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REVIEW

Engineering Biomimetic Nanoplatforms for Acute Lung Injury: From Mechanistic Insights to Translational Opportunities

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Abstract: Acute lung injury (ALI) remains a critical clinical challenge characterized by uncontrolled inflammation, oxidative stress, and immune dysregulation, with limited therapeutic options and high mortality. In recent years, biomimetic nanoplatforms—including those derived from cell membranes, extracellular vesicles (EVs), and hybrid biological interfaces—have emerged as transformative tools for ALI management. Unlike conventional nanocarriers, these systems reproduce natural intercellular communication and immune evasion mechanisms, thereby achieving precise lung targeting, sustained therapeutic delivery, and coordinated regulation of inflammation and tissue repair.This review provides a comprehensive and mechanistic overview of biomimetic nanoplatforms in ALI therapy, with an emphasis on membrane-derived, EV-based, and hybrid nanosystems. We further introduce less-explored biomimetic strategies, including protein-, bacterial-, and virus-inspired nanoparticles, to expand the conceptual framework of biological mimicry in pulmonary nanomedicine. Beyond summarizing progress, we critically discuss key translational barriers—immunogenicity, model fidelity, and large-scale manufacturing—and propose integrative solutions leveraging artificial intelligence, organ-on-chip technologies, and precision medicine approaches.By offering a unified perspective on the design, function, and translational roadmap of biomimetic nanotherapeutics, this review highlights how the integration of biology-inspired engineering and pulmonary pathophysiology could pave the way toward personalized and clinically viable nanomedicine for ALI.

Keywords: acute lung injury, biomimetic nanoplatforms, acute respiratory distress syndrome, biomimetic membranes, EVs

Introduction

ALI and its more severe manifestation, acute respiratory distress syndrome (ARDS), are life-threatening clinical syndromes characterized by diffuse alveolar damage, excessive release of pro-inflammatory cytokines ("cytokine storm"), and severe disruption of the alveolar epithelial and vascular endothelial barriers.[1–3] Despite continuous advancements in both clinical management and basic research, the mortality rate of ALI/ARDS remains alarmingly high, typically ranging from 30% to 50%, and no effective disease-specific therapies are currently available in clinical practice.[4–6] The pathogenesis of ALI is highly complex, involving massive infiltration of neutrophils and monocytes, aberrant release of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, reactive oxygen species (ROS)-induced oxidative stress, and multiple forms of regulated cell death including apoptosis, pyroptosis, and ferroptosis, all of which

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contribute to impaired pulmonary tissue repair.[2,7,8] ALI can be triggered by a wide range of direct (eg, bacterial or viral pneumonia, inhalation injury) or indirect (eg, sepsis, severe trauma, pancreatitis) insults, further complicating therapeutic strategy development.[7,9]

Currently, the clinical management of ALI/ARDS primarily relies on supportive care, including mechanical ventilation and fluid management.[10–12] Although pharmacological interventions such as corticosteroids, antioxidants, and immunomodulators have demonstrated partial benefits in certain patient populations, their limited targeting capability, poor bioavailability, and systemic side effects significantly restrict their overall efficacy.[10,13] Moreover, conventional therapies generally fail to simultaneously address the multifaceted pathological events of ALI—including immune dysregulation, oxidative stress, and barrier dysfunction—which greatly hampers their clinical utility.[5,14,15] Consequently, there is an urgent need to develop innovative therapeutic strategies with enhanced targeting capability, multimodal mechanisms of action, and favorable biocompatibility.[16,17]

In recent years, increasing preclinical evidence has highlighted the therapeutic potential of various biomimetic membranes—such as red blood cell membranes, macrophage membranes, platelet membranes, and their hybrid composites—due to their diverse targeting capacities and immune-modulatory properties.[18–20] Although existing reviews have summarized therapeutic strategies for ALI/ARDS based on membrane-coated nanotechnology and extracellular vesicle-inspired systems,[21] the field has witnessed rapid and substantial progress over the past two years, bringing forth novel concepts and design frameworks. In this review, we systematically summarize the latest advances in the application of biomimetic nanoplatforms for ALI therapy, with an emphasis on their design rationale, structural features, and multifaceted therapeutic mechanisms. Furthermore, we delve into the major translational challenges currently faced, including immunogenicity, safety, large-scale manufacturing, and regulatory hurdles, and offer perspectives on the future development of biomimetic nanoplatforms for precision pulmonary therapy. By establishing a comprehensive knowledge framework spanning from fundamental design to clinical translation, this review aims to provide valuable insights for researchers and facilitate the clinical advancement of this promising therapeutic paradigm.

Pathophysiological Mechanisms of ALI

ALI is fundamentally an acute inflammatory condition marked by the disruption of the alveolar epithelial and capillary endothelial barriers, involving a complex interplay of cellular components and signaling pathways.[22,23] The pathological cascade is typically initiated by direct or indirect insults such as infection, trauma, inhalation injury, or sepsis, leading to excessive immune cell activation, uncontrolled inflammatory cytokine release, and elevated oxidative stress. These events culminate in increased alveolar-capillary permeability and respiratory dysfunction.[24,25] Therefore, elucidating the core pathophysiological mechanisms of ALI is pivotal for developing highly targeted, low-toxicity therapeutic approaches and provides a robust theoretical foundation for the functional design of biomimetic nanotherapeutics.

In the early stages of ALI, the alveolar epithelial cells and pulmonary microvascular endothelial cells are among the first to be damaged.[5,26] Continuous stimulation by pro-inflammatory cytokines such as TNF-α and IL-1β, along with elevated levels of reactive oxygen species (ROS), leads to downregulation of intercellular junction proteins—including VE-cadherin, occludin, and ZO-1—accompanied by cytoskeletal rearrangement and the initiation of apoptotic pathways. These changes result in increased vascular permeability, alveolar edema, and reduced pulmonary compliance.[27–29] The loss of barrier integrity is not only a hallmark of early ALI but also lays the foundation for the amplification and propagation of inflammatory cascades.[30,31] (Figure 1) The cytokine storm represents a major driving force behind the progression of ALI.[32,33] Under persistent infectious or injury-related stimuli, alveolar macrophages and neutrophils become massively activated, releasing large quantities of pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β, as well as a range of chemokines that rapidly recruit and activate additional immune cells. This initiates a localized and systemic inflammatory amplification loop.[34] The resultant "waterfall-like" cytokine storm exacerbates alveolar damage and may eventually lead to multiple organ dysfunction syndrome (MODS).[35]

Dysregulation of immune cell function also plays a pivotal role in the pathogenesis of ALI.[36] Neutrophils are rapidly recruited to the alveolar space during the early inflammatory response, where they transmigrate across the endothelium and release proteolytic enzymes and ROS, contributing to tissue damage. Simultaneously, they induce alveolar macrophages to secrete anti-inflammatory cytokines such as IL-10, demonstrating a dual role in inflammation promotion and

