Вестник РУДН. Серия: МЕДИЦИНА
RUDN Journal of MEDICINE. ISSN 2313-0245 (Print). ISSN 2313-0261 (Online)
2026;30(2)
http://journals.rudn.ru/medicine

ИММУНОЛОГИЯ
IMMUNOLOGY

DOI 10.22363/2313-0245-2025-30-2-233-247
EDN GSEBMH

ОБЗОР
REVIEW

Highly differentiated cells in the therapy of acute respiratory distress syndrome

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Abstract. *Relevance.* Acute respiratory distress syndrome (ARDS) is a severe, life-threatening form of acute lung injury with a high mortality rate. In severe cases, pathological changes extend to the systemic level and manifest as cytokine storm syndrome. The lack of effective treatment options underscores the importance of exploring therapeutic approaches, including cell therapy. Interest in this treatment option increased during the SARS-CoV-2 pandemic, as evidenced by the numerous clinical trials registered for the use of cell preparations to treat ARDS. *The aim of the study:* Thus, this review summarizes preclinical and clinical studies on using highly differentiated cells, including immune system cells, to treat ARDS. To this end, we will describe key points in the pathogenesis of ARDS, including etiologic subtypes and stages, as well as the key cells involved and the results of their use in ARDS therapy. This review highlights the potential of using alveolar cells type 1 and type 2, as well as epithelial cells, for rapid lung regeneration after ARDS. Currently, there are no data describing the use of neutrophils, which trigger primary pathological changes in the lungs, for ARDS treatment. The use of macrophages, which play a key role in ARDS pathogenesis,

is limited by their ability to quickly repolarize. Natural killer cells (NK cells), regulatory T cells (Tregs), and invariant natural killer T (iNKT cells) have shown high efficacy in treating ARDS in preclinical and clinical studies. *Conclusion.* Thus, using NK cells, Tregs, and iNKT cells for ARDS cell therapy seems promising. However, the lack of standardized protocols for preparing and administering cell therapies, as well as small sample sizes, indicate the need for additional studies.

Keywords: ARDS, cell therapy, macrophage, iNKT cells, Treg, neutrophils, clinical trials

Funding. The work was supported by the state assignment No. 125050605838-9.

Author contributions. Kiseleva V.V. — conceptualization, drafting of the article, Miroshnichenko E.A. — design of tables and figures, Vishnyakova P.A. — conceptualization, drafting of the article, Kosyreva A.M. — drafting and revision of the article, Elchaninov A.V. — revision of the article, Fatkhudinov T. Kh. — process management. All authors approved the version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of interest statement. Authors declare no conflict of interest.

Ethics approval — not applicable

Acknowledgements — not applicable.

Consent for publication — not applicable.

Received 20.05.2025. Accepted 19.06.2025.

For citation: Kiseleva VV, Miroshnichenko EA, Vishnyakova PA, Kosyreva AM, Elchaninov AV, Fatkhudinov TKh. Highly differentiated cells in the therapy of acute respiratory distress syndrome. *RUDN Journal of Medicine.* 2026;30(2):233–247. doi: 10.22363/2313-0245-2026-30-2-233-247. EDN: GSEBMH

Introduction

Acute respiratory distress syndrome (ARDS) is a critical form of acute lung injury (ALI). It is characterized by impaired gas exchange and reduced lung compliance [1]. According to the Berlin definition, ARDS requires meeting three key criteria. These include an acute onset, bilateral pulmonary infiltrates on imaging (chest X-ray or computer tomography) not caused by cardiac failure, and a PaO_2/FiO_2 ratio of less than 300 mmHg [2]. The mortality rate in ARDS varies depending on disease severity and population, with a reported weighted pooled mortality of approximately 40% [3].

Current management of ARDS is primarily supportive, aiming to sustain vital organ function while the lungs heal. The cornerstone of this approach is lung-protective ventilation, which minimizes further ventilator-induced lung injury. Adjunctive strategies include prone positioning to improve oxygenation, careful sedation, and fluid balance management, often utilizing diuretics. In the most severe cases, extracorporeal membrane oxygenation (ECMO) serves as a salvage therapy to provide gas exchange directly [4]. The lack of treatments that directly address the underlying pathophysiology of ARDS has significantly intensified the search for new disease-modifying interventions. Cell therapy has emerged as a particularly promising avenue, supported by its established therapeutic role in a variety of conditions, from accelerating wound healing to treating neurodegenerative diseases. Since the first FDA-approved cell therapy product in 2010 [5], the field of advanced treatments has rapidly evolved, with over 30 gene and cell therapies currently approved [6], including the landmark 2023 approval of the first

CRISPR/Cas-based treatment for sickle cell disease [7]. However, this remarkable innovation and the growing complexity of therapy have simultaneously raised significant concerns about prohibitive costs and the difficulty of ensuring equitable patient access to treatment [8].

Although "cell therapy" is often equated with mesenchymal stem cells (MSCs)—valued for their multipotency, availability, and suitability for allogeneic use — advances in biotechnology now enable the application of more differentiated cell types. Additionally, strategies aiming to modulate specific pathogenic cell populations in situ represent a growing direction in ARDS treatment.

Thus, the objective of this review is to synthesize recent findings on ARDS pathogenesis, with a focus on alterations in immune cell populations, and to evaluate their translational potential for novel therapeutic interventions.

