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REVIEW

Bioactive Nanomaterials: Comprehensive Monitoring and Regulation of Acute Pancreatitis Induced Acute Lung Injury

Enoch Obeng[1–3,*], Akmal Ergashev[1–3,*], Qingqing Yao[3,4,*], Wencan Wu[3–5], Gang Chen[1,2,6]

[1]Department of Hepatobiliary Surgery, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, 325035, People's Republic of China; [2]Key Laboratory of Diagnosis and Treatment of Severe Hepato-Pancreatic Diseases of Zhejiang Province, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, 325035, People's Republic of China; [3]The Eye Hospital, School of Ophthalmology & Optometry, Wenzhou Medical University, Wenzhou, 325027, People's Republic of China; [4]State Key Laboratory of Ophthalmology, Optometry and Vision Science, Wenzhou Medical University, Wenzhou, Zhejiang, 325027, People's Republic of China; [5]Oujiang Laboratory (Zhejiang Laboratory for Regenerative Medicine, Vision and Brain health), Wenzhou, Zhejiang, 32500, People's Republic of China; [6]Zhejiang-Germany Interdisciplinary Joint Laboratory of Hepatobiliary-Pancreatic Tumor and Bioengineering, Wenzhou, Zhejiang, 325035, People's Republic of China

*These authors contributed equally to this work

Correspondence: Gang Chen, Department of Hepatobiliary Surgery, The first Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, 325035, People's Republic of China, Email chen.gang@wmu.edu.cn; Wencan Wu, State Key Laboratory of Ophthalmology, Optometry and Vision Science, Wenzhou Medical University, Wenzhou, Zhejiang, 325027, People's Republic of China, Email wuwencan@wmu.edu.cn

Abstract: Mounting evidence suggests acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) is a complication of acute pancreatitis (AP), a disorder associated with several health challenges, a common cause of multiple organ damage, and a contributing factor to mortality. The exact mechanism behind the disorder has not been fully understood over the years, although what is mostly known is that the intensity of the AP in turn plays a significant role in the state of the ALI/ARDS. The eradicative role via conventional/pharmacological intervention has caused only little impact over the years. However, the nanotechnological advancement over the years may set the stage for ameliorating the condition. This review seeks to expound on the possible potential embedded with bioactive nanomaterials tackling the limitations faced by conventional drugs by highlighting AP and its associated ALI/ARDS, the nanotechnological role in the face of the loopholes of the conventional intervention, and the use of bioactive nanomaterials ranging from anti-inflammatory to anti-oxidant for the modulation ALI/ARDS. In addition, other modulating effects of bioactive-nanoparticles, the application of nanocomposite/hybrid nanoparticles and the conclusion and future perspective encompassing the cytotoxic effect and other concerns. In all, understanding the mechanisms and the bioactive nanomaterials potential roles may create a platform that can be of potential clinical value.

Keywords: acute lung injury, acute pancreatitis, drug delivery, nanoparticle, inflammation, oxidative stress

Introduction

Acute pancreatitis (AP) is one of the basic phenomenal foundations for common abdominal disease. The emergence of this condition is not limited to local peripancreatic tissues but also to other organs and systems arising from the change in the inflammatory phase during the infection process.[1–4] Some immediate factors that can be associated with the inception of this condition are the abuse or misuse of alcohol and gallstone formation, which influences elements that drive the secretion of an enormous number of digestive enzymes, and further auto digestion which triggers inflammation, edema, bleeding and necrosis.[5–7] An annual estimation of approximately 300–500 cases/million is recorded around the globe. Although the majority happens to fall within a mild range, the increase in mortality is largely associated with severe cases which may constitute 15–20% of the cases recorded in general. Typically, the pathophysiological process is accompanied by the release of cytokine, inflammatory mediators, and the actuating of diverse signaling pathways causing more deteriorating effects in the body.[8–10] Interestingly, some reports have not limited the pathophysiological condition to

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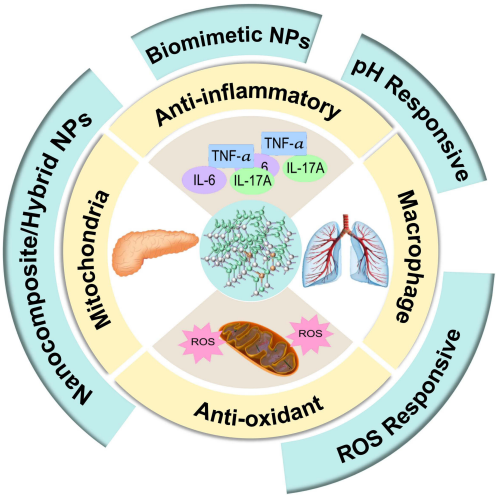
Graphical Abstract



inflammation but to the necrosis factor, which involves the necrosis of fat surrounding the peripancreatic and intra-pancreatic environment, with the indiscriminate digestion and destruction of the adipocytes by the excessively released and activated pancreatic enzymes. The process releases and breakdown triglycerides as part of the excessive pancreatic enzymes release to give a fatty acid and glycerol (unsaturated free fatty acid) which creates the platform for the release of more inflammatory mediators.[11,12]

The association between the systematic inflammatory response (SIR) and hypovolemia development, and the further release of chemokine and cytokine eventually causes the multiple organ dysfunction syndrome (MODS).[13–16] As at this stretch, it has been reported that the exact underlying mechanism seems not to be fully understood or appreciated, although the diverse signaling pathways have been studied in recent years. Among the organ dysfunction, the lung and intestines happen to be the immediate target organs, when it comes to AP and this is estimated to be the rapid cause of death in severe AP following infection.[13,17] Consequently, between the intestine and the lungs or other related organs, the lungs appear to be the leading organ to be easily affected under AP, hence acute lung injury (ALI). Further, clinically ALI is recategorized as a mild form and acute respiratory distress syndrome (ARDS). Firstly, these two conditions are characterized by distinct arterial oxygen pressure and inspired oxygen concentration ratio (P_{aO2}/ F_{iO2}).[18–21] Additionally, ALI/ARDS can be considered a respiratory failure disorder characterized by hypoxemia and diffuse alveolar damage on chest radiography, a significant factor of morbidity and mortality in severely ill patients.[13,22,23] Secondly, determinants associated with ALI emergence in relation to AP are the inflammatory mediators and the generation of ROS overtime.[24,25] Surprisingly, ALI/ARDS can in turn worsen the state of an AP, thus, an urgent call for an effective and reliable means to curtail the condition. The use of traditional therapies has not seen any significant progress over the years.

However, some conventional drugs emerge as very useful and then later prove to be inefficient. Also, clinical trials have not improved the situation either, since this needs ample time and critical analysis. The limitations and loopholes faced by the pharmacological industry might be dealt with and filled by the recent nanotechnological advancement. Over the years, nanomaterials ranging from organic to inorganic have seen substantial development in terms of their usage and progress. Could this mean the pharmacological industry could team up with the nanotechnological industry or the latter will replace the former? The future development will tell. Regardless of the alarming condition and increase in mortality, reports and reviews have only focused on some cellular activities and pathways involved without any novel remedy. This review seeks to focus on the process involved in the disease pathogenesis and the possible replacement of conventional therapeutics with a bioactive nanomaterial or infusing both for great success since the nano-drug/nanomedicine has already shown a great outcome following their usage. Hence, we elaborate on the AP its pathogenesis, clinical diagnosis

and management, the mechanism involved in the AP and ALI/ARDs and the link between both conditions, the limitation of conventional intervention, and the nanotechnological role in overcoming this limitation, bioactive nanomaterials consisting of the various nanoparticles being ROS responsive, pH-responsive employed in modulating AP induced ALI/ARDS. Also, we provide a detailed submission on biomimetic nanoparticles and the nanocomposite/hybrid nanoparticles effect in modulating the AP induced ALI/ARDS. Lastly the challenges, future perspective, and conclusion, with the notion of emphasizing the remarkable efficacy of nanodrug /nanomedicine for potential clinical usage.

Brief Overview of AP and Its Associated ALI/ARDS

AP is one of the many gastrointestinal conditions evident as an acute inflammatory condition that is accompanied by elevation in the pancreatic enzymes, sharp abdominal pains, and nausea.[26–29] Acinar cells which are the main functional unit of the pancreas are faced with the induction and accumulation of excess amount of trypsin, following the conversion of trypsin in the acini. Further, varying digestive enzymes involving the kinin system with a number of conditions cause the pancreatic parenchyma to undergo autodigestion.[30–33] In the activation of trypsin, primary injury can also serve as a cause, normally the elevation in intracellular calcium triggers extracellular calcium, a disfunction in the calcium reuptake inducing the cytosolic calcium within the acini. Also, the obstruction of the pancreatic duct by gallstones can serve as another great means by which the acinar can be damaged. Next, periampullary tumors, cystic lesions, and pancreatic head mass can also obstruct the pancreatic duct.[34–36] At least in every population of about 100,000, there are approximately 100–140 individuals with the condition of AP. Due to variability in their cause, it makes them even more difficult to predict at the early stage. Surprisingly, these disease condition contributes to the hospitalization of approximately 300,000 individuals annually with an estimated cost of 2.64 billion in 2024 alone in the US. Studies have concluded that even in patients with pancreatic cancer, AP could be the earliest presentation to observe and can be concluded within 12 months, even among patients whose conditions are not severe.[37] Surprisingly, some cases of AP recorded is either the overuse or misuse of the drug but other factors that could put the individual at risk of getting AP could be old age, obesity, smoking a positive status of HIV, and geographical region.[38,39] Population-wise, most individuals with the condition happen to be faced with mild to moderately severe states, while a few are faced with severe conditions and subsequently, mortality if unattended to.[37,40,41]

Also, although they can occur as an isolated condition or relapsing process, they can range from mild interstitial disease state to severe necrotic and extended organ failure state. As mentioned above, signs that have characterized them over the years have been the basis of diagnosis, examination of the abdominal pain, examination of the level of pancreatic enzyme (amylase and lipase), and testing of excessive consumption of alcohol and gall stones.[42,43] Reports show that AP becomes severe when local inflammation sharply progresses at a systemic level since complications are usually local or systemic related, at the systemic level inflammatory response can cause an organ failure. However, mild AP do not have such systemic complications or organ failure, those of the moderately severe may also be accompanied by local systematic complication and observation of the exacerbation of related chronic lung disease. Organ failure under severe AP can even show up in less than 48 hours, and this can be accompanied by mortality compared to moderately severe AP. Based on the Atlanta classification, the rate of organ failure could be transient, when it is less than 48 hours or persistent when the organ failure lasts for more than 48 hours.[44–46] What's more, AP can be categorized into interstitial edematous and necrotizing pancreatitis. The former is usually characterized by edema and inflammation of the peripancreatic tissues and the pancreatic parenchyma. The deterioration caused by the severity of the edematous pancreatitis yields necrotizing pancreatitis, usually after the unset of this condition, acute necrotic collections can be observed within 4 weeks while the peripancreatic fluid, in the latter. After 4 weeks, pseudocyst and walled-off necrosis can be observed aside from the observation of local complications such as splenic/portal vein thrombosis and the gastric outlet dysfunction can also persist.[47,48]

Pathogenesis of AP

AP has been associated with many causes as mentioned earlier, aside from alcohol and gallstone other causes such as hypertriglyceridemia (HTG) have been a known contributing factor, The HTG although underestimated, with a fasting serum triglycerides value above 150 mg/dL (1.7 mmol/L), has been recorded to be the huge cause of AP among those

who are pregnant.[49–51] Studies show the prevalence of AP in about 20.2% of patients with significantly high triglyceride levels and with more than $^{2}/_{3}$ of the patients falling within a (>2411/mg/dL) triglyceride quartile group. Also, an epidemiology study in China revealed a percentage of about 22 out of the total of 475 patients with triglycerides (.>1000 mg/dL) which does not seem to be quite a recent discovery but a trend observed for over a decade; meanwhile, the trend for the main cause happens to decrease over the years. However, the increase rate of the cause has been quite alarming with a sharp increment from 14.3% to 35.5% within a period. On the contrary, the opposite trend has been observed in the United States & Europe with the leading cause still being gallstones and alcohol. The trend in China has been associated with caloric intake and metabolic syndrome arising from the change in the lifestyle behavior of the recent population.[52–54] This condition is largely prevalent among the young, obese, and those with higher levels of diabetes.

