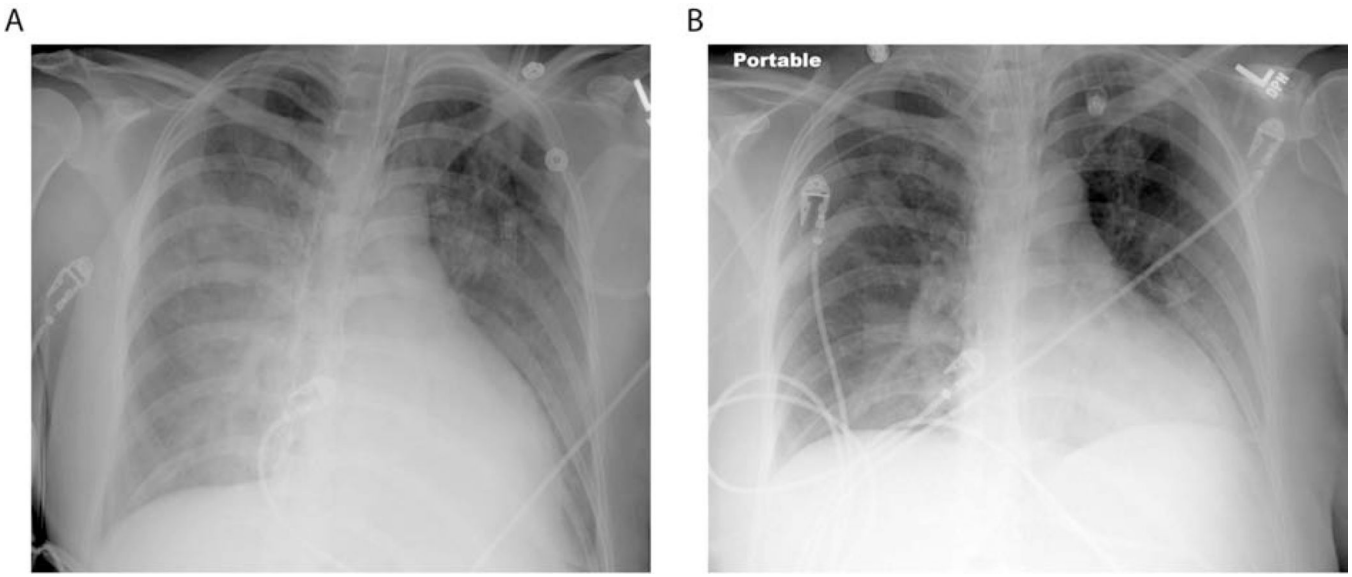

Figure 1.
Resolution of ARDS. Typical chest radiography findings in a patient with ARDS include patchy bilateral airspace opacities (A). During resolution, these changes improve significantly (B).

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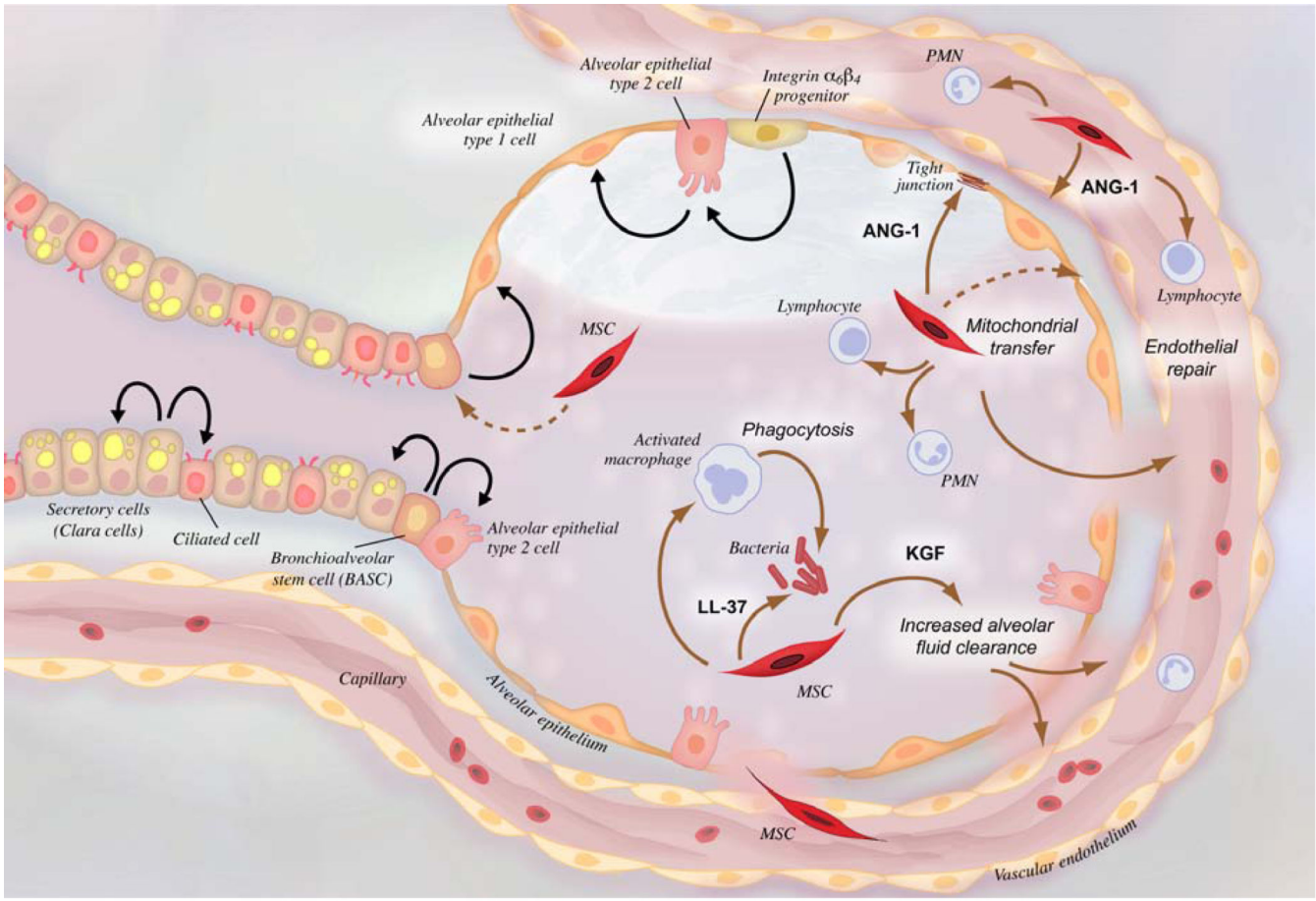