Key points of acute respiratory distress syndrome pathogenesis

In the previous reviews, the pathogenesis of ARDS was revealed in detail [9]. We highlighted key points in the pathogenesis of ARDS and some interesting facts necessary to understand the points of impact for the use of immune cells in the therapy of this condition.

Etiological subtypes of ARDS

A key feature of ARDS is its polyetiological nature. Its primary risk factors are categorized into two distinct groups. The first group involves direct lung injury, leading to pulmonary ARDS. This includes etiologies such as aspiration, inhalation of toxic substances, pulmonary infection, and blunt chest trauma [10]. The second group encompasses indirect lung injuries that originate outside the lungs, causing extrapulmonary ARDS. Examples are shock, sepsis, trauma, major hemorrhage, blood transfusions, poisoning, and cardiopulmonary bypass. These two etiological subtypes lead to divergent pathophysiological and histological changes [11]. In pulmonary ARDS, direct damage to the bronchial and alveolar epithelium occurs. This damage, resulting from factors like infection or contusion, leads to bronchial obstruction, atelectasis, and alveolar edema. Histologically, alveolar edema and intra-alveolar fibrin deposition are predominant features. Advanced stages are further characterized by significant collagen fiber formation and the presence of apoptotic neutrophils. Single-cell sequencing analyses reveal that pulmonary ARDS lung tissue contains elevated levels of B cells, neutrophils, and T helper (Th) cells. Conversely, it shows relatively lower counts of basophils, macrophages, monocytes, and dendritic cells compared to the extrapulmonary subtype [12]. In the second case, the initial insult is systemic, leading to damage of the pulmonary capillary endothelium. This injury triggers metabolic and structural alterations, which increase the permeability of the alveolar-capillary barrier. Consequently, plasma and blood cells extravasate into the lung interstitium, causing a pronounced thickening of the interalveolar septa. The resulting pathological pattern in the lungs is more diffuse than in pulmonary ARDS and is predominantly characterized by alveolar collapse rather than consolidation.

Stages of the acute respiratory distress syndrome

The course of ARDS includes three sequential phases: exudative, proliferative, and fibrotic [13]. The exudative phase begins with activation of innate immunity via Toll-like receptors on alveolar macrophages and epithelium. This triggers the recruitment of neutrophils and their formation of neutrophil extracellular traps (NETs). Simultaneously, levels of thrombin, TNF-α, and VEGF increase, destabilizing the endothelial VE-cadherin and epithelial E-cadherin junctions. This leads to disruption of the alveolar-capillary barrier, impaired fluid clearance, and the development of alveolar oedema, which defines this stage.

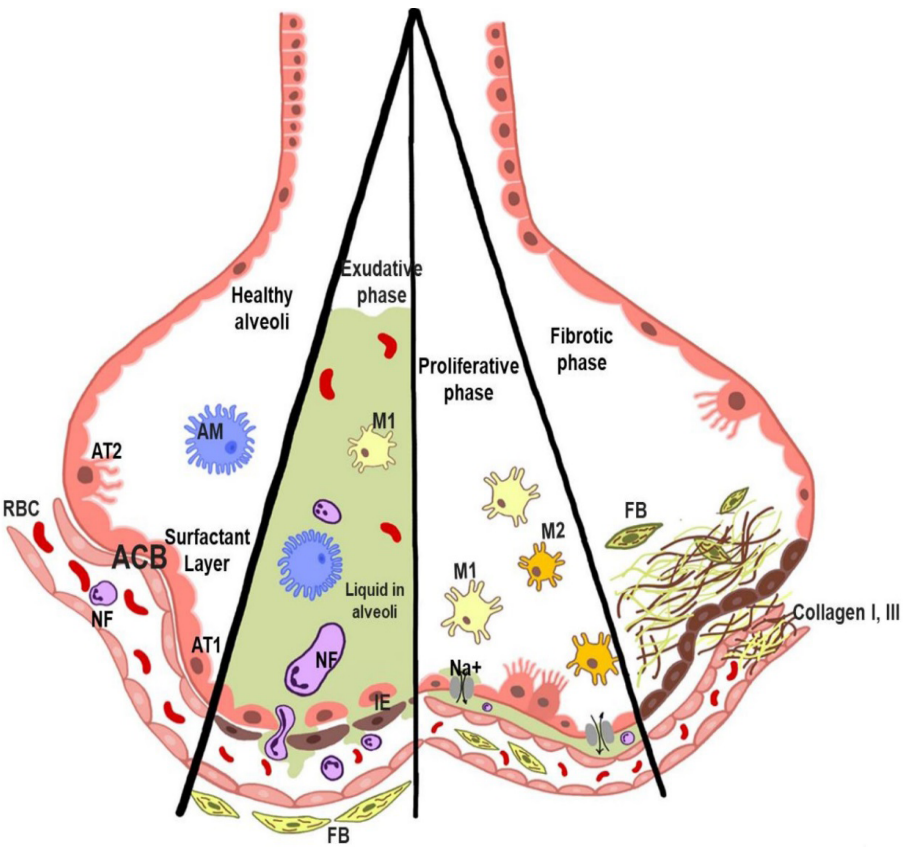
The proliferative phase focuses on inflammation resolution through three key processes: epithelial barrier repair, clearance of inflammatory cells, and restoration of alveolar fluid homeostasis. This stage involves proliferation of type II alveolar cells, fibroblasts, and myofibroblasts. Disease progression can then follow one of two paths. The first, favourable pathway leads to