On the etiology, primary hyperlipoproteinemia is divided into about five different phenotypes, and the secondary on the other hand is attributed to several conditions including pregnancy, hypothyroidism, medications, and when diabetes is poorly managed since obesity and diabetes can easily increase the level of triglycerides. Next, on the part of pregnancy, any physiological increase in the levels of triglycerides has a tendency to cause AP. Also, the pregnancy-associated disorder has been said to be linked to genetic dyslipidemia. Regarding genetics, the phenotype of primary hyperlipoproteinemia for example type 1 emanates from an autosomal recessive trait that yields chylomicrons and is usually observed in children, the type V although like type 1 is mostly found in adults with high tendencies of AP. Type IV can also be found among adults and may have other associated factors that induce them and therefore may not specifically stem from the elevated levels of triglycerides.[55–57] In addition, although reports indicate that alcohol can contribute to it via increasing the plasma very low-density lipoprotein (VLDL), there is no sufficient evidence to determine if this can be linked to genetic-related causes. Most importantly, medication associated complications yielding the HTG or AP in itself need to be paid attention to, a typical example is class Ia medication with tamoxifen and products that are estrogen related and class Ib medications which have propofol and furosemide component.[56–58]

Clinical Assessment, Diagnosis and Management Process

Some common and easy assessments that can be made include abdominal pain characterized by some sort of radiation into the back of the individual and may often be intensified upon eating, drinking, or being in a supine position. Other signs may include moderate-grade fever with nausea and vomiting. Following this can be a comprehensive history assessment and physical examination considering the presence of gallstone disease, alcohol usage, family history with regard to acute or chronic pancreatitis, trauma, and the use of some medication. Physical examination reveals the decrease sounds of the bowel and abdominal distention and other standard chemistry evaluations such as the liver panel test, amylase, and lipase. The presence of gallstone may have some indications such as increased levels of bilirubin and alkaline phosphatase. This can further be assessed with transabdominal ultrasound to determine the gallstones as well as the triglycerides. Next, computed tomography (CT) and magnetic resonance imaging (MRI) may also be employed for the management process during the assessment and diagnosis period. Interestingly, the above mention assessment and diagnosis fall under the revised Atlanta classification (RAC) which requires at least 2 of the diagnosis approaches to be used during the management process of AP. Usually, the common signs and symptoms determined by CT may also be other similar conditions that may have a semblance to the AP a typical example may be a perforated duodenal ulcer.[59–62]

Under chemical diagnosis a number of scores have been made to determine the condition of pancreatitis, this includes 1974–1977 by Rason et al, 1978–1984 Imrie et al and either scoring requires further assessment of the patient.[63–65] Also, 1985 had the APACHE-II model, and 2008 saw the bed side index model, the APACHE-II focused on variables that were not usually seen in critically ill patients, it was developed to predict variables associated with mortality. Aside from this, biomarkers have been employed to demonstrate some predictive effects a typical example is C-reactive protein (CRP).[66–69] The process of managing AP for some time now has been either fluid resuscitation for perfusion or nutritional support. The fluid resuscitation involves the administration of lactated Ringer solution and the titrating of intravenous fluid to correlate with the appropriate perfusion target because usually, there is a depletion of the intravascular volume as a result of the systemic edema arising from the AP. Also decrease in oral intake, vomiting, and other associated peripancreatic inflammation cause a decrease in the amount of fluid. And so this management process is expected to be done immediately after assessment and diagnosis prove the existence of the condition.[70–73] Another management process has been nutrition,

usually due to the catabolic state and the essential nutritional requirement arising from the systemic inflammatory response and also damage of the gut mucosal as a result of the intestinal vascular perfusion. Also, studies show the organ failure can occur as a result of intestinal permeability allowing the easy translation of the lumen bacteria into the mesenteric lymphatic and portal circulation. Report indicates that enteral nutrition replaces caloric loss and preservation of the state of the bowel mucosa allowing for easy intestinal motility. Usually, this must be done within 24 or 72 hours following the indication of the disease and admission. This has proven to be efficient and has a decreased mortality rate, systemic infection, and organ failure and normally should be with low fat. Additionally, other alternatives for oral nutrition can be nasoenteral nutrition.[74–77]

AP Induced Respiratory Complication

Respiratory disorders can differ based on hypoxemia which is a huge percentage of individuals diagnosed with AP and a few percentages with partial oxygen pressure. Most time, there is some correlation between hypoxemia and necrosis developed and this has been attributed to the deterioration of the pulmonary surfactant resulting in the loss of surface tension, mismatch of ventilation perfusion, and other mechanisms leading to the elevation of the intrapulmonary shunt.[78–80] Mostly, some recorded or increased in the mortality rate can be attributed to the extent of hypoxia, and patients under this condition will require some form of mechanical ventilation support with supplemental oxygen with other associated complications being renal and cardiovascular failure and subsequently death. Under the severity of hypoxemic complication lays some other complications such as acute respiratory distress syndrome (ARDS). It is reported that about a quarter of patients with AP may demonstrate ARDS and this can be observed within or after a week of the AP. The AP in itself is associated with the induction of intracellular pancreatic enzymes such as trypsin, thus activated trypsin obliterates the pulmonary vascular endothelium allowing for permeability and the movement of fluid into the alveoli which further interrupts the gaseous exchange, upon increment of the fluid in the alveoli.[81–83] Trypsin induces phospholipase A2 in the duodenum and this has been proven to cause destruction of the pulmonary surfactant phospholipid further yielding to the collapse of the alveolar.

Aside from this, it is been documented that a number of pro-inflammatory cytokines become involved at this point which allows for systemic inflammation. The elevation in some IL such as the IL-6 and IL −8 has been projected to be an indication of ALI/ARDS regarding the percentage of specificity and sensitivity. Normally, the immune response amplifies when neutrophils become exposed to inflammatory mediators. IL-8 for example can help recruit more neutrophils into the lungs. Also, the neutrophil is capable of adhering to the endothelial cells with the aid of P-selectin and intercellular adhesion molecule expression the degranulation or further releasing other substances that yield ALI.[84–86] Also, some studies indicate that ARDS can be observed in the second week as well, and an observation of elevated CT severity index can be associated with ARDS. The PaO2/FiO2 ratio following the monitoring of the blood gases should be less than 300 if ARDs are present; meanwhile, there may be an elevation in the alveolar-arterial gradient and under this circumstance it can be easily diagnosed if the condition is mild or severe such patient need ventilation support and the CT scan may be difficult.[87–90]

Usually, the AP associated ADS can be managed and treated as normal ADS. This involves using the assisted ventilation support or employing some form of oxygen therapy, and it can be an invasive or non- invasive mechanical ventilation, normally with low tidal volume (4–6 mL/kg) for a plateau pressure of, <30 cm H_2O to be maintained. Also, other conditions like the FiO2 and the PEEP could be adjusted based on the protocol of ARDS NET to attain SpO2 88–92%. Under mild respiratory acidosis, there is a need to avoid increasing tidal volumes. Further, some assessments such as the hemodynamic assessment could be made. Some pressure monitoring activities such as invasive blood pressure and central venous pressure can enable the establishment of the fluid status of a patient and can be done in combination with other assessments such as bedside echocardiography.[90–92] Some shock that can be developed during these periods is the sepsis-induced vasodilation and pulmonary vascular dysfunction. The former leads to capillary leakage while the latter, pulmonary hypertension and dysfunction of the right ventricle. An observation of an inferior vena cava distensibility index and a pulse pressure variation exceeding 18% and 12%, respectively, is an indication of fluid responsiveness. Also, fluid replacement should immediately be undertaken when RV failure is observed and the whole management process following assessment will require regular hemodynamic monitoring. Under AP-associated ADS, pneumonia can also develop when a patient requires some form of mechanical ventilation. Also, the individual

risks severe neuropathy-related illness. During the employment of mechanical ventilation, owing to sedation and neuromuscular blockers, this makes it difficult to remove or take such patient off the ventilation support.[92,93]

It is important to note that, Pneumonia in itself has varying causes ranging from being a bacteremia infection or just being hospital-acquired. According to the AP-associated Pneumonia, in the event of abdominal pain, fever, hypotension, bacteria such as *E. coli* could be easily translocated due to the permeability of the intestinal mucosa and compromise of the splanchnic circulatory. Further, the translocation of the bacterium from example infected pancreatic necrosis could result in pneumonia. Also, nosocomial infection can have some gram-negative and positive bacteria involved (Pseudomonas, Klebsiella or Acinetobacter, and Staphylococcus). Although studies have shown the employment of multiple indwelling catheters can also put an individual at risk of pneumonia, this still has bacterium or fungi infections involved.[94–96] Mostly, elevation in fever, purulence of secretion, and the need for oxygen may portray signs of pneumonia. This assessment can easily be made with chest x-ray, ultrasound and should have the administration of immediate antibiotics (broad-spectrum empirical antibiotics) administration sputum assessment together with other microbial cultures should be employed as well, and the specific and appropriated drug should be administered right away. Also, some microbiological and biochemical tests and evaluations can be made on CT scan results to quickly determine affected segments. Under this state, infections are managed by administering specific antibodies, nutritional supplementation, taking out infected catheters, and debridement of tissue that is infected.

Mechanism Involved and Linking of AP to ALI/ARDS

On the one hand, under the pathological process of AP, once autodigestion sets in, as a consequence of the release of an excessive number of digestive enzymes, this paves the way for inflammatory response, edema, and necrosis.[97,98] In the process, the pancreatic acinar becomes damaged which in turn triggers the proinflammatory mediators (cytokine and chemokine). Further activating the immune cells (innate and adaptive immunity) such as the neutrophils, dendritic cells, macrophages, mast cells, T cells, B cells, etc. Accordingly, systematic inflammation becomes obvious when several damaged molecular patterns (DAMP) are released, activating the infiltration of immune-associated cells and intensifying the release of inflammatory mediators.[99–101] Basically, the ALI/ARDS is the alteration of the state of the lung endothelial and epithelial barriers and encompasses loss of the alveolar-capillary membrane integrity and proinflammatory release which are characterized by cytotoxic mediators.[102–104] The loss of the alveolar capillary membrane integrity is primarily followed by the occupation of interstitial space and the alveoli by protein-rich fluid. The loss of membrane integrity has largely been associated with the neutrophil, upon insult, the neutrophil becomes accumulated and activated in pulmonary microvasculature, triggering diverse toxic mediators, breaching the vascular permeability, and finally directly impacting the epithelium.