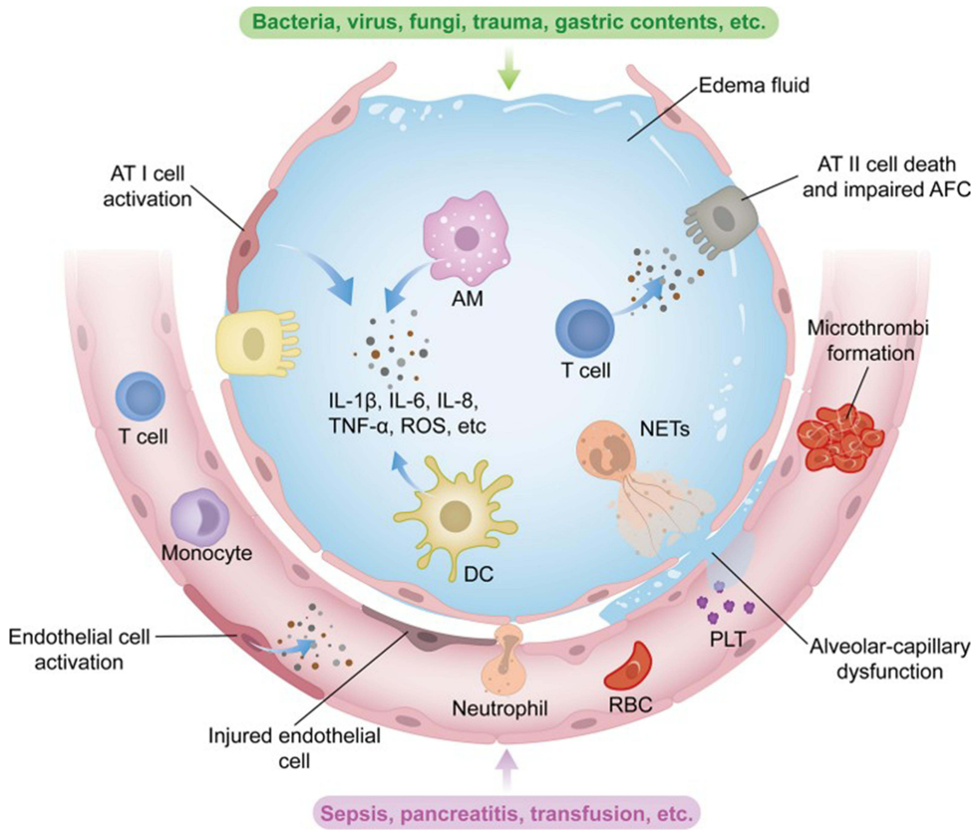

Figure 1 The pathophysiology of ARDS involves complex interactions among inflammation, alveolar–capillary barrier disruption, oxidative stress, and impaired fluid clearance. In pulmonary ARDS, direct epithelial injury caused by pneumonia or aspiration activates alveolar epithelial cells, macrophages, and dendritic cells, leading to cytokine and chemokine release that recruits immune cells into the airspaces. Infiltrating neutrophils amplify inflammation through reactive oxygen species (ROS) and neutrophil extracellular traps (NETs), further damaging the epithelial–endothelial interface. Endothelial activation promotes coagulation and microthrombus formation, resulting in protein-rich edema and hypoxemia. In extrapulmonary ARDS, circulating inflammatory mediators primarily injure pulmonary endothelium, which secondarily induces epithelial dysfunction and alveolar flooding.[29]

Abbreviations: AFC, alveolar fluid clearance; AM, alveolar macrophage; AT I, alveolar type I cell; AT II, alveolar type II cell; DC, dendritic cell; IL-1β, interleukin-1β; IL-6, interleukin-6; IL-8, interleukin-8; NETs, neutrophil extracellular traps; PLT, platelet; RBC, red blood cell; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-α.

immune regulation.[37,38] However, under pathological conditions, immune responses frequently become imbalanced: macrophage polarization skews toward the pro-inflammatory M1 phenotype, with a marked reduction in the anti-inflammatory and tissue-reparative M2 phenotype;[39–41] neutrophils release excessive neutrophil extracellular traps (NETs), aggravating alveolar structural injury;[42] and on the adaptive immune front, regulatory T cell (Treg) function is impaired, failing to initiate effective tissue repair mechanisms.[43] Amid this dysregulated immune environment, oxidative stress intensifies as ROS levels rise significantly within lung tissues. Major ROS sources include the NADPH oxidase system of activated neutrophils and dysfunctional mitochondria.[44,45] High concentrations of ROS induce lipid peroxidation, mitochondrial membrane potential collapse, and DNA damage, which in turn trigger various forms of programmed cell death—including apoptosis,[46] pyroptosis,[47] ferroptosis,[48] necroptosis, and PANoptosis—all of which collectively undermine pulmonary structural integrity and functional stability, necroptosis, and PANoptosis—all of which collectively undermine pulmonary structural integrity and functional stability.[49,50]

In summary, the pathological progression of ALI involves a complex and interwoven network of events—including barrier dysfunction, cytokine storm, immune dysregulation, and oxidative stress—each of which contributes to disease exacerbation. Given this multifactorial nature, nanotherapeutic systems integrating targeted recognition, multimodal intervention, and biomimetic functionality offer a promising avenue for precision ALI/ARDS therapy. Such platforms hold the potential to overcome the limitations of traditional treatments by simultaneously regulating multiple pathological pathways and promoting functional recovery of pulmonary tissues.

Classification of Biomimetic Nanoplatforms

In recent years, biomimetic nanoplatforms have emerged as promising therapeutic strategies for ALI, owing to their excellent biocompatibility, targeting capacity, and functional versatility. Based on their structural design and source of biofunctionality, these platforms can be broadly categorized into three major types: (i) cell membrane-coated nanoparticles, (ii) extracellular vesicle (EV)-mimetic nanocarriers, and (iii) artificial EV-inspired nanoplatforms.[51] Besides membrane- and EV-based platforms, emerging protein-, bacterial-, and virus-inspired biomimetic nanoparticles expand the diversity of nanoplatforms and are expected to provide new opportunities for ALI therapy.[52–54]

Cell Membrane-Coated Nanoparticles

By cloaking synthetic nanocarriers with natural cell membranes, these nanoparticles inherit glycosylation patterns and membrane protein compositions from source cells, thereby acquiring immune evasion and active targeting capabilities. For instance, red blood cell (RBC) membranes are rich in the self-marker CD47, which significantly reduces mononuclear phagocyte system (MPS) clearance and prolongs circulation time.[51] RBC membrane camouflage has been shown to extend nanoparticle half-life from 15.8 to 39.6 hours in vivo, offering advantages for sustained pulmonary circulation and trans-barrier drug delivery.[55] Macrophage membranes, enriched with inflammatory chemokine receptors such as TLR4, CCR2, and CXCR4, endow nanoparticles with innate inflammation-targeting properties, allowing for preferential accumulation at inflamed sites.[56,57] Similarly, platelet membranes carry a repertoire of vascular injury- and thrombosis-associated proteins, facilitating adhesion to damaged endothelium and thrombi. Coating nanoparticles with such membranes enables the construction of inflammation-targeted drug delivery systems or cytokine-neutralizing platforms, thereby enhancing disease-site specificity.[58,59] Furthermore, hybrid membrane strategies—formed by fusing two or more types of cell membranes via techniques such as serial extrusion—can integrate complementary functions. For example, combining RBC and macrophage membranes, or mesenchymal stem cell (MSC) and T cell membranes, can simultaneously confer prolonged circulation, immune evasion, and inflammation tropism.[19,60,61] Compared with single-source membranes, hybrid membranes exhibit a richer protein composition (eg, co-presence of CD47 and other self-recognition molecules), offering superior performance in immune escape, prolonged retention, and homotypic targeting.[19,62]

Extracellular Vesicle-Mimetic or Artificial EV-Based Nanocarriers

Capitalizing on the natural delivery and signaling functions of extracellular EVs, researchers have developed EV-based nanoplatforms with excellent biocompatibility and therapeutic potential in immune-compromised environments.[63,64] Two main strategies are employed: isolation of native EVs and construction of artificial EV mimetics.[65]

Native EVs are structurally stable, exhibit strong tissue tropism, and are well-suited for navigating the complex immunological landscape of lung tissue. Among them, mesenchymal stem cell-derived EVs (MSC-EVs) are particularly promising, as they are rich in anti-inflammatory and tissue-regenerative factors.[66] Their low immunogenicity and high pulmonary permeability also make them ideal candidates for intravenous administration.[67] Additionally, immune cell-derived EVs (eg, from macrophages or T cells) possess potent immunomodulatory functions and can deliver anti-inflammatory microRNAs or activate specific signaling pathways within inflamed tissues.[68–70] To address the limitations of native EVs—such as low yield and compositional heterogeneity—artificial biomimetic EV systems have been developed. These include EV-like vesicles generated by co-extrusion of liposomes with cellular contents or the use of polymeric nanocapsules that mimic EV structures while allowing precise control over size, charge, and surface functionalities.[71] Such artificial systems not only improve batch-to-batch consistency and production scalability but also enhance pharmacokinetic profiles while retaining EV-like biofunctions.[71]

Preclinical Studies of Biomimetic Nanoplatforms in ALI Models

Biomimetic nanoplatforms have demonstrated considerable therapeutic potential in preclinical models of ALI. By harnessing the natural functionalities of cell membranes, these platforms offer a multifaceted therapeutic approach, including inflammation targeting, immune modulation, antioxidation, and anticoagulation.[72,73] In the following sections, we systematically summarize recent preclinical advances in ALI animal models, categorized by the cellular source of membrane materials (Figure 2).