normalized gas exchange via alveolar cell regeneration. The second, less favourable pathway involves fibroblast invasion into alveolar spaces through breaches in the basal lamina [14]. During this remodelling, hyaline membranes are cleared by macrophage phagocytosis or become infiltrated by fibroblasts. The interstitial space, rich in collagen and elastic fibers, hosts interstitial fibroblasts (IFs). Buechler et al. categorizes fibroblasts across organs into two principal subtypes: universal and specialized, the latter existing in either a steady-state or activated (perturbed) form [15]. Close crosstalk between alveolar macrophages (AMs) and IFs is essential for regulating extracellular matrix remodelling and driving fibroblast activation into contractile myofibroblasts, a process relevant in both health and disease [16, 17].

The final, fibrotic phase is marked by chronic scarring and vascular occlusion. As ARDS is a systemic condition, pulmonary recovery is contingent on overall clinical improvement. Activated fibroblasts proliferate and deposit collagen types I and III, forming fibrotic foci that lead to either slowly resolving or permanent architectural distortion. Notably, in influenza-associated ARDS, the fibroblast secretome can shift; for instance, production of ADAMTS4 protease by activated fibroblasts correlates with severe disease and increased mortality [18].

The main stages of ARDS pathogenesis are summarized in Figure.

In healthy lungs, endothelial and alveolar epithelial integrity is mediated by vascular endothelial cadherin (VE-cadherin) and E-cadherin respectively. Type I and type II alveolar epithelial cells are involved in maintaining an osmotic gradient for the removal of fluid from the alveoli into the interstitium of the lung. A key component necessary for the creation of the osmotic gradient is the sodium channel (ENaC). Initially, there



Pathogenesis of Acute respiratory distress syndrome. AT1 — type I alveolar cells, AT2 — type II alveolar cells, AM — alveolar macrophages, ACB — alveolar-capillary barrier, NF — neutrophils, RBC — red blood cells, FB — fibroblasts, IE — interstitial edema

is activation of the innate immune system via Toll-like receptors on pulmonary epithelium and alveolar macrophages. Recruitment of neutrophils to the lungs occurs and NETs are formed. Thrombin, tumor necrosis factor-α (TNF-α), and vascular endothelial growth factor (VEGF) are increased, leading to destabilization of VE-cadherin bonds. Neutrophils migrating to the focus of inflammation cause damage to the epithelium. Simultaneously with the disruption of the alveolar-capillary barrier, alveolar fluid clearance is impaired. As a result, the formation of pulmonary oedema occurs. Therefore, the first stage of the disease is called the exudative stage. Resolution of inflammation requires restoration of the alveolar epithelial barrier, removal of inflammatory cells and restoration of alveolar fluid clearance. Type II alveolar cells, fibroblast and myofibroblasts proliferate in this phase. The proliferative phase transitions smoothly into the fibrotic phase. There is an accumulation of collagen and fibrin with subsequent occlusion of vessels and loss of alveoli of their functions.

Key cells involved in acute respiratory distress syndrome pathogenesis and approaches to treating based on targeting these cells

The alveolar-capillary barrier, consisting of endothelial cells, type I alveolar epithelial cells (AEC1), type II alveolar epithelial cells (AEC2) and basement membranes, takes the main blow in developing ARDS. In addition, both innate (macrophages, neutrophils) and adaptive (T and B lymphocytes) immune cells are actively involved in the pathogenesis of ARDS. Currently, all of the cell types described are under close research scrutiny. The data obtained can be used both to deepen knowledge of the pathogenesis of ARDS and to develop new approaches to its therapy based on their use.

Endothelial cells

In physiological conditions endothelial cells (EC) are known to regulate the balance between the processes of coagulation and fibrinolysis. Normally, they inhibit coagulation by binding antithrombin III on the endothelial surface, endothelial production of tissue factor pathway inhibitor (TFPI), expression of thrombomodulin, activation of protein C and production of tissue plasminogen activator (t-PA) [19]. In inflammatory diseases, including ARDS, endothelial anticoagulant function is impaired by NF-kB-dependent mechanisms. It was experimentally shown that inhibition of NF-kB in the endothelium leads to increased barrier function of the vascular wall, decreased neutrophil infiltration in the lungs, liver, kidneys, heart and small intestine, as well as decreased thrombin-antithrombin complexes in the blood [20]. The glycocalyx of the endothelial lining, composed of glycosaminoglycans, proteoglycans, and glycoproteins, plays an important role in maintaining barrier function. Disruption of the glycocalyx leads to NO release, vasodilation, and increased vascular permeability [21]. In experimental models of LPS-induced endotoxemia and in patients with SARS-CoV-2, a thinning of the glycocalyx on the surface of the endothelium of pulmonary capillaries was observed. This facilitates the interaction of neutrophils with adhesion molecules on EC, their rolling and edge-standing [22]. Vascular endothelial cells of alveolar capillaries can be involved in regenerative processes. In [23] it was shown that the alveolar capillary endothelium, like the alveolar epithelium, consists of two intermixed cell types. The first cell type is the “aerocytes”. It is specialized for gas exchange and leukocyte transport and is unique to the lung. The other cell type, termed gCap (“general” capillary), is specialized to regulate vasomotor tone. It functions as a stem/progenitor cell in capillary homeostasis and repair. Aerocytes (aCap) may be particularly important in lung injury because they are the likely site of leukocyte trafficking, which is primarily a capillary function in the lung [24]. They specifically express adhesion and leukocyte sequestering genes. gCap cells function as specialized stem/progenitor cells that replenish the alveolar capillary endothelium during maintenance and repair. gCap cells express genes encoding MHC class II components, suggesting that they present antigens. In addition, gCap cells express a vasoconstrictor (Edn1) that can signal to the endothelin type A receptor