Reports indicate that this may not be the only means for the development of ALI/ARDS. Nonetheless, edema is an important factor following the injury of the alveolar epithelium; however, the action of the neutrophil cannot be exempted from the development of the alveolar epithelium injury since the neutrophil infiltration via the epithelial barrier increases resulting in the injury.[105–107] On the other hand, the pathogenesis of the ALI/ARDS is firstly observed as diffuse alveoli damage with pneumocyte necrosis and the influx of inflammatory cells. This further leads to type II pneumocyte hyperplasia and proliferation of the fibroblast under a proliferation phase. The physiochemical alteration of the homeostasis, pulmonary endothelial together with the epithelial barrier is further mediated by the release of vasoactive and cytotoxic substances. In addition, this is characterized by intra-alveolar edema, endothelial cell damage, contraction of distal airways, and the sequestration of leukocytes (Figure 1).[108–110] On a large note, the lung blood-air barrier becomes damaged as a result of inflammatory cells and their mediators.[24,25] It is interesting to note that, the recruitment of neutrophil pneumocytes and macrophages evident in the AP are equally recruited at the varying phase of the ALI/ARDS by some chemokines such as interleukin 8 (IL-8), monocyte chemoattractant protein (MCP)-1 and have largely been associated with the level of some pancreatic enzymes such as the protease (elastase), phospholipase A_2 and the activation of neutrophil.[111,112] The neutrophil promotes the ROS generation, the release of other pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) and can further occasion several intracellular signaling pathways (signal transducer and activator of transcription 3 (STAT3), mitogen-activated protein kinases (MAPK) signaling pathways, nuclear factor kappa B (NF-*k*B), activator protein-1 (AP-1) and NOD-like receptor protein 3 (NLRP3) etc.[113–115] Normally, HPME'S become damaged under ALI/ARDS. However, MMPS, a form of zinc-dependent endopeptidases (MMP-2 and MMP-9),

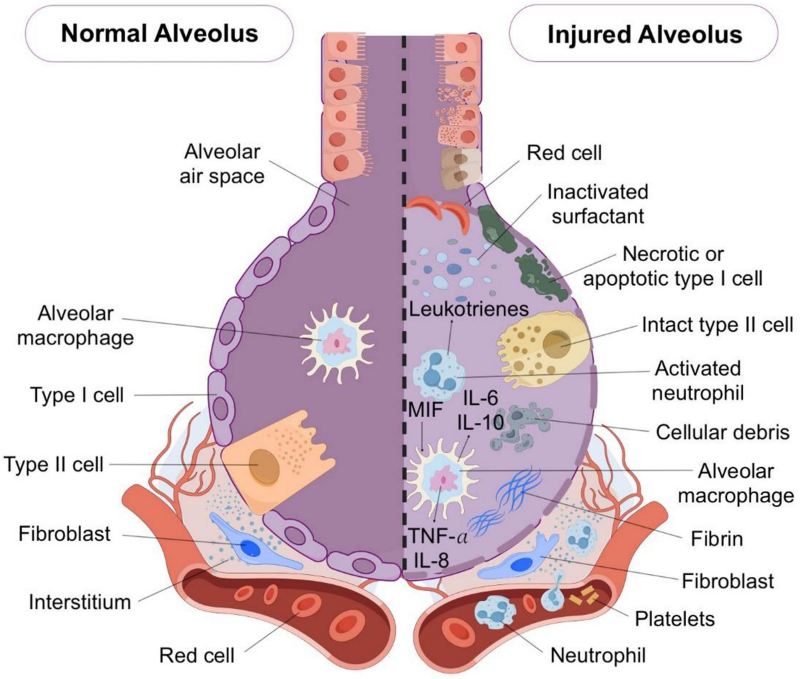


Figure 1 Schematic representation of normal Alveolus and injured Alveolus.

is secreted by HPMECS which happens to be involved in the permeability of the lung and further exacerbation of the condition (Figure 2).[116–118]

Inflammatory Response and Oxidative Stress

Principally, an inflammatory response is induced out of the accumulation of excessive free fatty acids (FFA). Under this condition, there is induction of lipotoxicity after pancreatic lipase breakdown triglycerides into FFA. The intensity and extent of damage caused largely depend on the lipotoxicity. Thus, the lipase release by the pancreatic acinar cells hydrolyzes the triglycerides to give FFA, in return the FFA induces an inflammation reaction which elevates the level of intracellular calcium and subsequently acinar necrosis. Aside from this deteriorating effect, the FFA can induce ischemia, and induction of active trypsin to further trigger auto-digestion which causes damaging effects to the acinar and vascular endothelial cells. Further, they pave the way for the activation and function of some inflammatory mediators which include IL-6, IL −10, TNF-α, etc.[119–122] Proinflammatory factors as a key initiator of lung injury, their activities impact the human lung microvascular endothelial cells (HPMECS), altering the permeability of the alveolar, blood oxygen saturation, and causing pulmonary edema, etc. Among the inflammatory factors are the proinflammatory cytokines which include IL-1β, IL-6, IL-17A, TNF-α, endotoxins, and high-mobility group box protein 1 (HMGB1), a typical DAMPs.[123–126] The release of the chemokine plays a prominent role in the presence of the neutrophil in the pulmonary microvasculature.[127,128] For example, the TNF-α from activated macrophage plays a significant role in the systematic inflammatory response, large levels of cytokine release during AP within lung parenchyma occur via macrophage and the P38 mitogen-activated protein kinase pathway.

Hence, the pathogenesis of AP closely corresponds to the TNF-α activity in terms of its emergence and development. Conventionally, the binding of TNF-α to the TNF receptor R1 (TNF-R1) instigates the interactions with TNF-R1 related death domain (TRADD) protein, receptor-interacting protein (RIP), and TNF-R related factor 2, which triggers the activation of other intracellular cascade and NF-*k*B.[129–131] Also, the IL-8 can be closely tied with mortality, when found in the air space of ARDs patients via the CD18, which is engaged in the traffic of polymorphonucleocyte (PMN) into the lung tissues. Additionally, they can be activated via the synergistic activity of the IL-17A and TNF-α. Further, the synergistic activity of the TNF-α and IL-17A can also increase the expression of IL-6 which in turn advances the release of the CXCL family of

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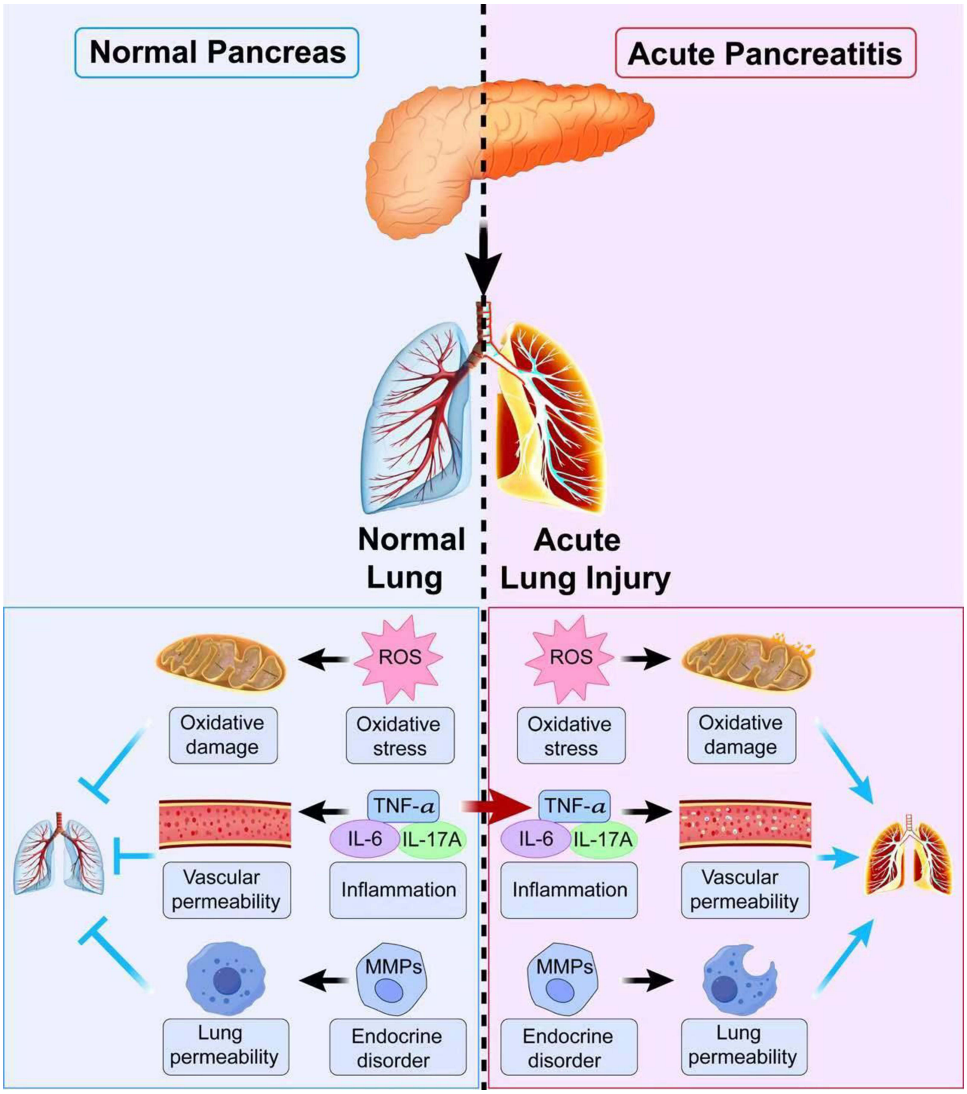

Figure 2 Diagrammatic representation of the mechanism of acute pancreatitis induced lung injury.

chemokines.[132–135] Usually, the IL-6 allows apoptosis, inhibits proliferation, activates the JAK2/STAT3, and is involved in the inflammatory process allowing the expression of adhesion molecules on the endothelial cells for the release and movement of leukocytes to the subendothelial stroma. Interestingly, IL-17A is also implicated in the pathogenesis of ALI by promoting lung neutrophil aggregation for pulmonary and pancreatic edema and further lung damage and can be expressed within serum and bronchoalveolar lavage fluid (BALF). Next, the JAK2/STAT3 signaling pathways allow the expression of intercellular adhesion molecule (ICAM-1) under AP. Nevertheless, due to the association of ICAM-1 with leukocyte adhesion and migration, this intensifies the inflammatory response or the endothelial cell injury.[136,137] Consequently, this process can successionally lead to the activation of NF-*k*B and the induction of ALI. Also, the IL-1β belonging to the family of the IL1 cytokine can be activated by the Protein 3 (NLRP3) inflammasome and NF-*k*B. The IL-1β are also involved in cell proliferation, differentiation, and apoptosis, and their activation promotes ALI/ARDS.