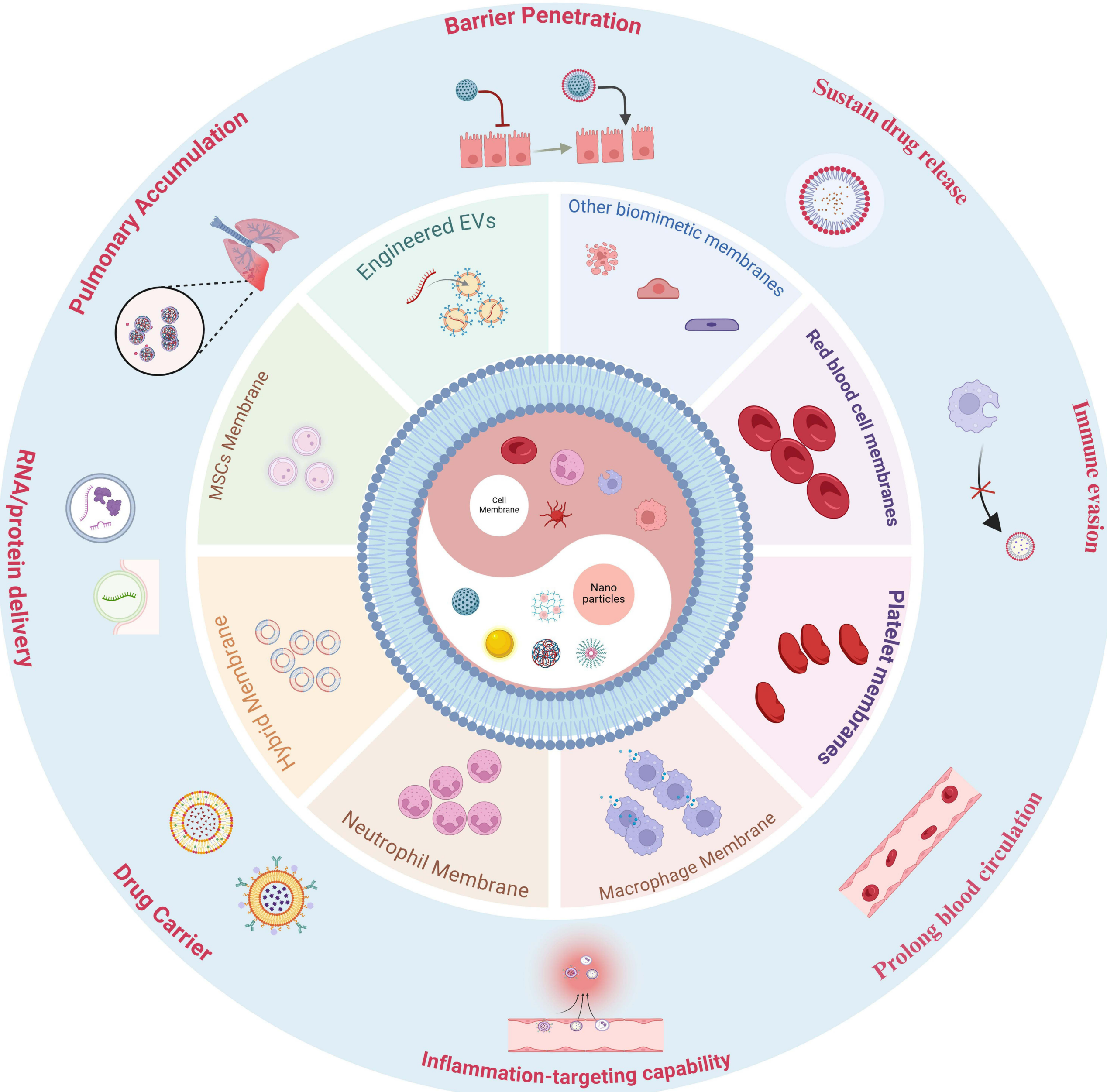

Figure 2 Therapeutic Potential of Engineering Biomimetic Nanoplatforms in the Treatment of Acute Lung Injury (ALI).

RBC Membrane-Coated NPs

Due to their exceptional biocompatibility, low immunogenicity, and prolonged circulation half-life, red blood cell (RBC) membranes have been widely utilized in drug delivery systems.[74,75] When applied to ALI therapy, RBC membrane coatings enhance nanoparticle stability in circulation and promote pulmonary retention. Liu et al developed a RBC membrane-coated PLGA nanoparticle (γ3-RBCNPs), functionalized with a γ3 peptide targeting intercellular adhesion molecule-1 (ICAM-1), which is highly upregulated at sites of infection. The core was loaded with ciprofloxacin to eliminate *Klebsiella pneumoniae*. The RBC membrane not only endowed the particles with immune evasion and extended blood circulation time but also enhanced targeting to inflamed endothelium—such as TNF-α-activated HUVECs—and inflamed lung tissues in septic mice, demonstrating potent anti-infective efficacy and improved pulmonary accumulation.[76]

Macrophage Membrane-Coated Platforms

Macrophage membranes inherently recognize and bind pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide (LPS), and can neutralize pro-inflammatory mediators, thereby halting downstream inflammatory cascades.[56,57] Leveraging these properties, macrophage membrane-coated nanoparticles have been extensively explored as "inflammation sponges" for ALI treatment.

Zhao et al engineered mesoporous polydopamine nanoparticles coated with macrophage membranes (MM@mPDA-PM NPs), loaded with the anti-inflammatory alkaloid peimine. This platform demonstrated precise targeting of inflamed lung regions, potent antioxidant properties, and robust anti-inflammatory effects both in vitro and in vivo. Transcriptomic analysis revealed that the system downregulated key inflammatory mediators—including myeloperoxidase (MPO), neutrophil elastase (NE), and peptidylarginine deiminase 4 (PAD4)—thus inhibiting neutrophil extracellular trap (NET) formation. Additionally, the nanoparticles suppressed NF-κB and JAK/STAT signaling and promoted M2 macrophage polarization, effectively restoring immune homeostasis and mitigating ALI-associated inflammation[77] (Figure 3).

To address the persistently elevated reactive oxygen species (ROS) and cytokines in ALI, Liang et al developed a polymeric biomimetic system (mem HMP) with both ROS-scavenging and cytokine-neutralizing capabilities. The platform was constructed via copolymerization of alkene-modified hyaluronic acid with a ROS-responsive hyperbranched poly(amino ketal) (HBPAK), and coated with membranes derived from M1-polarized macrophages via electrostatic adsorption. The resulting nanocarriers exhibited strong anti-inflammatory and antioxidant activity in vitro and in vivo. Upon pulmonary administration, mem HMP significantly reduced neutrophil infiltration, oxidative stress, and lung tissue damage in LPS-induced ALI models.[78]

In another study, Zhao Yue et al developed a PLGA-based nanoparticle cloaked with neutrophil membranes (Neutrophil-NP-TLR4) to deliver siRNA targeting Toll-like receptor 4 (TLR4). This system effectively silenced TLR4 in macrophages and inflammatory cells within the inflamed lung microenvironment, downregulated key inflammatory cytokines such as TNF-α and IL-1β, and inhibited critical signaling molecules including TRAF6, XIAP, and NF-κB. Moreover, the platform restored expression of aquaporins AQP1 and AQP5, alleviating LPS-induced pulmonary injury.[79] Collectively, macrophage membrane-based platforms leverage their innate inflammation-recognition capabilities, coupled with intelligent nanocarrier design, to achieve multi-target regulation and precise intervention in ALI.