(Ednra) on pericytes; they also express endothelial nitric oxide synthase (Nos3) and prostaglandin I2 synthase (Ptgis), making them a source of vasodilators. In the experimental model of ARDS, robust apelin expression has been demonstrated in gCap, stem-like ECs that give rise to apelin receptor-positive, highly proliferative progenitor cells responsible for replenishing all depleted endothelial cell pools, including aCap that rebuild the air-blood barrier [25]. Other work [26] has identified macrovascular endothelium (maECs), microvascular endothelium (miECs), and a novel population of Car4-high ECs in the mouse lung. Car4-high ECs express a unique gene signature and ligand-receptor analysis indicates that they are primed to receive reparative signals from alveolar type I cells. After acute lung injury, they are preferentially localized in regenerating regions of the alveolus. Influenza infection reveals the emergence of a population of highly proliferative ECs, likely derived from multiple miEC populations, that contribute to alveolar revascularization after injury. These findings highlight the critical role of ECs cells in the regenerative process in ARDS mediating lung microvascular repair and provide insights for the development of novel regenerative strategies for the treatment of ALI and ARDS.

Type I alveolar epithelial cells

Alveolar epithelial cells (AEC1 or AT I) are large flat cells that cover more than 95% of the alveolar surface area and promote efficient gas exchange [27]. In healthy lung this cells maintain fluid and ion balance by expression aquaporin-5 (AQP5), which is crucial for water movement across the lung epithelium, helping maintain the optimal amount of alveolar lining fluid and amiloride-sensitive epithelial sodium channel (ENaC) and various potassium channels, which help regulate ion fluxes and maintain the electrochemical gradient necessary for fluid balance [28, 29]. They express receptors like TLR4 and RAGE, which can initiate inflammatory responses upon sensing microbial products [27]. Emerging evidence suggests that AEC1 cells are involved in protein transport and translocation via transcytosis, contributing to the regulation of macromolecules across the alveolar epithelium. The potency of this cell type in the therapy of ARDS remains to be explored.

Type II Alveolar Epithelial Cells (AEC2 or AT II)

The main functions of AEC2 in healthy lungs are surfactant production, secretion, and regeneration of alveolar epithelium [30]. It is shown that in humans, cell trapping in the transition state leads to the development of fibrosis. AEC2 cells regulate the immune response by synthesizing surfactant and other anti-inflammatory proteins and lipids as stated above. These cells help repair damaged lung tissue, rapidly proliferating and differentiating into AEC1 cells after epithelial cell injury. Therapy with freshly isolated enriched fraction of AEC2 cells from HCl-LPS-induced ARDS rats led to the effects similar to MSC therapy. A significant decrease in total protein and IgM in bronchoalveolar lavage (BAL) was shown, indicating a decrease in epithelial permeability. The results of counting the number of neutrophils in BAL fluid and myeloperoxidase (MPO) activity showed a decrease both during treatment with MSCs and during treatment with AEC2 cells. Thus, it can be assumed that AEC2 therapy has great potential [31].

Neutrophils

Normally, neutrophils are located in the lung microvasculature beyond the airspaces [10]. This pool of lung neutrophils exists in a dynamic equilibrium with circulating neutrophils, allowing for rapid response to infections or other stimuli [32]. The proinflammatory environment that forms in the alveoli during the development of ARDS promotes the recruitment of neutrophils. Here, neutrophils are activated and release reactive oxygen species, proteases, and proinflammatory lipid mediators such as prostaglandins and leukotrienes [33]. It is shown that in sepsis, a common complication of which is ARDS, neutrophils are marginalized in capillaries due to increased expression of adhesion factors — E-selectin, ICAM-1 and V–CAM-1 — on endothelial cells. Adhesion of activated neutrophils to the vascular wall and their transmigration into tissues leads to further activation of endothelial cells, completing the “vicious circle” [34]. As a result, exudate penetrates the pulmonary parenchyma and alveolar

airspace. Gas exchange is disrupted and hypoxia occurs [35]. In the sheep model of ARDS, it was shown that alteration of perfusion mechanisms leads to an increase in dead space, an early marker of mortalit [36]. Formation of NETs is another antimicrobial defense mechanism, hyperactivation of which can lead to tissue damage. NETs are composed of DNA, histones, and proteases and, when released into the airspace during the development of ARDS, can increase inflammation by activating the NRLP3 inflammasome, which initiates localized release of interleukin-1-β and interleukin-18 [37]. NETs hyperactivation can also promote thrombosis.