Figure 2.

Schematic of an injured alveolus and adjacent alveolar duct. Potential mechanisms of MSC therapeutic effects in ARDS are shown with brown arrows. Black arrows depict lineage relationships during cell turnover. Abbreviations: MSC, mesenchymal stem cell; PMN, polymorphonuclear leukocyte; ANG-1, angiopoietin-1; LL-37, cathelicidin; KGF, keratinocyte growth factor.

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Table 1

Summary of lung progenitor studies

Reported stem/progenitor*	Injury model	Injured cells	Finding	Ref
type II AECs in rats	nitrogen dioxide	AECs	electron microscopy and autoradiography suggested that type II AECs self-renew and produce type I AECs	36
type II AECs	bleomycin; targeted diphtheria toxin	type I & II AECs; type II AECs	SPC lineage tracing showed replacement of both types I and II AECs	35
fraction of type II AECs	hyperoxia	type I AECs	replacement of both types I and II AECs via EGFR/KRAS signaling	37
BASC expressing Scgb1a1 and SPC	naphthalene; bleomycin	clara cells; AECs	these cells at the junction of bronchioles and alveoli self-renewed and had multipotent differentiation in culture	28
BASC	naphthalene; hyperoxia	clara cells; terminal bronchioles and type I AECs	Scgb1a1 lineage tracing showed that BASCs replace airway but not alveolar epithelium	29
BASC	bleomycin	AECs	Scgb1a1 lineage tracing showed that BASCs produce types I and II AECs	30 31
basal cells	naphthalene	Clara cells	KRT5 lineage tracing showed basal cells self-renew and make new clara and ciliated cells in the airways	26
human c-kit expressing cells	cryo-injury	All epithelial cell types	c-kit+ cells engrafted into mouse lung and produce airways, alveoli, and blood vessels	34
P63-expressing bronchiolar cells	influenza	All epithelial cell types	massive wave of Krt-5 expressing cells appeared to migrate from airways and form new alveoli	38

* all murine unless otherwise specified

Abbreviations: AECs, alveolar epithelial cells; BASC, bronchioalveolar stem cell; Scgb1a1, secretoglobin 1A1; SPC, surfactant protein c; KRT5, keratin 5; EGFR, epidermal growth factor receptor.

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Table 2

Challenges to the implementation of exogenous cell-based therapies for ARDS

Potential barrier	Details
consistency of the cell product	cell handling, passage number, reagents (especially animal-derived)
quality control	screening for bloodborne pathogens, endotoxin limits, viability after thaw, cytogenetics
potency	assay should be simple, fast, reliable, and predictive of therapeutic effects in patients
IND-enabling animal data	GMP and GLP practices, standardized procedures for shipping, storing, freezing, thawing, diluting, washing, and administering; use of large animal models
best delivery route	airway or intravenous
IND submission	highly technical and labor intensive

Abbreviations: IND, investigational new drug; GMP, good manufacturing practice; GLP, good laboratory practice.