Neutrophil-Mimicking Nanocarriers

Neutrophil membranes possess intrinsic inflammation-homing properties, enabling autonomous migration toward inflamed tissues. This makes them ideal candidates for early intervention in ALI [77,78]. Various neutrophil membrane-cloaked nanocarriers have been developed, showing great potential in inflammation-targeted drug delivery, immune regulation, and tissue protection.[80–82]

Small interfering RNA (siRNA) holds therapeutic promise in ALI by silencing pro-inflammatory genes. However, its clinical application is hindered by poor in vivo stability and a lack of targeted delivery. To overcome this, researchers engineered neutrophil membrane-coated PLGA nanoparticles (Neutrophil-NP-TLR4) for pulmonary delivery of TLR4-targeted siRNA. This platform exhibited excellent lung-targeting capacity, significantly suppressed TNF-α and IL-1β expression, inhibited key TLR4 pathway mediators (TRAF6, XIAP, and NF-κB), and restored AQP1/5 expression. As a result, it markedly alleviated LPS-induced lung damage. Notably, the system demonstrated favorable biocompatibility and pulmonary specificity, without inducing notable toxicity, highlighting its potential for clinical translation of siRNA therapeutics in ALI.[83]

Beyond nucleic acid delivery, neutrophil-mimicking platforms also show promise in protein drug delivery. Given the excessive activation and infiltration of neutrophils during ALI pathogenesis, Huang et al developed a neutrophil membrane-coated liposomal system (aFGF@NMLs) to deliver acidic fibroblast growth factor (aFGF) for sepsis-induced ALI. Neutrophil membranes provided injury-homing capability, enhancing pulmonary accumulation. In vitro, aFGF@NMLs demonstrated superior pro-inflammatory cytokine binding, enhanced cellular uptake, antioxidative, and anti-inflammatory effects. In vivo, the system reduced cytokine levels, mitigated alveolar epithelial apoptosis, and improved lung function and histopathology, validating its therapeutic efficacy[84] (Figure 4).

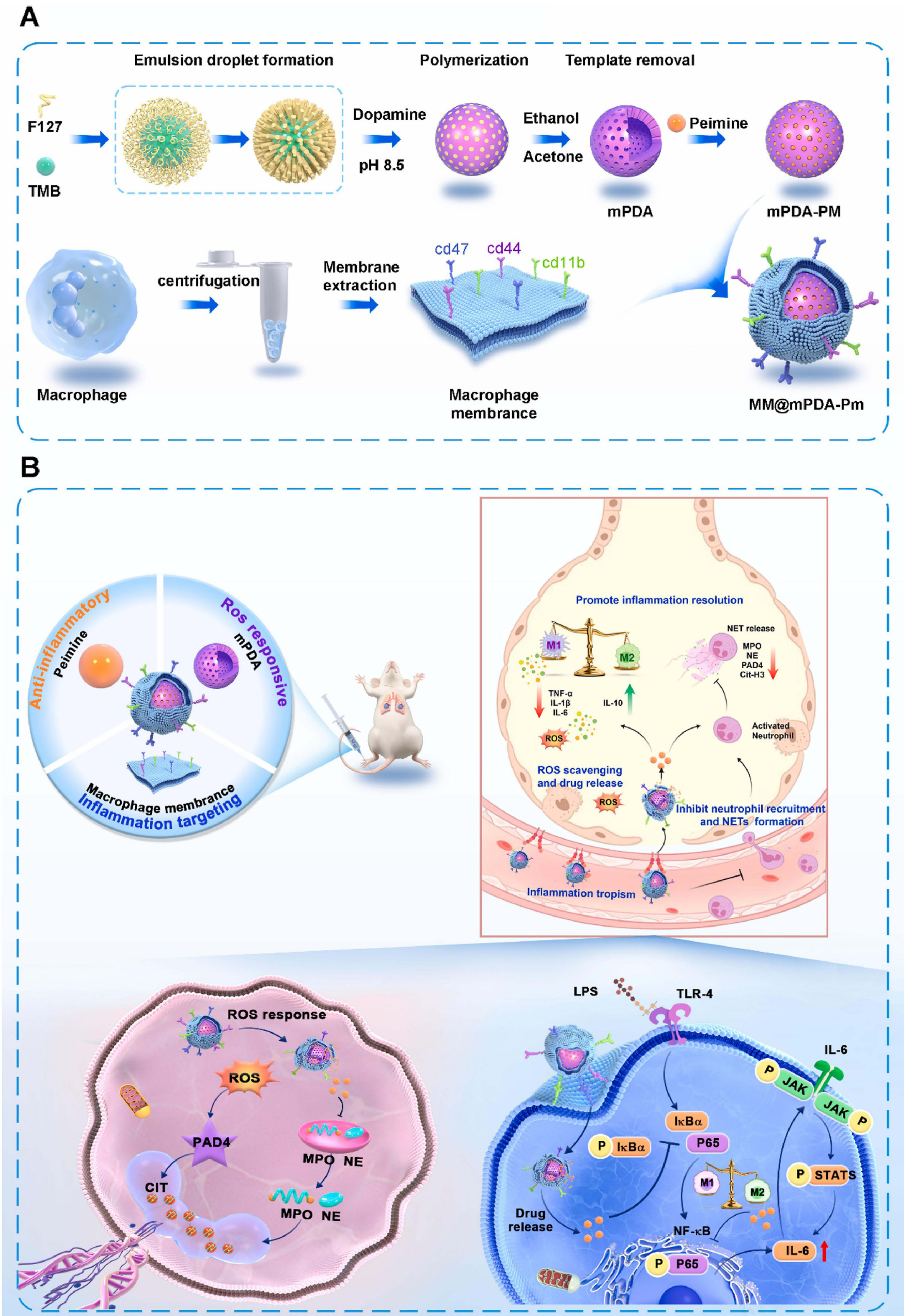

Figure 3 Schematic illustration for the preparation of MM@mPDA-PM NPs and the therapeutic mechanism against. (A) The preparation of MM@mPDA-PM NPs. (B) The therapeutic mechanism of MM@mPDA-PM NPs.[77]