Also, the P38 mitogen-activated protein kinase (MAPK) and c-Jun N terminal kinase (JNK) are engaged in apoptosis, cell proliferation, and tumorigenesis.[138–140] What's more, the P38 MAPK regulates gene transcription, translation and promotes inflammatory cytokine/mediator release, involved in the pathogenesis of both AP and ALI/ARDS.[141–143] Following ischemic injury or hemorrhagic shock the JNK, extracellular signal-regulated kinase (ERK) as well as the P38 MAPK can be activated. ERK under this state permits cell damage and death.[144–146] Further, the nuclear factor erythroid-2-

related factor 2 (Nrf2) turns out to be one secured pathway for suppressing oxidative damage and can modulate cellular oxidation and homeostasis reduction, a key factor for alleviating SAP and regulating ALI/ARDS.[147–149] The Nrf2 is capable of binding to the Kelch–like ECH-associated protein 1 (Keap 1) but dissociates under stress. On top of that, the Nrf2 and its downstream gene HO-1 can be activated by TNF-α, upstream of the Nrf2 is the intracellular energy sensory AMP-activated protein kinase (AMPK). The AMPR can activate the Nrf2 via the Akt kinase and glycogen synthase kinase 3 beta (GSK3β). Besides, other factors that can promote the expression of the Nrf2 is the LXA4, an anti-inflammatory and anti-oxidant mediator, the quinone oxidoreductase-1 (NQO1), which is also involved in the pathway function of the Nrf2.[150–153] Furthermore, other molecule connected to the inflammatory response is the pyrogenic receptor P2X7 belonging to the P2X family which is engaged in the activation of diverse pathways such as the pathways involving MAPKS, NF-*k*B, and those that are involved in ROS generation. Interestingly, they can activate NLRP3. Another factor that can promote neutrophil recruitment is the laminin gamma 2 (LAMC2) for leukocyte -cell adhesion and endopeptidase regulation. Studies show that LAMC2 is expressed and connected to the early phase of ALI/ARDS.[154–156] Also, the protein kinase C (PRC) belonging to the phospholipid-dependent serine/threonine kinase which exists in various isoforms has been reported to be one pathway through which inflammatory mediators are overproduced and released into the lungs and even has their associated substrate src-inhibited C kinase substrate (SSeCKS) over expressed in ALI/ARDS.[157–159] It's important to note that, oxidative stress remains one pivotal factor in the initiation of the ALI/ARDS pathogeneses under AP. The over generation of ROS can be fostered by neutrophil activation resulting in oxidative damage. Noteworthily, this damage caused by oxidative stress is not limited to the pancreas or lungs but can deteriorate to other organs as well (Figure 2).[160–163]

Nanotechnological Role under the Loop Holes of the Conventional Interventions

Plasmapheresis administration requires the central venous access and with that they may have associated infection or the development of some allergic conditions at the end. Also, they can be costly and sometimes may even not be available for use. Normally, since much of this will have to do with the triglyceride level, there is a possibility of employing insulin, allowing the promotion of fatty acid metabolism in cells that are insulin sensitive. Insulin is capable of activating lipoprotein lipase (LPL), allowing for the degradation of chylomicron and further the suppression of the levels of triglycerides. Although not as compared to the plasmapheresis which can suppress the levels of triglycerides between 50–80%, the insulin suppression of triglycerides can be as much 50–75%. Also, studies shows that insulin can inhibit adipocyte lipase that are hormone sensitive, thus preventing the release of FFA.[164–167] Another drug is the heparin which is mostly used alone or used in combination with insulin. Like, the insulin, the heparin can elevate the level of lipoprotein lipase aiding to lower the level of triglycerides by yielding FFA. However, this can also deplete the lipoprotein lipase stores in the plasma subsequently leading to chylomicrons increase and reports show that patient administered with such drug can bleeding severely.[168–170] Other approach employed is the hemofiltration, a method used to remove urea nitrogen, amylase and suppressing the plasma cytokine and systemic inflammatory response. However, accumulating evidence indicates the prevalence of organ failure under this therapy.

Also among other therapies is the employment of fibrates, studies show it among a first-line medication used however the complications that comes with it include elevation in cholelithiasis, creatinine and myopathy. Next, other drugs used previously, however, tend to have low triglycerides reducing effect an example is the statins although when used in combination of any of the above drug may show some potency. The pemafibrate unlike just-fibrate may have some potency in cellular studies.[171,172] Aside from the pemafibrate, is the ANGPTL3 & ApoC-III inhibitors. The ApoC-III hinder TG–rich-lipoprotein and has high tendency of dealing with triglycerides and reducing the risk of AP development. Similarly, the ANGPTL inhibits the function of lipoprotein lipase and further triglyceride hydrolysis and can equally reduce the level of triglycerides to about 76%. In addition, the above-mentioned drug has some effect to some extent. However, when hypertriglyceridemia is found among patient with AP, serum triglycerides are also advised to be checked. AP patient with HTG may show severe complication and that when such diagnosis is made patient must be administered with adequate fluid resuscitation and other forms of support. Also, some initial drug that can be administered is insulin and should be monitored under every 12 hours till the triglyceride level get to below 500 mg/dL.[173–176]

Also, in an attempt to counter ALI/ARDS and its significant role in mortality, critical attention has been paid to the improvement of ventilation and other critical care, where pressure more than 35 cm H_2O is avoided with even the least oxygen (< 60% FiO) for positive pressure ventilation.[177–180] Additionally, under open lung ventilation, the provision of the optimum amount of positive expiratory-end pressure (PEEP) with minimal tidal volume ventilation (4–8 cc/Kg) ensured the recruitment and overdistension of the alveolar. Nevertheless, studies show that this process might not be adequate to facilitate improved lung injury or avoid a cyclic collapse, and some of the conditions example PEEP might not be the same for all patients making it quite difficult.[181–183] Further, some approaches such as the prone positioning have equally been employed, an approach still associated with ventilation and perfusion and involves the flipping of the patient to temporarily correct the mismatch of patient ventilation and perfusion. Despite the fact that the improvement of patient oxygenation has been established, there has been some sort of doubt, conversely, the process is known to have a significant impact on the mortality rates.[184–186] Next regarding the fluid management approach, the pulmonary edema intensifies under high hydrostatic pressure and low oncotic pressure, consequently promoting the oxygenation and abate of the severity of the injury. Other approach has been proper feeding to prevent under-feeding, over-feeding, or weakness. Substantially, this enteral nutrition and even omega-3-fatty acid containing feeds have the possibility of decreasing the mortality rate.[187–190] Also, pharmacological approaches such as the treatment with drugs (Ketoconazole, Lisofylline, Procysteine, Surfactant, etc). have been reported to be unsuccessful (Table 1), also the all the management process mentioned above do not guarantee the complete removal of the condition without reoccurrence.[191–195] When it comes to ALI/ARDS one key factor that can be targeted is the modulation of the release or activity of the neutrophil and macrophage in relation to the epithelial and endothelial cells. The reason is that they serves as the platform for the release of potent pro-inflammatory cytokines such as the IL-1β, IL-6, and TNF-α hence targeting their release or activity could help in the modulating of the disorder.[196–199]

In recent years, advances in nanotechnology have set the pace for the fabrication and development of several drugs for specific targets. Nanovesicles have been harnessed for eradicating lung infections that are bacteria related, which operate under the guides of antigens to help target and kill the infectious bacteria. Aside from that, diverse drug delivery system has been developed with nanoparticles including polymeric micelles (pm), nanogels, lipids, peptides, and other related enzymes for the effective delivery of drugs for the treatment of lung related disorders.[225–228] Most importantly, this rapid advance has inspired the fabrication and testing of varying biomaterials with great therapeutic efficacy. Some with anti-inflammatory, and antioxidant effects which include carbon nanomaterials, metallic oxides nanoparticles, and noble metal nanoparticles which have extensively been employed in the treatment of some diseases, such as neurodegenerative disease, acute kidney injury, bowel disease, stroke, diabetes, sepsis, and acute liver disease.[229–232] Interestingly, few have focused on the application of these nanomedicines in treating ALI/ARDS (Table 2). However, the concerns raised and the anatomical structure of the lungs will require the use of peculiar functional materials other than just any nanomaterials factoring the particle size, particle

Table 1 Conventional Treatment Approach to ALI/ARD

Treatments	Usage	Effect	Ref.
Glucocorticoids	No merit	Harmful	[192]
Inhaled nitric oxide (NO)	No merit	Ineffective	[200]
Ketoconazole	No merit	Ineffective	[201]
Liposomal PGE 1	No merit	Ineffective	[202]
Lisofylline	No merit	Ineffective	[191, 203]
N-acetylcysteine	No merit	Ineffective	[204]
Procysteine	No merit	Ineffective	[205]
Salbutamol IV	No merit	Ineffective	[206]
Others			
Beta carotene	No merit	Ineffective	[207]
Glutamine	No merit	Ineffective	[207]
Ibuprofen	No merit	Ineffective	[207]
Keratinocyte growth factor	No merit	Ineffective	[208]
Statins	No merit	Failed	[208]

Table 2 Nanomaterial as Therapeutic Platforms for ALI/ARDS

Materials	Treatment	Mechanism	Animal Model	Efficiency	Ref.
PAE-CD-MOF	Acute lung injury	Reducing inflammatory factors	Rat (LPS-induced)	Effective	[209]
BSANPS	Acute lung injury	Inhibition of inflammation	Mouse (LPS-induced)	Effective	[210]
D-SEL	Acute lung injury	Macrophage polarization/suppression of proinflammatory cytokine	Mice (LPS-induced)	Effective	[211]
CM@Nar-NPs	Acute lung injury	Decrease ROS level/ Suppression of inflammation	Mice (LPS-induced)	Effective	[212]
FMN@BSA NPs	Lung injury and fibrosis	Blocking NLRP3 inflammasome	Mice (BLM-induced)	Effective	[213]
MPSS-CSNPs	Acute lung injury	Suppression of pro-inflammatory cytokine	Rat (LPS-induced)	Effective	[214]
CS-PBA-Cro	Radiation-Induced lung injury	Inhibition of inflammation/regulating of oxidative stress	Mice (20 Gy X-rays (1.5 Gy min^{-1})	Effective	[215]
PSLipos-L-NAC	Acute lung injury	Ligand-directed macrophage-mediated therapeutic	Mouse (BLM-induced)	Effective	[216]
GdCl3	Acute lung injury/Acute pancreatitis	Regulating CYLD expression/ inhibiting NF- κβ activation	Rat (sodium taurocholate-induced)	Effective	[217]
Apocynin	Lung injury	Suppressing NLRP3 inflammasome activation and NF-κβ signaling		Effective	[218]
MSM	Lung injury/Acute pancreatitis	Inhibition of inflammation	Mice (caerulein-induced)	Effective	[219]
AK-137@FN	Acute lung injury/ acute gout arthritis	Anti-inflammatory activity	Mouse (LPS-induced)	Effective	[220]
nFMs@Amp	Pulmonary injury	Elimination of *S. pneumoniae*	*Streptococcus pneumoniae* infection	Effective	[221]
γ3-PLGA NPs	Acute lung infection	Antibacterial/reduce inflammation	*Pseudomonas aeruginos*a infection	Effective	[222]
Fe-Cur NPs	Acute lung injury	Suppression of inflammatory cytokine	Mice (LPS-induced)	Effective	[223]
ZPM@PDE	Acute lung injury	E-cadherin increase and decreasing of α-SMA levels	Mice (LPS-induced)	Effective	[224]

composition, stability in vivo, biocompatibility, and biodegradability. This review bridges that gab providing the stage for application of bioactive materials as alternative therapeutics in place of the setbacks of the conventional treatment.