Thus, excessive neutrophil recruitment and their hyperactivation at the site of inflammation lead to tissue damage and progressing ARDS. Targeting these processes can be used as an approach to the therapy of ARDS. Molecules of most interest are chemokine receptor antagonists such as CXCR2 or CXCR4, the inhibition of which reduces neutrophil infiltration into the lung, and antibodies against CD11b/CD18 or ICAM-1 integrins, which limit the interaction of neutrophils with the endothelium [38–40]. The following approaches may lead to suppression of neutrophil hyperactivation: use of neutrophil elastase (NE) inhibitors (e.g., sivelestat), which reduce protease-mediated lung and alveolar damage, the use of NADPH-oxidase (NOX) inhibitors that reduce the production of reactive oxygen species (ROS) thus limiting oxidative stress in the lungs in ARDS and phosphodiesterase (PDE) inhibitors (e.g., pentoxifylline) that attenuate proinflammatory cytokine release and neutrophil priming [41]. The latter has even been the subject of a clinical trial. Undoubtedly, suppression of excess NETs formation is also an approach to therapy of ARDS DNase I degrades NET DNA, reducing alveolar obstruction and inflammation. Inhibitors of peptidyl arginine deiminase 4 (PAD4) which is a transcriptional coregulator and catalyzing the conversion of histone H3 arginine residues to citrulline residues prevent NET formation by inhibiting histone citrullination [42]. Considering the therapy of ARDS from the point of view of neutrophils represents a great opportunity and shows positi ve results, but a great limitation is the need for action in the early stages of the disease, when neutrophils are particularly active [43, 44].

Macrophages

Normally, AM in the lung have an anti-inflammatory phenotype, whereas macrophages recruited from blood monocytes have a pro-inflammatory phenotype [45, 46]. The outcome of ARDS is determined by the balance of pro- and anti-inflammatory macrophages [35]. In the exudative phase, cytokines and other proinflammatory substances are released in response to inflammation, which activate resident AM and circulating neutrophils. In this stage, proinflammatory macrophages dominate under anti-inflammatory cells. Activation of macrophage pattern- recognising receptors leads to the formation of an inflammasome in which caspase-1 promotes the maturation of interleukin (IL) 1 and IL18 [47]. Disease progression can be severe if the maturation process of the inflammasome is disrupted [48]. CXCL8, also known as IL8, secreted by macrophages and endothelial cells during the development of inflammation, leads to the recruitment of neutrophils to the site of inflammation [49]. In the proliferative phase of ARDS pro-inflammatory macrophages are succeeded by anti-inflomatory macrophages which remove cellular debris and release anti-inflammatory cytokines. It was shown that defective efferocytosis can lead to the prolonged inflammation observed in ARDS. Fine regulation of the macrophage's ratio in the last stage of the disease is essential for a favorable outcome at the fibrotic phase since high M2 activity can lead to fibrosis [35].

Given the peculiarities of ARDS and the potential role of macrophages in this process, it is reasonable to speculate that targeting macrophage phenotypes in an anti-inflammatory manner may improve the outcome or alleviate the course of the disease. To date, there are no reported clinical studies using adoptive macrophage transfer. In Kosyreva's pilot study in a mouse model of LPS-induced ARDS, infusion of chemically M2-polarized RAW 264.7 macrophages was shown to promote the movement of lymphocytes from their depots in immune organs to the lungs, as well as to reduce the pro-inflammatory marker CD38 in the lungs and to express the anti-inflammatory markers Arg1,

Vegfa and Tgfb. However, treatment of ARDS with M2-polarized macrophages did not change the number of neutrophils in the lungs, and Arg1 protein levels in the lungs decreased throughout the treatment period, suggesting the need for other polarization approaches to use macrophages as a therapeutic agent [50].

The use of genome modification strategies is of great interest in this case, for example, due to the possibility of creating cells that express a specific protein, as was shown in the work of Huiying Liu. In a mouse model of LPS-induced ARDS, the authors demonstrated a therapeutic effect and reduced mortality when using macrophages with stable expression of IL4 [51].

To date, one work has been presented on the use of Crispr/Cas technology to obtain anti-inflammatory macrophages [49]. Chi Liang and colleagues used electroporation to knock out tumor necrosis factor receptor 1 (TNFR1) and overexpress IL-4 using Cas9-ribonuclear proteins (Cas9-RNP). In a rat model of osteoarthritis, compared with macrophages and M2 exosomes, L–M2a macrophages demonstrated significantly better therapeutic effects, successfully resolving inflammation, restoring tissue homeostasis, and promoting cartilage regeneration [52].

An interesting approach using M2 macrophage-derived nanovesicles and lung-targeting liposomes coupled to fabricate hybrid liposomes-nanovesicles (LNVs) was proposed by researchers from China [53]. In a mouse model of ARDS, they showed that the integrated nanosystems lead to a reduction of inflammation through decreased inflammatory cell infiltration, curbed cytokine storms, and alleviation of oxidative stress.