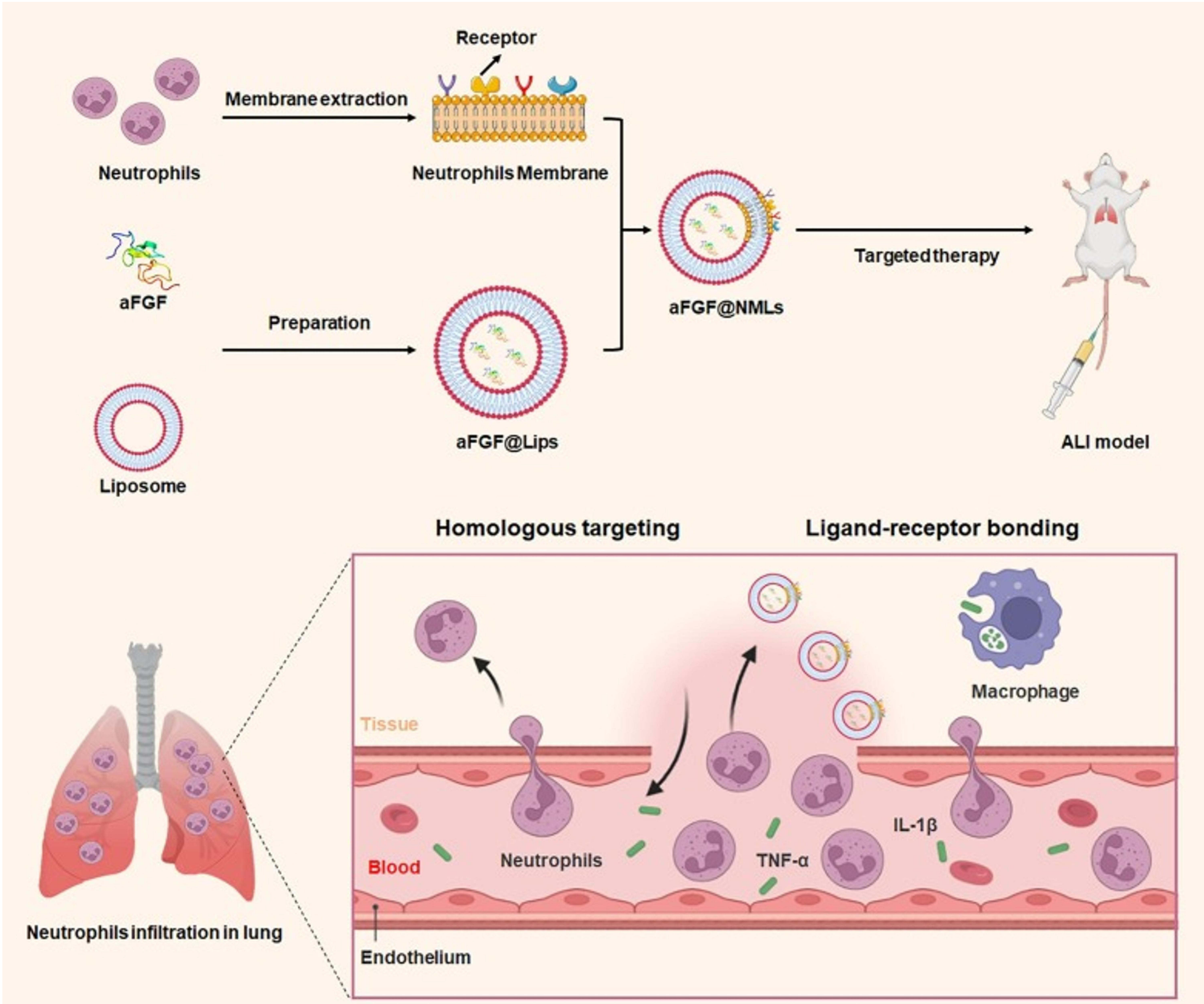

Figure 4 Targeted therapy of neutrophil membrane-coated liposome loaded acidic fibroblast growth factor (aFGF@NMLs) for treating sepsis-induced ALI.[84]

To address the challenges of glucocorticoid delivery in respiratory diseases, Yang et al designed a neutrophil membrane-functionalized metal-organic framework (MOF) system (UiO66-Dex@NMP) for inhalation-based delivery of dexamethasone (Dex). The UiO66 MOF afforded high drug-loading capacity, while neutrophil membrane functionalization enhanced mucus penetration and inflammation-targeting. The platform exhibited sustained drug release in vitro, traversed mucus barriers effectively, and achieved lung-specific accumulation in vivo. It significantly alleviated LPS-induced inflammation and tissue damage, overcoming limitations of traditional Dex inhalation therapies such as low deposition and short duration of action.[85] Owing to their superior inflammation-recognition and homing capabilities, neutrophil-mimicking nanocarriers offer a versatile and effective strategy for delivering diverse bioactive agents in ALI.

Biomimetic Platelet Membrane-Coated Nanoparticles

Platelet membranes possess intrinsic inflammation-homing capabilities, enabling specific recognition of endothelial injury and binding to inflammatory and coagulation factors.[58,59] Among various biomimetic platforms, platelet membranes have garnered significant attention in the field of targeted drug delivery for ALI due to their unique biological functions.

To enhance the stability and targeting efficiency of tea polyphenols (TP), a natural anti-inflammatory compound, in ALI treatment, Hua Jin et al developed platelet membrane-coated TP nanoparticles (PM@TP-NPs). These were fabricated using an emulsion-solvent evaporation method to encapsulate TP, followed by coating with platelet membranes to confer excellent biocompatibility and inflammation-targeting ability. In an LPS-induced ALI mouse model, PM@TP-NPs significantly reduced macrophage and neutrophil infiltration, suppressed NLRP3 inflammasome activation, and inhibited the release of pro-inflammatory cytokines. This effectively alleviated pulmonary vascular hyperpermeability and tissue damage. Targeting assays demonstrated that the nanoparticles selectively accumulated in inflamed lung tissue, particularly within vascular endothelial cells, with minimal retention in healthy lungs, indicating a strong inflammation-responsive targeting capacity and promising potential for pulmonary anti-inflammatory therapy.[86]

Building on this platform, Hua Jin's team further designed a dual-drug delivery system (PM@Cur-RV NPs) encapsulating both curcumin and resveratrol for synergistic treatment of ALI. Administered via pulmonary inhalation, the system exhibited excellent lung accumulation and biocompatibility. Animal studies revealed that PM@Cur-RV NPs significantly reduced vascular leakage and pro-inflammatory cytokine levels, alleviating histopathological damage. Mechanistically, the platform promoted macrophage polarization toward the M2 phenotype and inhibited key epigenetic processes such as histone lactylation, thereby exerting anti-inflammatory and immunomodulatory effects at both cellular and molecular levels.[87]

Considering that corticosteroids, while potent anti-inflammatory agents, can lead to serious adverse effects with repeated or high-dose use, Peihong Lin et al developed a platelet membrane-coated liposomal system (PM-LPs@Dex) for targeted delivery of dexamethasone in ALI therapy. Combining the high drug-loading capacity of liposomes with the inflammation-homing ability of platelet membranes, this system offered improved stability and sustained release properties. It demonstrated enhanced uptake by inflammation-associated cells and significantly prolonged circulation time. In ALI animal models, PM-LPs@Dex effectively mitigated pulmonary tissue damage, reduced pulmonary edema and inflammatory cell infiltration, and suppressed pro-inflammatory cytokine expression, showcasing excellent therapeutic potential.[88]

Additionally, Yue Zhao et al engineered a platelet membrane-coated biomimetic nanoparticle system (PM@ASIV-NPs) for targeted delivery of astragaloside IV (ASIV) to inflamed lung tissue. Through the integration of network pharmacology and molecular docking, the system demonstrated favorable lung-targeting and biocompatibility. In ALI models, PM@ASIV-NPs effectively reduced inflammatory cytokine expression, scavenged reactive oxygen species (ROS), and promoted the release of anti-inflammatory mediators, ultimately improving pulmonary inflammation and survival outcomes.[89]

In summary, platelet membrane-based biomimetic platforms play a pivotal role in targeted pulmonary delivery of anti-inflammatory agents. Their superior inflammation-homing capacity, endothelial affinity, and ability to modulate the immune-coagulation axis render them particularly valuable in treating ALI and ARDS, warranting further development.

Hybrid Membrane-Coated Nanocarriers

Hybrid membrane-coated nanocarriers combine the functional advantages of two or more different cell membrane sources to achieve "functional complementation." This strategy not only enhances targeted delivery efficiency but also broadens adaptability to complex pathological environments, such as concurrent multi-source inflammation, bacterial infection, and pulmonary barrier dysfunction commonly seen in ALI.[60,61]

Zhengyu Lin et al developed a hybrid membrane-coated nanoparticle platform composed of neutrophil and alveolar epithelial cell membranes for targeted delivery of rifampicin to treat methicillin-resistant *Staphylococcus aureus* (MRSA)-induced ALI and bacteremia. The resulting dual-membrane nanoparticles, with an average diameter of ~191 nm and a surface potential of –2.7 mV, integrated the bio-recognition features of both source cells, enabling enhanced bacterial binding and epithelial cell uptake. Compared to single-membrane nanoparticles, the hybrid system demonstrated nearly a twofold increase in pulmonary targeting efficiency and effectively eradicated planktonic, biofilm, and intracellular MRSA. It significantly reduced bacterial burden, inflammatory cytokine levels, and histopathological damage, highlighting its therapeutic potential for complex infectious ALI.[90]

Mesenchymal Stem Cell Membrane-Based Platforms

Mesenchymal stem cells (MSCs) and their derived membranes are rich in anti-inflammatory mediators, antioxidant enzymes, and regenerative signaling molecules. They can modulate multiple pathological processes in ALI, including inflammatory cascades, apoptosis, oxidative stress, and tissue repair.[91,92] MSC membrane-derived biomimetic platforms preserve the immunomodulatory functions of MSCs while circumventing the immunogenicity and safety risks associated with live-cell therapies.[93,94]

Hua Jin et.al developed a stem cell membrane-coated nanoplatform (CM@Nar-NPs) for the delivery of naringin in ALI treatment. This system exhibited excellent dispersibility and biocompatibility, with the ability to actively target inflammation-activated macrophages, efficiently scavenge ROS in lung tissues, and significantly reduce inflammatory cytokine expression, thereby improving histopathological outcomes and survival in ALI mouse models. Mechanistically, CM@Nar-NPs promoted macrophage polarization toward the M2 phenotype, exerting sustained anti-inflammatory and immunoregulatory effects. These findings underscore the promise of MSC-mimetic nanocarriers in managing ALI and sepsis-associated pulmonary injury[95] (Figure 5).