Bioactive Nanoparticles

Truly a nanoparticle size is determined in the bioactive state and dictates the interaction with biological system at some point, and this has been attributed to the fact that the size directly influences surface area and interfacial features, further determining the capability in carrying and binding of a bioactive molecules to a surrounding target. As sizes of nanoparticles impact the pharmacokinetics so is the accumulation and circulation impacted by the shape of the nanoparticles. Also, the nanoparticle charge can have a great influence on the internalization being it hydrophilic or hydrophobic. This can be considered as key factors in the design and synthesis process. Further chemical modification made on the surfaces of such nanoparticles determines how bioactive they can be with respect to their accumulation, localization and internalization, making them suitable for peculiar therapeutics purpose. In effect, it can be said that these modifications [size, morphology, surface charge, functional groups, etc.] allows them to easily interacts with cells, tissue or protein eliciting biological reaction or response. Report shows that some nanoparticles (30–60 nm) demonstrate cellular uptake in varying mammals which is due to the fact that the sizes of these nanoparticles allow them to be easily encapsulated by cell membranes forming vesicles and allowing for internalization. Normally during the encapsulation process, an interaction between a plasma protein and the encapsulated nanoparticle or nanodevice may form a protein layer referred to as the protein corona; this development alters the physiochemical properties and the bioactivities and may determine the pathobiological and other outcomes.[233–236] Also, those with (10–100m) have high target accumulation with great chances of accumulation in the liver and finally getting expelled through urine.[237–240]

As mentioned earlier, some metallic oxides NPs, noble metal NPs, and carbon nanomaterials have been utilized for varying forms of diseases and disorders among them, molybdenum (MO) has gained much attention owing to its functionalities and has been deployed in bio-detection, biosensing, cancer therapy, etc.[241–244] Yan Jiayang used molybdenum nanodots, having good biocompatibility and antioxidant properties (Figure 3A–D), the nanodots were able to suppress the NLRP3-dependent pyroptotic

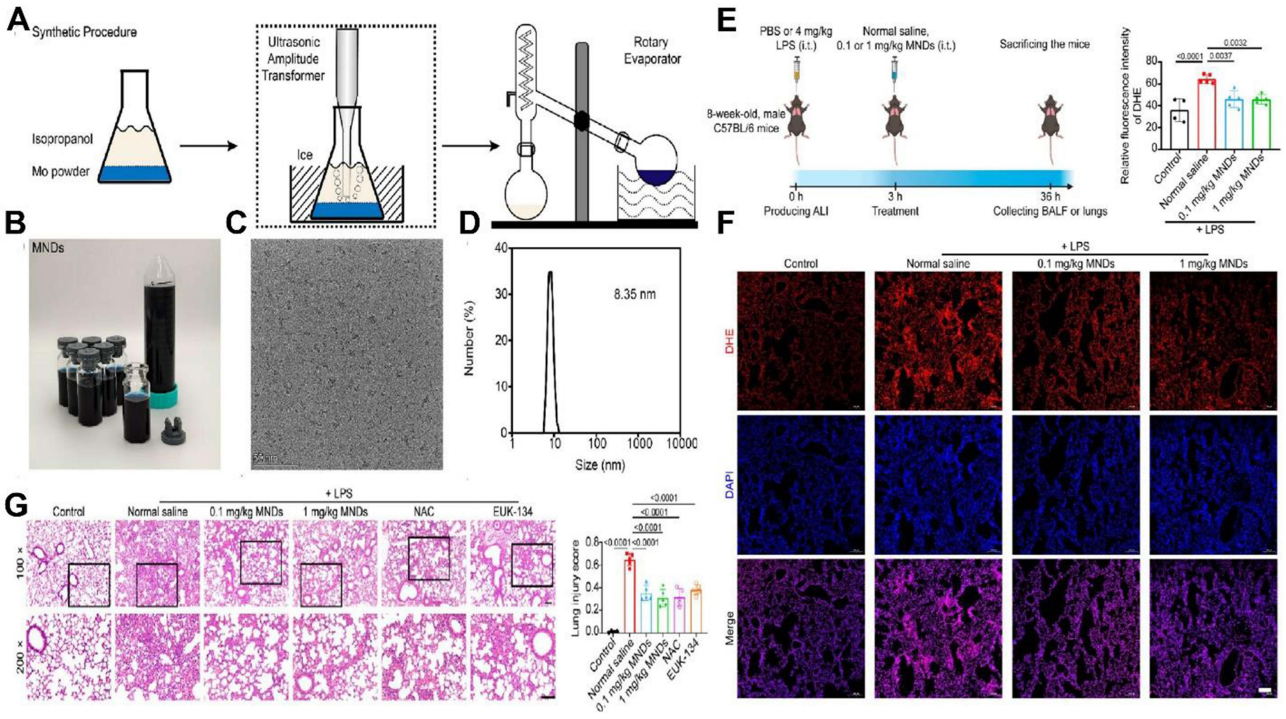

Figure 3 (**A**) The process of MND synthesis. (**B**) Image of MNDs in saline solution. (**C**) TEM image of MNDs. (**D**) Hydrodynamic size of MNDs (**E**) Diagrammatic illustration of the establishment and treatment schedule of LPS-induced ALI mice and the relative fluorescence intensity of DHE. (**F**) DHE (red) and DAPI (blue) staining sections of lungs of mice in control, normal saline, 0.1 mg/kg MNDs, and 1 mg/kg MND groups. (**G**) H&E staining sections of lungs of mice in control, normal saline, 0.1 mg/kg MNDs, 1 mg/kg MNDs. $p < 0.0001$, $p < 0.0032$, $p < 0.0037$. Reprinted with permission from Yan J, Tang Z, Li Y, et al. Molybdenum Nanodots for Acute Lung Injury Therapy. ACS Nano. 2023;17:23872–23888. Copyright 2023, American Chemical Society.[244]

pathways activation, a pathway that is linked to the pathogenesis of ALI. H_2O_2 induced apoptotic cells were significantly reduced with a remarkable decline in the ROS concentration in RAW 264.7 cells. Assessment of their antioxidant efficacy was in line with the in vitro studies. Also, the examination of the bronchoalveolar lavage fluid (BALF) and dihydroethidium (DHE) staining lung tissue 36h post disease, showed the inhibition of ROS generation (Figure 3E and F). Interestingly, the accumulation of pulmonary edema based on the wet/dry ratio of the lung demonstrated the suppression of pulmonary edema and proteinaceous exudates under the ALI. Similarly, the levels of MPO and proinflammatory cytokines were drastically reduced (Figure 3G).[244] Additionally, based on the transcriptomic profile, a number of genes were downregulated and upregulated which were in association with some pathways such as the NF-*k*B, TNF-α, IL-17, chemokine signaling pathway, a possible indication of the therapeutic activity of the MNDs in attenuating ALI/ARDS. Mo, like any other nanoparticle, can exist as a trace element essential for plants and animals and is equally involved in a number of oxidative and reductive functions, having an extensive application in biomedicine, agriculture, chemical engineering, etc., even employed as lubricant additives, electrical application, suppression of smoke, metallurgical additives and many more.[245–249]

Furthermore, other nanoparticles like cerium oxide nanoparticles (CNP) have been employed in treating ALI and coronavirus associated ARDS. CNP can act as nanocarriers bearing radical features based on its multivalent (+3, +4) oxidation state.[250–254] Niemiec et al reported on the use of CNP with microRNA-146a (CNP-miR146a) in the forestallment of ALI/ARDS. Also, because ALI is associated with inflammatory and oxidative stress response, the CNP-miR146a was projected to impede oxidative stress, inflammatory infiltration, and suppression of pro-inflammatory cytokine. Most importantly, the CNP shielded the miRNA from oxidative stress related damage and at the same time redressed the negative charge for cellular uptake. It is noteworthy that the miRNAs in their normal state may be unstable in reaching their targets due to their negative charge and the possibility of ubiquitous tissue nucleases triggered degradation.[255–259] The application of CNP-miR146a in bleomycin-injured mice, a model for ALI/ARDS indicated elevated CD45+ cells reduced significantly upon treatment with CNP-mi146a (Figure 4A–F). The