The use of macrophages in cell therapy, including ARDS, has great potential. However, the ability to change phenotype depending on the microenvironment creates difficulties in their use in clinical practice and the long-term effects of genetically modified cells have not been studied. It should be noted that the use of these cells is limited by the relative complexity of their isolation and expansion, especially n humans. These limitations have favoured the study of macrophages as cellular drug targets for improving the outcome of ARDS. Potential drugs and targets are shown to reduce AM pyroptosis. The phytogromone Abscisic acid [54], a natural polysaccharide derived from the East Asian terrestrial orchid Bletilla striata (BSP), and the antioxidant luteolin contribute to the reduction of AM pyroptosis and a more favorable disease outcome [55, 56]. Among substances of non-plant origin, Dynasore (inhibits GTPase activity) has shown efficacy in reducing pyroptosis [54]. A transcription factor that is comprehensively involved in inflammation Basic helix-loop-helix family member e40 (Bhlhe40) has been shown to be a macrophage target that improves outcomes of ARDS [57].

NK cells

NK cells or granular lymphocytes play a crucial role in linking innate and adaptive immune system activity [58]. Lung NK cells are generally thought to originate and develop in the bone marrow, and then migrate to the lungs. In human lungs, NK cells, accounting for about 10–20% of the lymphocytes, are located in the parenchyma and are not detected outside of it. NK cells are categorized based on the level of expression of CD56 (bright (br) and dim) and CD16 and include two broad subsets: CD56br/dimCD16– and CD56dim CD16+. CD16– NK cells are less differentiated and have low cytolytic ability, but produce greater amounts of IFN-γ and TNFα than their CD16+ counterparts [59]. Conversely, CD16+ NK cells are more differentiated and has high cytolytic activity. Human lung NK cells are mostly composed of the CD56dimCD16+ subset. Despite the well-differentiated phenotype, both human and mouse lung NK cells are hypofunctional in homeostasis. Human lung NK cells are hyporesponsive to stimulation by target cells (irrespective of priming with IFN-α) compared with peripheral blood NK cells. This may be caused by suppressive effects of alveolar macrophages and soluble factors in the epithelial lining fluid of the lower respiratory tract [60]. NK cells are cytotoxic, but do not carry a lineage-specific receptor like T and B lymphocytes. NK cells recognize virus-infected or tumorigenic cells without the presence of antibodies or major histocompatibility complexes (MHC).

The use of NK cells as a cell therapy for ARDS was extensively studied in relation to Covid19 because they play an important role in the pathogenesis of Covid-associated ARDS due to the ability of activating receptors, such as NKG2D, to exhibit antiviral activity. There are 17 registered studies devoted to their use in Covid-19 [61]. NK cells' plasticity is provided by activating and inhibitory receptors on their surface. Killer Ig-like receptors (KIR) genotype has been shown to influence recovery from COVID-19 [62]. NK cells play a significant role in the pathogenesis of ARDS by promoting neutrophil recruitment through the regulation of CXCR2+, CCL2 и CCL7 [63,64]. It has been shown that NK cells and CD4 T cells were reduced in ARDS patients.

The advantages of NK-cell therapy include the absence of the risk of graft-versus-host disease (GVHD) or cytokine release syndrome, as well as direct antiviral activity. A variety of approaches are being developed for the use of NK in Covid19 therapy, from infusions of activated NK cells to CAR-NK technology (NCT04324996). Also, NK cells are administered both as maintenance (NCT04280224) and as a stand-alone therapeutic agent (NCT04900454) [65–68].

T Cells

T cells are cells of the adaptive immune system that have a large number of subtypes differing by the type of T cell receptor, coreceptor molecules, type of major histocompatibility complex (MHC) molecule recognized and, of course, by the production of effector molecules [69]. T helper and T killer cells are distinguished based on the expression of CD4 or CD8 coreceptor molecules.

Regulatory T cells

Regulatory T cells (Tregs) are the subtype of the CD4 cells and play important role in lung homeostasis. Tregs are mainly categorized into two groups, one is natural Tregs (nTreg) which develop in thymus, the other is named as induced Tregs (iTreg) which are converted from naïve CD4+ T cells and could be generated both in vivo and in vitro [69]. Based on the level of expression of Forkhead box P3 (Foxp3), Foxp3+ and Foxp3- populations are distinguished. FOXP3+ Tregs are responsible for keeping immune tolerance, which can prevent allergic and autoimmune diseases as well as inhibit the anti-tumor or anti-pathogen immune responses [70]. Treg cells exert immunosuppressive effects by secreting anti-inflammatory cytokines such as IL-10. Regulatory T-cells promote pulmonary repair by modulating T helper cell immune responses in lipopolysaccharide-induced acute respiratory distress syndrome [71]. In a model of sepsis-induced ARDS in PTENM-KO/β-cateninM-KO knockout mice, the involvement of HMGB1/PTEN/β-catenin signaling in regulating Treg development in ARDS was demonstrated [72]. The participation of Tregs in the restoration of the lung epithelium was shown in the work of Mock JR et al [73]. The close relationship of immune system components in the pathogenesis of ARDS was shown in the work of Cheng L et al. IL-6 and IL-23 secreted from IL-33-activated DCs leads to normalization of the Th17/Treg ratio [74]. Secreted phosphoprotein 1 (SPP1) increases the Th17/Treg and M1/M2 ratios by suppressing VHL expression and ubiquitination-dependent degradation of HIF-1α, thereby exacerbating ARDS [75].