Extracellular Vesicle–Based Biomimetic Nanoplatforms

EVs are nano-sized lipid bilayer vesicles naturally secreted by cells and play essential roles in intercellular communication and regulation.[96] Owing to their native membrane structures, excellent biocompatibility, and functional protein expression, engineered EVs have emerged as an innovative therapeutic strategy for inflammatory diseases, including

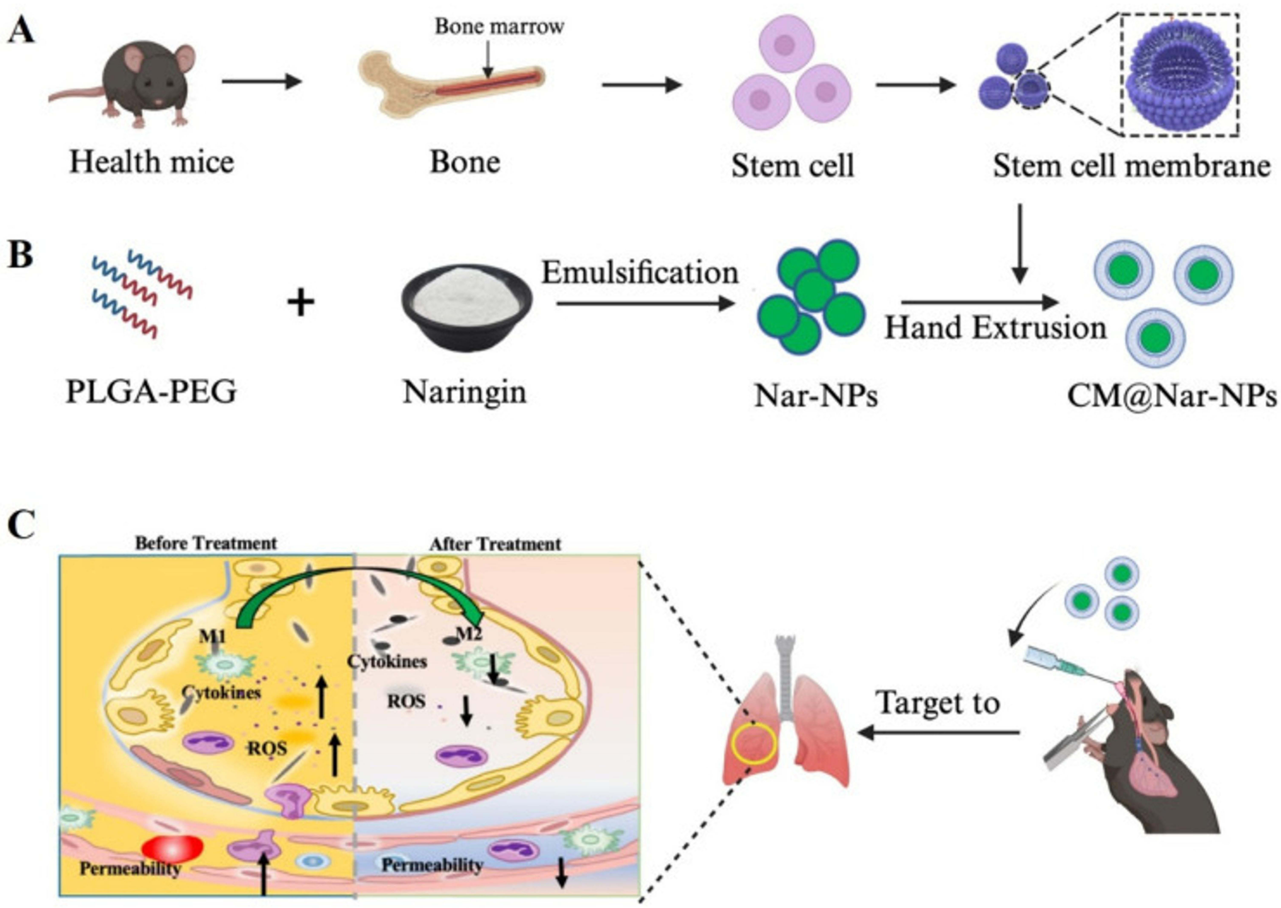

Figure 5 Schematic illustration of the preparation and therapeutic mechanism of CM@Nar-NPs for ALI treatment.(**A**) Mesenchymal stem cell membranes (CM) were extracted from healthy mouse bone marrow.(**B**) Nar-loaded PLGA nanoparticles (Nar-NPs) were prepared via an emulsification–evaporation method and coated with CM by membrane extrusion to form CM@Nar-NPs.(**C**) After intratracheal administration, CM@Nar-NPs target inflamed lungs, suppress ROS production and cytokine release, and promote macrophage polarization toward the M2 phenotype, thereby alleviating inflammation. (↑ and ↓ indicate increase and decrease, respectively).[95]

ALI.[97] Inspired by the natural homing ability of platelets, Qingle Ma et al developed platelet-derived EVs (PEVs) for targeted delivery of the anti-inflammatory small molecule TPCA-1 in pneumonia-associated ALI. Leveraging platelets' inherent affinity for inflamed endothelium, the PEVs precisely accumulated in inflamed pulmonary tissues, significantly suppressed neutrophil infiltration and cytokine storm, mitigated lung injury, and ultimately improved survival outcomes in vivo.[98]

In parallel, engineered EVs have also been explored for the delivery of therapeutic nucleic acids and gene-editing tools. Although CRISPR/Cas9 systems based on EVs have shown effective DNA editing, strategies for acute inflammation targeting via RNA editing remain limited. To address this, Tianwen Li et al developed a functional EV platform to deliver CasRx (Cas13d) along with optimized guide RNAs (gRNAs) for short-lived, RNA-level knockdown of pro-inflammatory mediators. By tandem expression of CasRx and multiplexed gRNAs, the system effectively inhibited macrophage activation and suppressed key cytokines such as TNF-α and IL-6. In LPS-induced ALI and sepsis models, this platform markedly attenuated tissue inflammation, improved multi-organ function, and enhanced survival, highlighting the transformative potential of RNA-editing EVs in acute inflammatory therapy[99] (Figure 6).