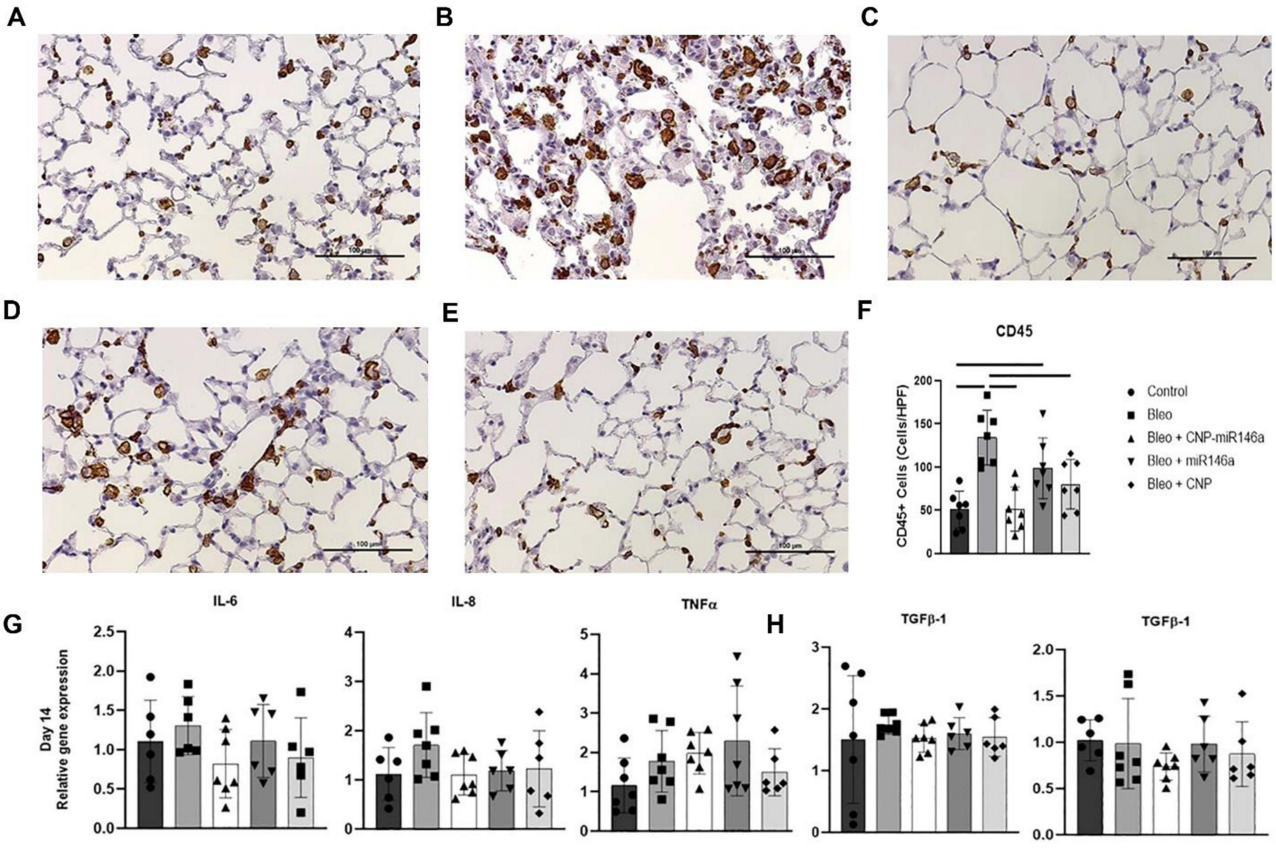

Figure 4 (**A**–**E**) Reduction of inflammatory cell infiltrate with CNP-miR146a, CD45+ stained following bleomycin instillation (**F**) CD45+ cells present in lung samples were significantly higher in bleomycin-injured lungs, and Treatment with CNP-miR146a and CNP alone significantly reduced inflammatory cell infiltrate number (**G** and **H**) Relative gene expression of pro-inflammatory markers 14-days after bleomycin injury. Bleomycin injury significantly raised IL-6, IL-8, TNFα, and TGFβ-1 gene expression compared to controls. Reprinted from Nanomedicine: Nanotechnology, Biology and Medicine, Niemiec SM, Hilton SA, Wallbank A, et al. Cerium oxide nanoparticle delivery of microRNA-146a for local treatment of acute lung injury. 2021;34:102388. Copyright 2021, with permission from Elsevier.[260]

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effect of CNP-miR146a demonstrated by real-time quantitative polymerase-chain reaction (RT-qPCR) showed the lowering of IL-6 gene and other genes which had previously significantly been expressed (Figure 4G). Additionally, the TGFβ-1 elevation following the ALI/ARDS model was remarkably suppressed by CNP-miR146a (Figure 4H).[260] Also, the miR146a as an anti-inflammatory miRNA is capable of inhibiting tumor necrosis factor 6 (TRAF6) and the NF-*k*B which modulates the release of IL-6, IL-8, and TNFα cytokine which are actively engaged in the pathogeneses of ALI, hence the synergistic role demonstrated with CNP.[260–264]

ROS Responsive Nanoparticles/Nanozymes

The challenge of obtaining an effective therapy seems to be lacking, resulting in poor prognosis whereas the role of inflammation cannot be ignored, under the pathogenesis of the ALI. Diverse forms of inflammatory cytosine are released following the activation of macrophages and neutrophils. Studies shows that the induction of inflammation can complex pathophysiological process to grapple with a single treatment. Also, these activities have significantly been ascribed to the overgeneration of ROS and myeloperoxidase (MPO) further exacerbating the condition.[265–269] Generally, some anti-inflammatory and antioxidant drugs such as curcumin or vitamin have stupendously been used for scavenging and in pulmonary disease. Although the setbacks that have been associated with the single use of the drugs have been, the lessened target specificity over time and their inability to ward off large and prolonged antioxidant release. Accordingly, this outlines the need and importance of nanoparticles existing as nanozymes equipped with the capabilities of ROS-scavenging.[270–272] There are varying free radicals which include the ROS (O^{2-}, •OH, H_2O_2) reactive nitrogen species (RNS) (NO), usually they are released and scavenged within the human body, thus creating a balance to prevent any stress or damage. However, during inflammation, inflammatory cytokine and mediators happen to impede the function of the free radical scavengers, leading to oxidative stress response, where there is an imbalance in the free radical release-scavenging function inducing oxidative damage to lipids, proteins, DNA and further aggravating the inflammatory condition.[273–277] Nanomaterials with enzymatic properties which are simply referred to as nanozymes bear a number of advantages such as ease of synthesis, stability, and the cost of storage unlike natural enzymes.[278–281] Also, some do exhibit features of antioxidant systems such as catalase (CAT) peroxidase (POD), oxide dismutase (SOD), and glutathione peroxidase (GPx) with the ability to scavenge for ROS and RNS. The emergence of nanozymes has stepped down numerous inflammation-related diseases. And among the nanomaterials, the metals nanomaterials, transitional metal dichalcogenides (TMDCs), and other hybrid or composite materials may exist as nanozymes in this area for antibacterial, anticancer, and antitumor activity.[282–286]

Yu Yang et al employed $FeCl_3$ and Curcumin to give FeCur NP nanozymes (Figure 5A) equipped with ROS scavenging and anti-inflammatory properties. Fe^{3+} was essential for the anti-oxidant nanozymes function and the curcumin for anti-inflammatory properties. Demonstrating the stability of the drug in water, PBS, and cell culture medium, FeCur NPs significantly suppress the level of ROS (Figure 5B). Regarding the suppression of inflammation, the nanozyme functioned to decrease inflammasomes and intracellular Ca^{2+}. Also, analysis of the level of cytosine a small form of proteins directed towards the promotion of inflammation demonstrated a decreasing level and normalization of cytokine (Figure 5C), while therapeutically targeting the lung tissue (Figure 5D).[287] Irrespective of the selectivity and structural difference existing between compounds, combining the nanoparticle with the anti-inflammatory compound demonstrates some form of therapeutic potency unlike when singly employed as mentioned earlier.[287–289] Similarly, Yue Wu examined the antioxidant and anti-inflammatory effect of conjugating 4–phenylboronic acid pinacol ester (PBAP) unto chitosan hydroxyl group for Ceria (Ce) NPs and resatorvid (RT) delivery (Figure 6A–C). Following the internalization into cells in a time-dependent mode, the intensity of intracellular ROS intensified (Figure 6D) after the stimulation with H_2O_2. However, the Ox-CS/Ce NPs and Ox-CS/CeRT NPs significantly decreased which indicated the suppression of the intracellular ROS. In addition, the Ox-CS/CeRT NPs downregulated the mRNA expression of IL-6, IL-1β, and TNF-α, which was attributed to the synergistic activity of the NPs (Figure 6E). Additionally, the possibility of apoptosis induction was shown to be impeded by the Ox-CS/CeRT NPs (Figure 6F) and further demonstrated the ability to allow the accumulation of DiR (fluorescent) in the lungs of the treated mice (Figure 6G).[272] Some NPs such as the Ce NPs have the capability of exerting an anti-oxidant effect via the reversible oxidative state of Ce^{3+} and Ce^{4+} and are potent for diverse ROS-related disorders ranging from Alzheimer's disease, sepsis, ischemic stroke, etc.[290–292] Critically,

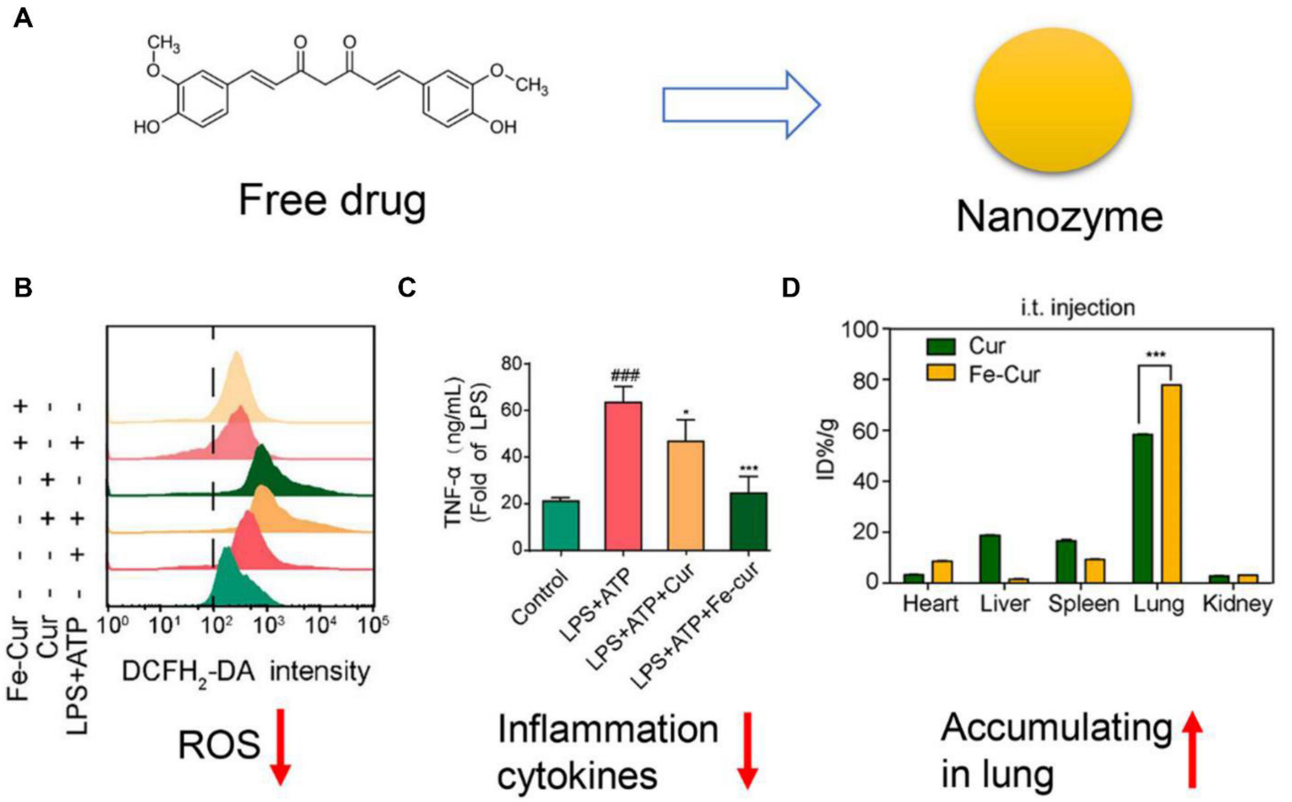

Figure 5 (**A**) Schematic representation of the Nanozyme (**B**) Fe-Cur NPs demonstrates enhanced functionalities compared to free drug curcumin in decreasing the intracellular ROS levels, (**C**) Suppressing the inflammation cytokines (TNF-α), and (**D**) Assembling in the lung tissue. ###$p < 0.001$ vs control group. *$p < 0.05$ and ***$p < 0.001$. Reprinted from Duan X, Liu B. A Nanozymatic Solution to Acute Lung Injury. ACS Cent Sci. 2022;8:7–9. https://creativecommons.org/licenses/by-nc-nd/4..[287]