In ARDS Tregs play a crucial role in controlling the immune response; they maintain the physiological level of other immune cells activation, proliferation and function thus ensuring autotolerance and balance of the whole immune system [76]. In severe cases of ARDS, CD4+ T cells may become exhausted due to chronic stimulation by persistent inflammatory signals. This exhaustion leads to impaired immune responses and increased susceptibility to secondary infections, further complicating the clinical course of ARDS. Adoptive transfer of CD4+CD25+Foxp3+ Tregs to LPS — induced Rag1-deficient (Rag1-/-) mice model with loss of functional activity of B and T lymphocytes resulted in decreased levels of pro-inflammatory cytokines and increased levels of TGF-beta [77]. These data formed the basis of the treatment strategy for two patients with COVID-19 — associated ARDS [78]. Patients with severe disease were administered 1×108 allogenic Tregs derived from cord blood per dose intravenously two or three times. After a few days of administration, a decrease in the level of inflammatory markers was

noted [78]. This study was further developed with the support of Cellenkos, Inc. A randomized, placebo controlled, multi-center trial was conducted with the participation of 45 patients who received different doses of allogeneic Tregs three times (NCT04468971). The absence of negative effects from the administration of non-HLA-matched cells and the effectiveness of therapy, expressed in the absence of the need for intubation after 28 days from the administration of the first dose of the drug, were shown [79, 80].

Natural killer T

Natural killer T (NKT) cells are innate-like T lymphocytes that share surface markers and functional characteristics with both NK cells and T cells. Invariant natural killer T (iNKT) cells are a unique subset of T cells with aβ T-cell receptor and cell surface molecules similar to ones on NK cells. Unlike other T cells, they recognize glycolipid antigens presented by CD1d [81]. Shortly upon activation, iNKT cells can rapidly secrete abundant amounts of cytokines, predominantly IFN-γ and IL4, which allows them to activate or regulate other immune cells, such as dendritic cells, B cells, NK cells, CD8+T cells, and CD4+T helper cells, through cytokine stimulation or cognate interaction. In the lungs iNKT-cells make up 5–10% of all lymphocytes and inhabit interstitial space and the vasculature [82]. In ARDS patients, the peripheral blood NKT cell fraction was reduced (median 0.02% versus 0.05% in controls) while activation marker CD69 was elevated (median 25.4% versus 9.55%) along with IL-17 production (median 24.1% versus 3.50%). Moreover, bronchoalveolar lavage fluid contained a higher NKT cell count than blood and was associated with proinflammatory cytokine release and enhanced extracellular matrix protein expression. Activation of the IL-33/ST2 axis in ARDS models leads to recruitment of iNKT cells, and blockade of the CD1d pathway reduces inflammation and injury. Clinical data show negative associations between NKT cell reduction and both the PaO2/FiO2 ratio and albumin levels, and a positive association with C-reactive protein. Park et al. found that NKT induced IL-17 production by NKT cells from ARDS patients, which could stimulate neutrophil recruitment and tissue damage, as well as ECM protein expression in fibroblasts, potentially contributing to fibrosis in later stages of ARDS.

Adoptive transfer of allogenic iNKT, named ‘agenT-797’, at different doses was used in an open-label clinical trial (NCT04582201) for Covid19 treatment and showed positive results. Safety of HLA-mismatched cells has been demonstrated in this research. Administration of ‘agenT-797’ resulted in increased levels of IL-1RA and decreased levels of proinflammatory cytokines. A high 30-day survival rate was shown (70% versus 10% in the control group) [83]. A limitation of the study is the small sample size. Also, its results cannot be easily extrapolated to ARDS caused by causes other than COVID-19.

The use of iNKT cells for the treatment of ARDS is limited by the high probability of fibrosis and inhibition of the functional activity of cells by a highly proinflammatory environment in the lungs in ARDS.

B cells

B cells are found in inducible bronchoassociated lymphoid tissue (iBALT) in the lungs. iBALT is a poorly organized, poorly expressed aggregate of lymphoid cells that develops rapidly in response to infection, chronic inflammation, or autoimmunity. The main functions of B cells in lungs are lung-specific immunity and tolerance. ARDS leds to imbalance in B cells which is confirmed by the results of single cell RNA-sequencing performed by Dan He and colleges. At the same time, high level of B cells correlated with a favourable prognosis. Zhun Sun and colleagues have shown an important anti-inflammatory role of B Cells in ARDS [84]. In a mouse model of LPS-induced ARDS, it was shown that IL-10 is produced predominantly by B cells during the recovery process after ALI. Mechanically, IL-10 produced by B cells suppresses the activation and recruitment of macrophages and reduces the production of keratinocyte chemoattractant (CXCL-1), which recruits neutrophils to the lungs. The presence of IL-10-producing B cells shortly after ARDS onset

has been associated with better survival rates. It can be suggested that the use of adoptive transfer of B cells highly expressing IL10 is a potential cell therapeutic drug.

Key immune cells involved in ARDS pathogenesis and their potential use for treatment this pathology summarize in Table.

Conclusion

Due to the heterogeneity of its pathogenesis, ARDS requires an individualized treatment approach. Cell therapy may be a promising treatment option, as shown in preclinical studies. In addition to stem cells, which have been shown to be safe in many studies, therapy using highly differentiated immune cells or aimed at altering their functional properties in vivo has great therapeutic potential in the resolution of ARDS. Genetic modification techniques open new horizons in the possibility of increasing the therapeutic efficacy when using cells in the treatment of ARDS. However, many aspects of cell therapy applications remain controversial, such as standardization of cell product preparation and processing, dose and number of administrations, etc., and multicenter studies are needed to improve the validity of preclinical results. Nevertheless, this review shows that both in vivo adoptive transfer of immune cells and in vivo targeting of immune cells have great potential in the field of ARDS therapy.