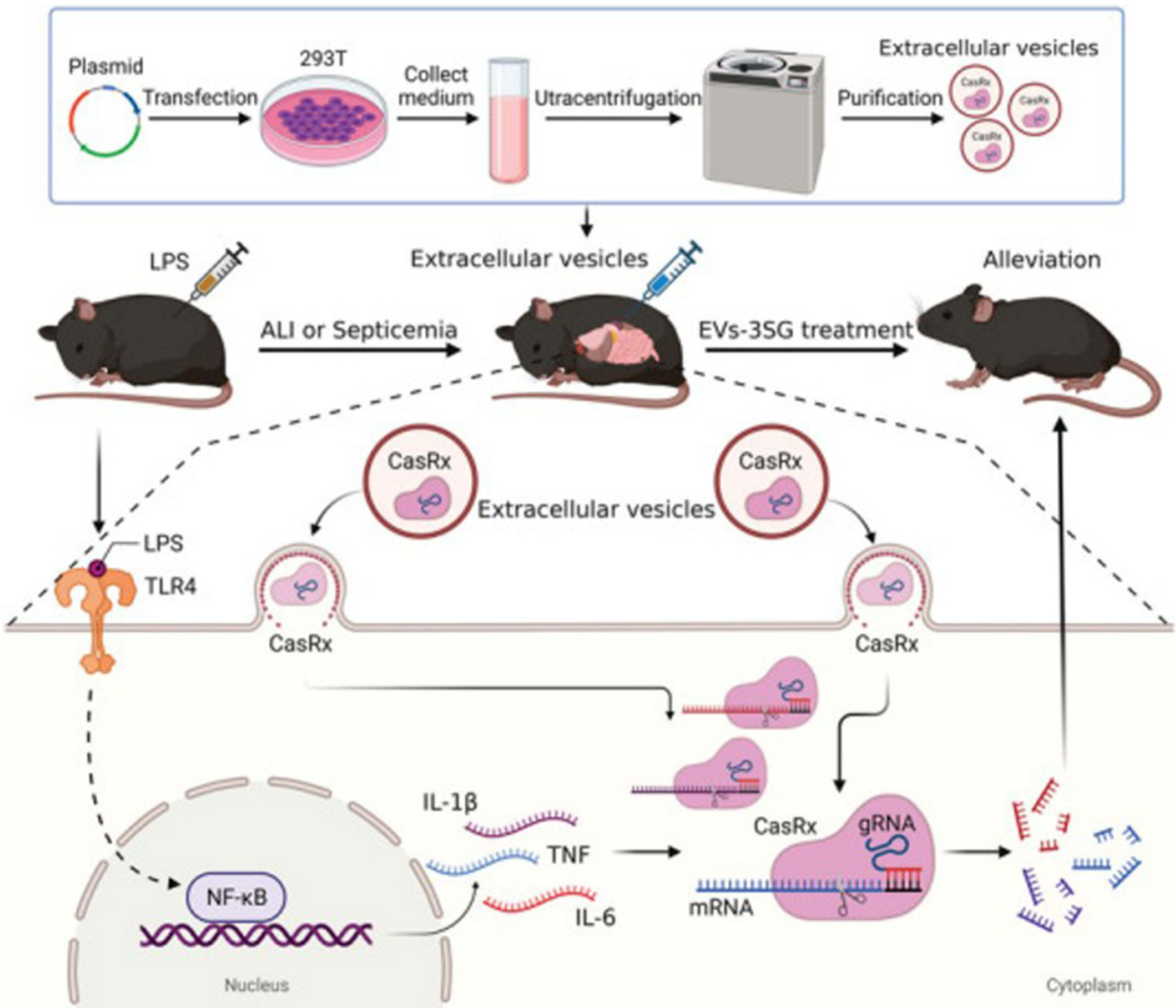

Figure 6 Schematic illustration of engineered EVs delivering a CRISPR/CasRx RNA-editing system. Engineered EVs encapsulate the CasRx/gRNA complex to specifically degrade TNF, IL-1β, and IL-6 mRNAs, thereby suppressing LPS-induced cytokine storms and alleviating acute inflammatory responses in mice.[99]

Other Biomimetic Membranes

Beyond commonly used sources such as red blood cell and macrophage membranes, researchers have increasingly explored alternative membrane types—such as apoptotic cell membranes, alveolar epithelial cell membranes, and pulmonary endothelial cell membranes—to construct biomimetic nanocarriers with enhanced targeting and therapeutic capacity for inflammatory lung diseases like ALI.

Apoptotic cell membranes present "eat-me" signals, such as exposed phosphatidylserine, which are specifically recognized by phagocytes and can promote immune cell uptake [97]. This innate recognition pathway offers a promising mechanism for inflammation-site targeting. Based on this, researchers designed a zirconium-based metal-organic framework (UiO-66) coated with apoptotic cell membranes (ACM@U) for the delivery of fibroblast growth factor 21 (FGF21), aimed at rebalancing macrophage-mediated immunity in ALI. By mimicking apoptotic exocytosis signals, ACM@U facilitated targeted interaction and uptake by lung-resident macrophages, leading to local enrichment of FGF21. In vivo studies showed significant suppression of pro-inflammatory cytokines (eg, TNF-α, IL-6) and promotion of M2-type macrophage polarization, thereby alleviating pulmonary inflammation and injury. This strategy not only enhanced the bioavailability of FGF21 but also established a paradigm for membrane-assisted immune reprogramming[100] (Figure 7).

MicroRNA-155 (miR-155) is a well-recognized pro-inflammatory regulator in ALI, primarily by inhibiting suppressor of cytokine signaling 1 (SOCS1) and exacerbating cytokine expression.[101] To efficiently suppress miR-155, Chuanyu Zhuang et al developed biomimetic cell membrane-derived nanovesicles (CMNVs) from murine alveolar epithelial cells to deliver cholesterol-conjugated antisense oligonucleotides (AMO155c). These nanocarriers preserved cell-type specificity and demonstrated superior stability (~120 nm) and targeting capacity compared to conventional carriers like PEI25k or natural exosomes. In animal models, AMO155c/CMNV significantly down-regulated miR-155, restored SOCS1 expression, and reduced pro-inflammatory cytokine release, indicating excellent anti-inflammatory activity and pulmonary targeting, and highlighting the potential of biomimetic nanocarriers for oligonucleotide delivery.[102]

Poor water solubility has limited the clinical application of berberine.[103] To overcome this, Chengkang Jin constructed diselenide-crosslinked berberine nanomicelles coated with alveolar epithelial cell membranes (MM-NPs). Exploiting the tissue affinity of lung-derived membranes, the platform actively targeted damaged pulmonary tissues. In ROS-rich microenvironments, diselenide bonds are cleaved to trigger berberine release, enabling inflammation-specific therapy. In vitro and in vivo experiments confirmed the system's biocompatibility and ROS-responsiveness, effectively suppressing cytokine expression and reducing tissue injury without observable toxicity, offering a novel strategy to enhance the therapeutic potential of natural compounds for ALI.[104] Fang Wang et al further developed polyester-based nanoparticles coated with pulmonary endothelial cell membranes (endothelial membrane-coated particles, EM-Ps), which retained critical adhesion molecules (eg, ICAM-1, VCAM-1). These molecules allowed EM-Ps to bind to circulating neutrophils and monocytes. Under inflammatory conditions, EM-Ps leveraged leukocyte migration to achieve "hitchhiking transport" to inflamed lung tissues. In ALI models, this strategy facilitated precise accumulation in injured regions and significantly reduced local inflammation. This work expands the scope of membrane-biomimetic nanomedicine and offers a new concept for leukocyte-assisted drug delivery.[105] In summary, diverse cell membrane-derived biomimetic strategies have demonstrated substantial versatility and mechanistic specificity in ALI therapy. Whether through apoptotic mimicry to facilitate phagocytic uptake, organotropic targeting based on tissue origin, or indirect delivery via immune cell migration, these platforms offer powerful tools for precision pulmonary therapy and hold significant promise for translational advancement.

In summary, diverse cell membrane-derived biomimetic strategies have demonstrated substantial versatility and mechanistic specificity in ALI therapy. However, although many platforms have shown targeted regulation of inflammation, oxidative stress, and immune signaling (Section 4), most studies remain focused on in vitro/in vivo phenotypic outcomes, with limited systematic molecular mechanism validation. Future work should integrate disease models with mechanistic readouts to strengthen the direct correspondence between material design and ALI pathogenesis.