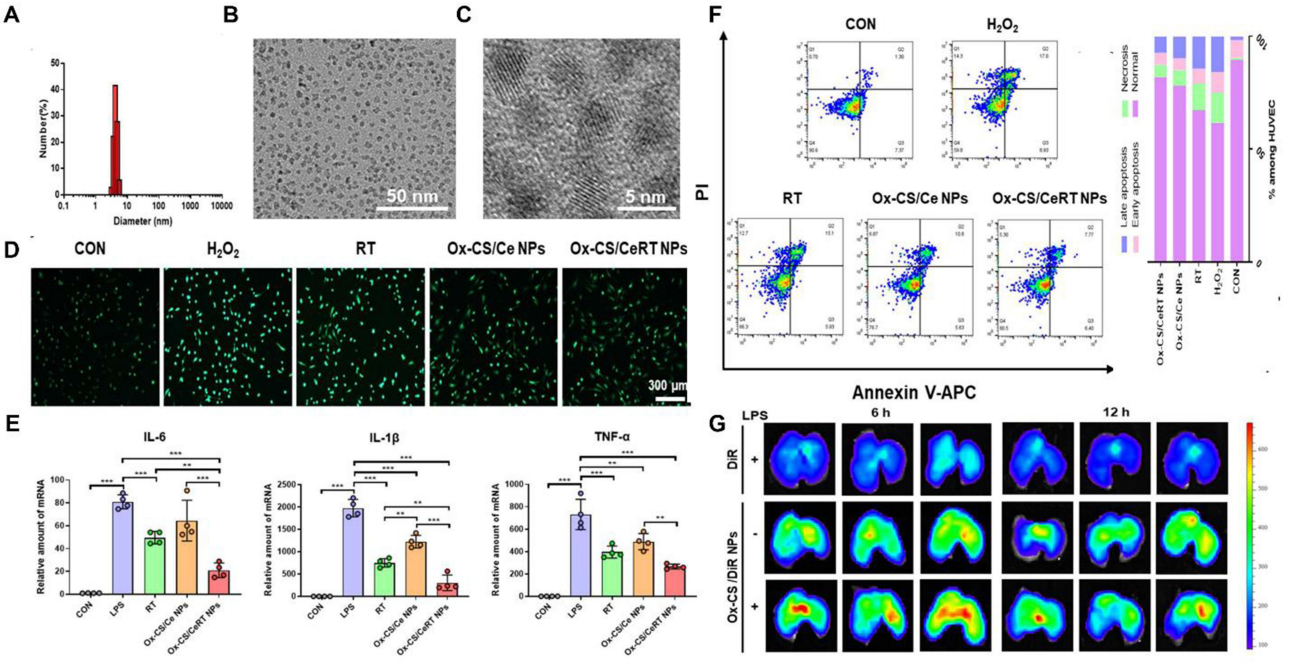

Figure 6 (**A**) Size distribution of Ce NPs. (**B** and **C**) TEM images of Ce NPs, 50 nm and 5 nm respectively. (**D**) Intracellular ROS of H_2O_2- stimulated HUVECs after different interventions for 12 h (**E**) The mRNA levels of pro-inflammatory cytokines in HUVECs after LPS treatment. (**F**) Flow cytometry profiles and quantitative analysis of fluorescence intensity in HUVECs. (**G**) Lung fluorescence intensity in free DiR or Ox-CS/DiR NPs treated ALI mice and Ox-CS/DiR NPs. **$p< 0.01$, ***$p < 0.001$. Reprinted from Wu Y, Zhang Y, Tang X, et al. Synergistic anti-oxidant and anti-inflammatory effects of ceria/resatorvid co-decorated nanoparticles for acute lung injury therapy. J Nanobiotechnology. 2023;21:502.http://creativecommons.org/licenses/by/4.0/.[272]

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the role of ROS in the pathogenesis of the ALI/ARDS happens to be one means for the further activation of inflammatory signals and intensification of the immune response. Usually, the action of the neutrophil as an immune response ends up being detrimental following the release of toxic mediators for the combat of pathogens. Contrarily the continuous release in response to the presence of pathogen and overproduction results in the accumulation of the ROS.[293–296]

Additionally, the use of nanocarriers has a significant prospect when it comes to targeting and therapeutics. This demonstrates the possibility of nanoparticles entering the endothelium to target the lung tissues.[297–300] Particularly, the use of drug delivery systems which are stimuli responses has gained attention in recent years. Some of these drugs are capable of even delivering therapeutic agents in inflamed lung tissue, a typical example is those with folic acid modification and equipped with the ability to target macrophage and deliver antibiotics within the microenvironment of inflammation.[301–305] Also, formulated polymers can be made to carry payloads and release them based on interaction, for example, hydrophobic-to-hydrophilic phase facilitated by the ROS.[306–308] Zihe Zhai et al fabricated a ROS responsive and inflammatory regulatory nanoplatform by encapsulating dexamethasone acetate (Dex) in a poly(1,4 phenyleneacetonedimethylene thioketal (PPADT) and polythioketal urethane (PTKU) NP, where the Dex was expected to be released following inflammation (Figure 7A). The overexpression of ROS by LPS was significantly reduced as a result of the ROS scavenging ability of PTKNPS and the intrinsic inflammatory function of Dex, thus a demonstration of the combined effect (Figure 7B and C). Further, Elisa revealed the significant suppression of cytokine levels via a synergistic activity (Figure 7D–F). Also, PTKNPS@Dex administration prolonged the rate of survival of mice and reduced edema fluid content (Figure 7G–I).[309]

Reports indicate that the nature of the bond in the polymer main chains could impact the ROS responsiveness. Accordingly, NPs, in this state, can eradicate the ROS reducing the oxidative damage and allowing the safe release of drugs to target inflammation in response to the high amount of ROS. Also, such NPs can effectively modulate pathways that are immune and inflammation linked and can even be modified or functionalized via conjugation and grafting of moieties and sheath molecules to step up their efficacy.[310–312] Furthermore, other polymers such as the PDA with biocompatibility and biodegradability have been harnessed for drug delivery, cancer therapeutics, molecular imaging, etc. Next, the presence of phenol groups on their surface is capable of turning them into free radical scavenging agents.[313–316] Hence, He Zhao et al used

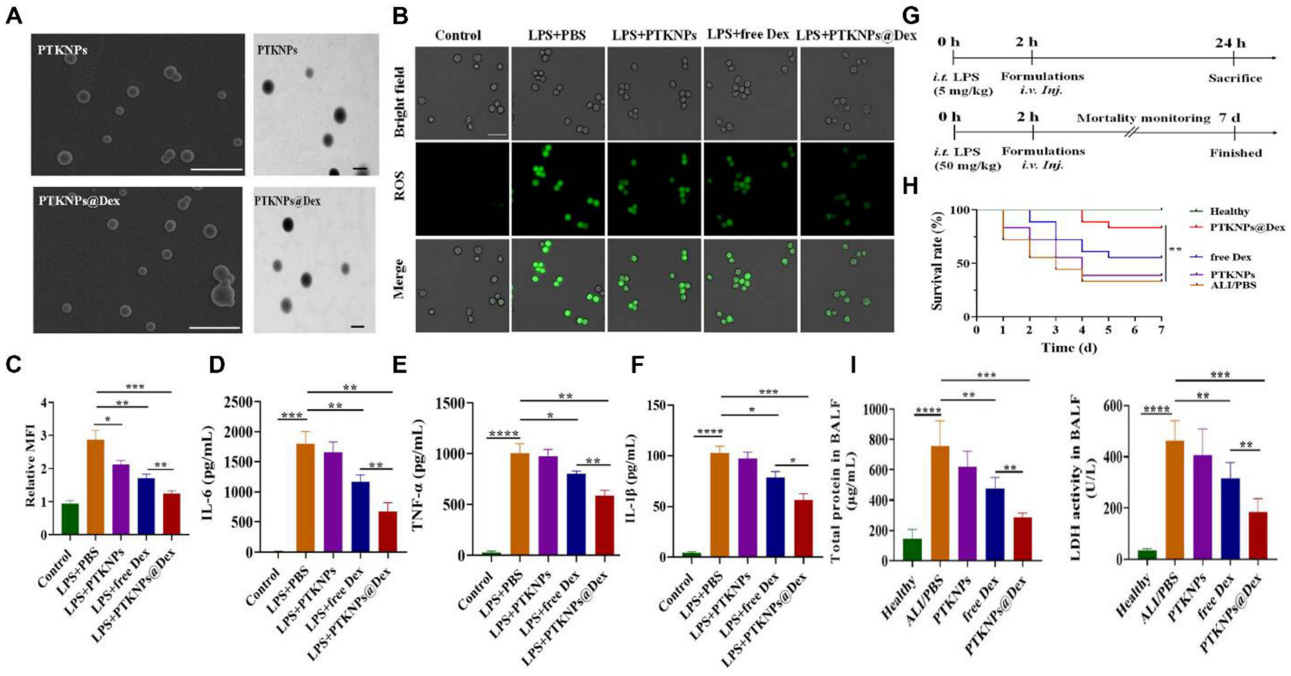

Figure 7 (**A**) SEM and TEM images of PTKNPs and PTKNPs@Dex (**B**) Representative images and (**C**) relative mean fluorescence intensity of intracellular ROS generation in RAW264.7 cells. (**D**) IL-6, (**E**) TNF-α, and (**F**) IL-1β secreted by RAW264.7 cells after activation by LPS and treatment. (**G**) Experimental schedule of the ALI study in vivo. C57BL/6 mice were intratracheally injected with LPS to establish the ALI model. (**H**) Mice survival rate. n = 12–18 mice/group (**I**) total protein and LDH in the BALF. *p < 0.05, **p < 0.01, ***p < 0.001, and ****p < 0.0001. Reprinted from Zhai Z, Ouyang W, Yao Y, et al. Dexamethasone-loaded ROS-responsive poly(thioketal) nanoparticles suppress inflammation and oxidative stress of acute lung injury. Bioact Mater. 2022;14:430–442.https://creativecommons.org/licenses/by-nc-nd/4.0/.[309]