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Key cells involved in ARDS pathogenesis and their potential use for treatment this pathology

Function in normal lung	Involvement in the pathogenesis of ARDS	Strategies for use as potential therapy
Alveolar macrophages		
Immunological tolerance in alveoli and surfactant catabolism;Anti-inflammatory phenotype	The acute phase secretion of proinflammatory cytokinesThe proliferative-fibrotic phase efferocytosis and reorganizing the matrix.	Enhancing phagocytosis:Regulating macrophage polarizationInhibiting pyroptosisExosome therapy
Neutrophils		
First line of defense against pathogens by phagocytosis and NET fo rmation	Releasing reactive oxygen species (ROS), reactive nitrogen species (RNS), proteases, and pro-inflammatory cytokines like IL-6 and NET formation	Inhibition of Neutrophil Recruitment Suppression of Neutrophil Hyperactivation Targeting Neutrophil Extracellular Traps (NETs)
Invariant natural killer T cells (iNKT)		
Regulation of immune tolerance in lung and regulation of other immune cells through cytokine stimulation or cognate interaction	Participation in the development of inflammation in the acute phase	Adoptive transfer of inkt cells in clinical trial nct04582201
T Cells (Tregs)		
Maintain immune system homeostasis and preventing autoimmune diseases	Promote the clearance of neutrophils from the alveolar spaceSecrete anti-inflammatory cytokines such as il-10 and tgf-β	Adoptive transfer of tregThere is clinical trial nct04468971 with promising results
B cells		
lung-specific immunity and tolerance	Decreased quantity in ARDS	Introduction of B cells, highly producing IL-10

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Высокодифференцированные клетки в терапии острого респираторного дистресс-синдрома

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Аннотация. *Актуальность.* Острый респираторный дистресс-синдром (ОРДС) — это тяжелая, угрожающая жизни форма острого поражения легких с высоким уровнем смертности. В тяжелых случаях патологические изменения распространяются на системный уровень и проявляются в виде синдрома цитокинового шторма. Отсутствие эффективных вариантов лечения подчеркивает важность изучения терапевтических подходов, включая клеточную терапию. Интерес к этому варианту лечения возрос во время пандемии SARS-CoV-2, о чем свидетельствуют многочисленные клинические исследования, зарегистрированные для использования клеточных препаратов для лечения ОРДС. Целью исследования стало обобщение доклинических и клинических исследований по использованию высокодифференцированных клеток, включая клетки иммунной системы, для лечения ОРДС. В работе рассмотрены стадии развития ОРДС с точки зрения участвующих в них клеток иммунной системы, а также этиологические подтипы. Описаны существующие на настоящий момент доклинические и клинические исследования использования иммунных клеток в терапии ОРДС. В этом обзоре подчеркивается потенциал использования альвеолярных клеток 1-го и 2-го типов, а также эпителиальных клеток для быстрой регенерации легких после ОРДС. В настоящее время отсутствуют данные, описывающие применение нейтрофилов, вызывающих первичные патологические изменения в легких, для лечения ОРДС. Использование макрофагов, играющих ключевую роль в патогенезе ОРДС, ограничено их способностью к быстрой реполяризации. Естественные клетки-киллеры (NK-клетки), регуляторные Т-клетки (Treg) и инвариантные естественные клетки-киллеры (iNKT-клетки) показали высокую эффективность в лечении ОРДС в доклинических и клинических исследованиях. *Выводы.* Таким образом, использование NK-клеток, Treg и iNKT-клеток для клеточной терапии ОРДС представляется перспективным.

Однако отсутствие стандартизированных протоколов подготовки и введения клеточной терапии, а также небольшой размер выборки указывают на необходимость дополнительных исследований.

Ключевые слова: ОРДС, клеточная терапия, макрофаги, клетки iNKT, Treg, нейтрофилы, клинические испытания

Информация о финансировании. Работа выполнена при финансовой поддержке Государственного задания No. 125050605838-9.

Вклад авторов. Киселева В.В. — концептуализация, составление черновика статьи, Мирошниченко Е.А. — дизайн таблиц и рисунков, Вишнякова П.А. — концептуализация, составление черновика статьи, Косырева А.М. — составление черновика и редактирование статьи, А.В. Ельчанинов — редактирование статьи, Фатхудинов Т.Х. — управление процессом. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Информация о конфликте интересов. Авторы заявляют об отсутствии конфликта интересов.

Этическое утверждение — неприменимо.

Благодарности — неприменимо.

Информационное согласие на публикацию — неприменимо.

Поступила 20.05.2025. Принята 19.06.2025.

Для цитирования: *Kiseleva V.V., Miroshnichenko E.A., Vishnyakova P.A., Kosyreva A.M., Elchaninov A.V., Fatkhudinov T. Kh.* Highly differentiated cells in the therapy of acute respiratory distress syndrome // Вестник Российского университета дружбы народов. Серия: Медицина. 2026. Т. 30. № 2. С. 233–247. doi: 10.22363/2313-0245-2026-30-2-233-247. EDN: GSEBMH

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