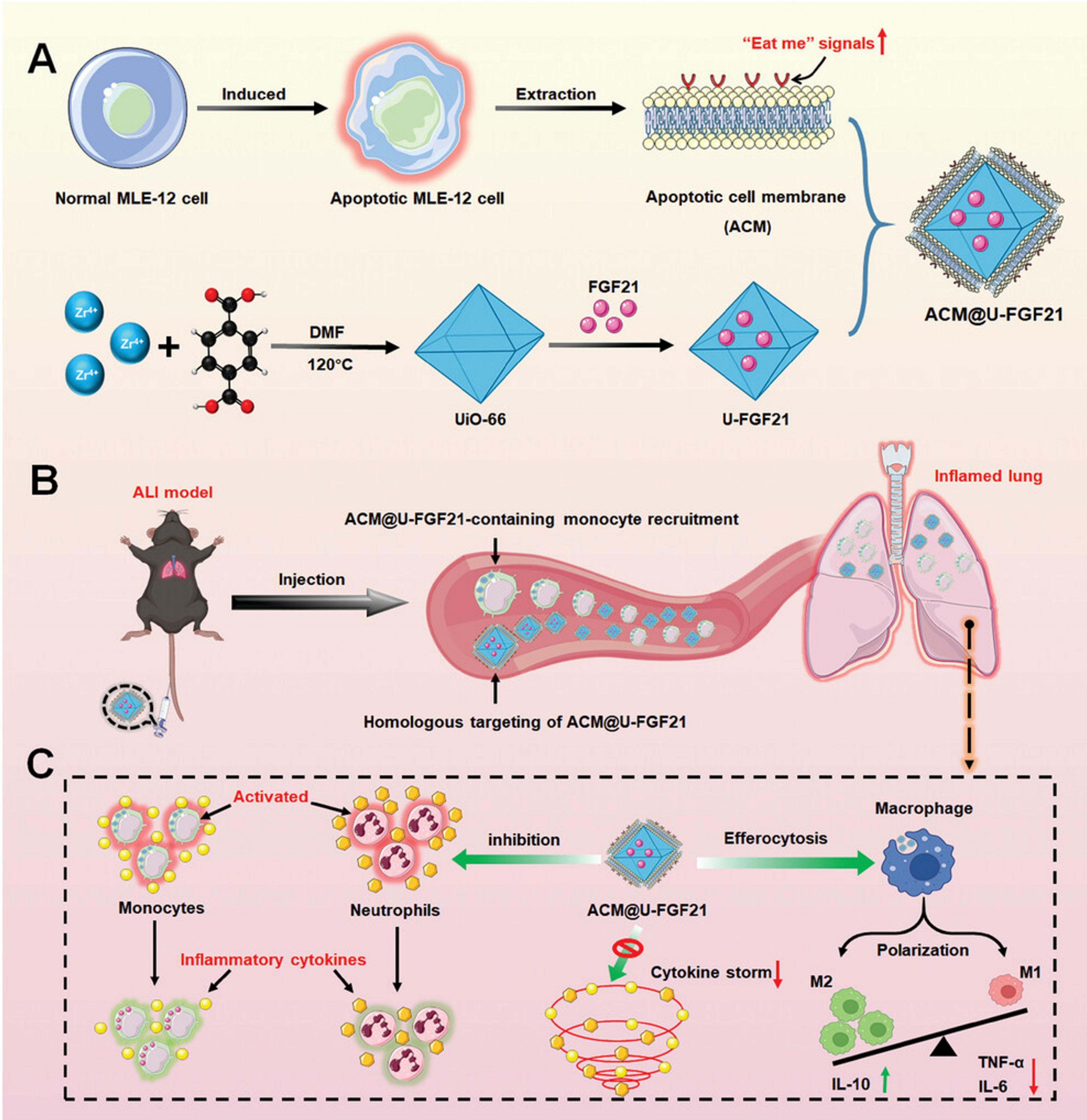

Figure 7 Schematic illustration of ACM@U-FGF21 for treating LPS-induced ALI.(**A**) Apoptotic lung cell membranes carrying "eat me" signals were coated onto FGF21-loaded UiO-66 nanoparticles.(**B**) ACM@U-FGF21 accumulates in inflamed lung tissue via homologous targeting and monocyte recruitment.(**C**) The nanoplatform alleviates inflammation by suppressing pro-inflammatory cytokine secretion and modulating macrophage polarization.[100]

Challenges and Future Perspectives

Biomimetic nanoplatforms offer distinct advantages for ALI therapy, including high biocompatibility, immune evasion, lesion-specific targeting, and the ability to integrate multiple therapeutic modalities such as anti-inflammatory, antioxidative, and regenerative functions. Compared with conventional nanocarriers, their natural surface composition enables improved pharmacokinetics and reduced off-target toxicity, which are particularly advantageous in the delicate pulmonary microenvironment.[106,107] Despite the remarkable therapeutic potential and multifunctionality of biomimetic nanoplatforms in the treatment of ALI, their clinical translation faces considerable hurdles. A comprehensive strategy is urgently needed to address challenges related to immunological safety, model fidelity, scalable manufacturing, and technological integration.

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First, immunogenicity and long-term biosafety remain central concerns limiting their broader application. Although membrane-camouflaged nanoparticles and exosome-based carriers exhibit inherent biocompatibility, issues such as membrane source heterogeneity, residual immunostimulatory components, and the physicochemical properties of the nanomaterials themselves may still provoke immune activation or tolerance responses in vivo.[19,108] Most current studies are limited to short-term safety evaluations, lacking systematic investigations into chronic toxicity, metabolic accumulation, and long-term biodistribution. Therefore, comprehensive toxicological assessments and pharmacokinetic studies are imperative prerequisites for clinical advancement.

Second, significant discrepancies in immune context, pathological progression, and response mechanisms between animal models and human ALI hinder translational efficacy. Rodent models, which dominate preclinical studies, fail to fully replicate the complex microenvironment of human pulmonary injury, often resulting in poor reproducibility in clinical settings. It is thus critical to develop more human-relevant platforms, such as lung organ-on-chip systems and immune-reconstituted large animal models, to enhance the predictive accuracy and translational value of early-stage studies.

From a manufacturing perspective, the extraction and assembly of natural biomaterials—such as cell membranes and exosomes—remain technically demanding and poorly standardized. These processes are highly sensitive to the state of source cells and environmental variables, posing major challenges to large-scale production and batch-to-batch consistency. Accordingly, the development of efficient, controllable purification and assembly techniques, along with the establishment of GMP-compliant quality control systems, will be pivotal in driving the industrial translation of biomimetic nanoplatforms.

Moreover, interdisciplinary integration offers promising opportunities for the intelligent design of next-generation nanotherapeutics. Artificial intelligence-assisted structural optimization and high-throughput screening can rapidly identify optimal design parameters from large datasets. Lung-on-chip platforms can mimic the local pulmonary microenvironment, enabling in vitro drug efficacy and toxicity profiling, thereby improving preclinical throughput and reliability.

As precision medicine continues to evolve, personalized nanotherapeutics are expected to play an increasingly vital role in managing ALI and related inflammatory lung disorders. By incorporating patient-specific genomic, transcriptomic, and immunoprofiling data, personalized biomimetic nanosystems can be designed with targeted responsiveness and therapeutic synergy, allowing for precise modulation of inflammation and enhanced tissue repair. Such approaches hold great promise in improving therapeutic outcomes while minimizing adverse effects, paving the way for safer and more effective clinical interventions.

Collectively, while biomimetic nanoplatforms possess unparalleled potential in achieving precise and multifactorial intervention for ALI, their complexity in source materials, fabrication, and quality control still poses obstacles to large-scale application. Future work should therefore strive to balance their biological advantages with practical considerations of safety, reproducibility, and manufacturability to accelerate clinical translation.

Conclusion

Biomimetic nanoplatforms represent a promising frontier in the treatment of ALI, offering exceptional biocompatibility, multifunctional integration, and targeted delivery capabilities. By emulating natural cell membranes, these platforms enable multi-target modulation of inflammation, immune responses, and oxidative stress, thereby enhancing the specificity and safety of drug delivery.

Their programmable architecture and integration of diverse mechanisms provide flexible therapeutic strategies. With the continued advancement of materials science and biomedical engineering, biomimetic nanoplatforms are poised to become powerful tools for the management of ALI and other complex pulmonary diseases. However, most studies remain at the proof-of-concept stage, and critical barriers—including immunological safety, production scalability, and model relevance—must be overcome to achieve clinical translation.

Looking ahead, interdisciplinary collaboration, technological innovation, and patient-tailored design will be essential in accelerating the clinical application of biomimetic nanomedicine, ultimately delivering more effective and safer therapeutic options for patients suffering from ALI.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Consent Statement

No individual personal data is included in the study.

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Disclosure

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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