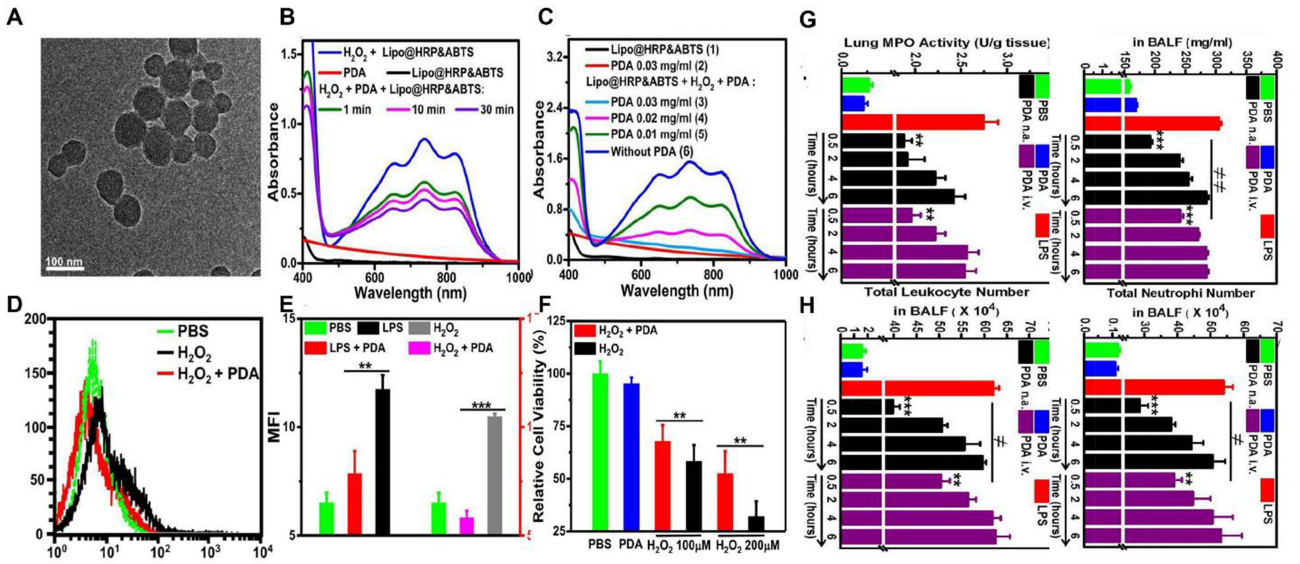

Figure 8 (**A**) TEM image of PDA nanoparticles (**B**) UV-Vis-NIR absorbance spectra changes of the reaction solutions measured at different time point after incubation. (**C**) The absorbance was originated from the Lipo@HRP&ABTS probe in the presence of H_2O_2 (**D**) Raw 264.7 cells as detected by the flow cytometer using DCFH-DA. (**E**) Mean fluorescence intensity (MFI) calculated based on the flow cytometry. (**F**) The relative viabilities of Raw 264.7 cells incubated with H_2O_2 with or without PDA. The therapeutic responses following administration of PDA at different intervention time points including the lung MPO activity (**G**), the total protein concentration, the total leukocyte number (**H**), and the total neutrophil number. Used with permission of Royal Society of Chemistry, from Polydopaminenanoparticles for thetreatment of acuteinflammation-inducedinjury, Zhao H, Zeng Z, Liu L, et al, 10, 15, 2018 copyright; permission conveyed through Copyright Clearance Center, Inc.[317]

PDA with ROS scavenging activity demonstrated against H_2O_2 a common form of ROS (Figure 8A). Their evaluation showed decreased H_2O_2 concentration within the solution following the conversion of colorless ABSTS into greenish after oxidation (Figure 8B and C). The PDA was able to decompose H_2O_2, increasing the rate of oxygen production and emphasizing the possible role of PDA as an H_2O_2 scavenger, and as a catalyst endowed with the ability to trigger the decomposition of H_2O_2. Next, the PDA was able to annul the cytotoxic effect of H_2O_2 in cells (Figure 8D–F) and downregulated the LPS induced pro-inflammatory cytokine TNF-α which was evident in the in vivo study following the significant downregulation of myeloperoxidase (MPO) activity, leukocytes, neutrophil and protein concentration a demonstration of the therapeutic effect for ALI/ARDS (Figure 8G and H).[317] H_2O_2 is a common chemical compound which pH dependent and can be used as a reducing or oxidizing agent. In the presence of impurities or catalysts, they decompose although they can be affected by temperature, pressure, exposure to direct sunlight, solution concentration, etc.[318–320]

pH Responsive Nanoparticles

Another form of nanoparticle capable of being employed for drug delivery is the pH-sensitive or responsive nanoparticle. Interestingly, this nanoparticle can exist as liposome, lipoplexes, polyplexes, and polymeric micelles operating physical and chemical cues. In general, nanoparticles can be modified or fabricated to be responsive to changes for onsite drug delivery or release.[321–325] This stimulus can be either physical (ultrasound, temperature, magnetic field) or chemical (enzymatic related activities, pH, redox potential, and ionic strength). In recent years nanoparticles that respond to pH gradients can operate at the cellular, tissue, or organ level designed to exist in varying forms of micro-environment with some having the means to elude acidic endosomal compartments.[326–330] Zhang Yang Can et al designed an anti-iCAM-1 coated NP for targeting the lung endothelia while delivering anti-inflammatory agents under low pH in the inflammatory microenvironment. The NPs (TPCA-1) targeted the inflamed endothelial by increasing in response to activated TNF-α upon incubation with HUVEC, a demonstration of the endothelial targeting ability (Figure 9A–C). Similarly, the mean fluorescent intensity increased drastically (Figure 9C). Also, the nanoparticle was able to target the endothelial nanotherapeutically under pH which increased drastically at a pH of 6.5, 15h from 20% to 90% indicating the release was pH triggered and also sensitive in acidic microenvironments or tissues (Figure 9D). Surprisingly, the NPs and drug were able to accumulate in the lung demonstrating the successful delivery by the NPs (Figure 9E and F).[312]

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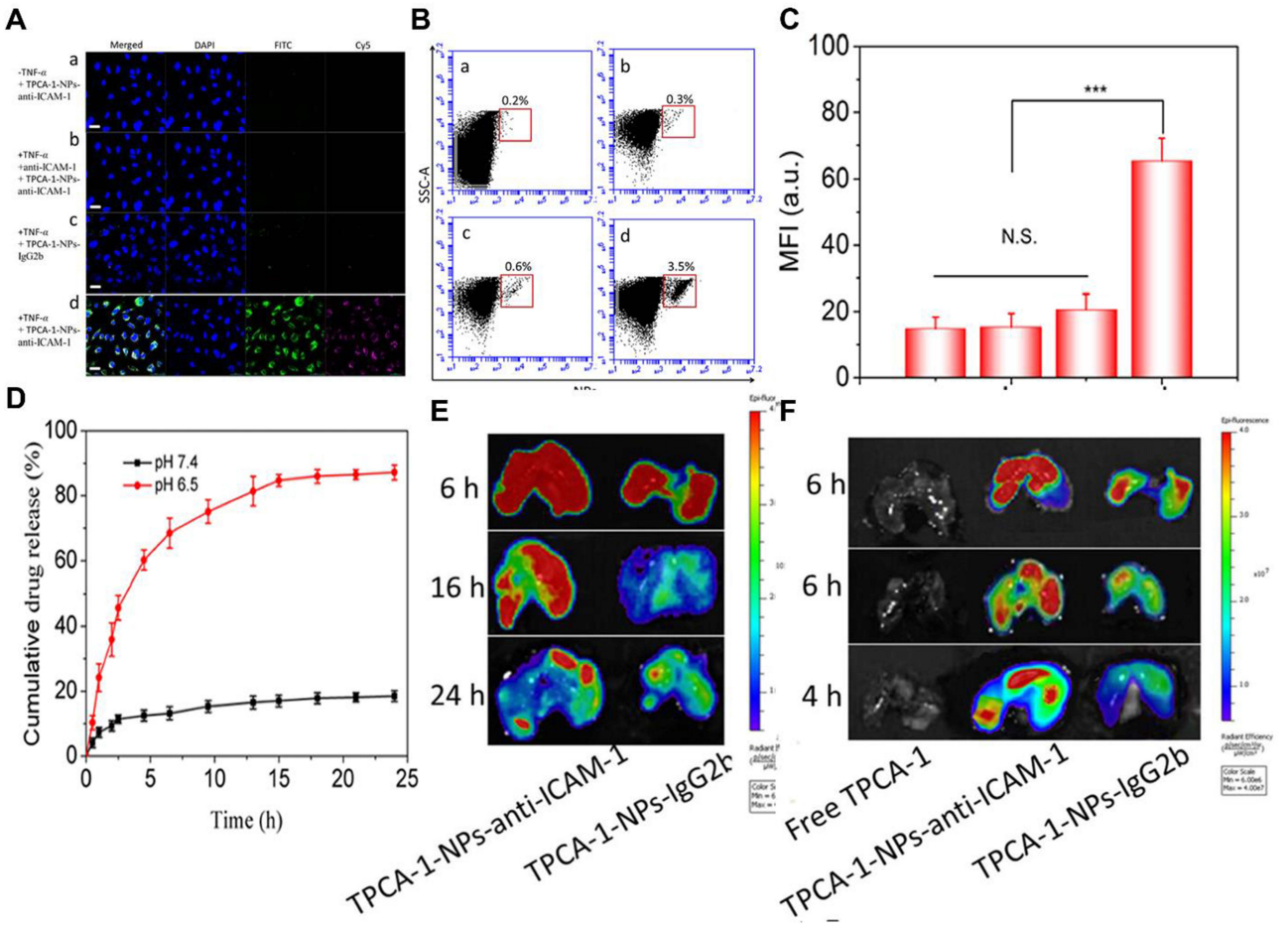

Figure 9 (**A**) Confocal laser scanning microscopy (CLSM) images showing interactions between HUVECs and NPs. (**B**) HUVECs were treated with endothelial targeted nanotherapeutics, TNF-α-activated HUVECs were treated with anti-ICAM-1, and incubation with endothelial targeted nanotherapeutics, TNF-α-activated HUVECs treated with nonendothelial targeted nanotherapeutics and with endothelial targeted nanotherapeutics. (**C**) HUVECs with different treatments analysis and flow cytometry following incubation with NPs. (**D**) In vitro release of TPCA-1 from endothelial targeted nanotherapeutics in PBS at different pH. (**E**) The fluorescence of FITC-labeled NPs and (**F**) Cy5-labeled TPCA-1 measured using IVIS. Reprinted with permission from Zhang CY, Lin W, Gao J, et al, pH-Responsive Nanoparticles Targeted to Lungs for Improved Therapy of Acute Lung Inflammation/Injury. ACS Appl Mater Interfaces. 2019;11:16380–16390. Copyright 2019, American Chemical Society.[312]

Due to the fact that the various sections of the systems within the body function and have their characteristic pH, the NPs carrying the drug must be modified in such a manner before a safe delivery can occur. Thus, this may come with challenges upon reaching their targets, and the concerns over the years have been the possible toxicity, degradability, and systematic exposure. In spite of this, the challenge has been overcome with the use of biodegradable polymers with negligible toxicity based on their concentration or constituent to ensure the delivery of drugs and bioavailability.[331–335] It's worth noting that organ-specific drug delivery has been made less complicated by employing NPs (polymers) that swell based on a pH and collapse in response to unfavorable pH. Furthermore, others are fabricated to function based on a surface charge change to respond to the favorable pH. Normally if the NP is positively charged, it can be loaded with anionic drugs, such NP develops a partial negative charge based on deprotonation building and electrostatic repulsion which allows the delivery or release of drug.[336–340] In addition, selective targeting ligands can also be resorted to, this includes vitamins, small peptides, and lectins.[341–345] Su Meiling et al fabricated a pH-responsive DXM-PEI-mannose (DPM) prodrug (Figure 10A) for targeting the lung tissues, achieving sustained delivery of the drug at the inflammatory site. The use of PBS as the release solvent demonstrated stability at pH 7.4 (37 °C) with no change in particle size (Figure 10B). However, at a pH of 5.0, the particle size increased indicating sensitivity to a weak acid environment (Figure 10C). In addition, the drug at different concentrations exhibited minimal effect and showed about 80% viability even after exposure to 100 μg/mL of the drug for 24 hrs. (Figure 10D). Further, the drug uptake was significantly high

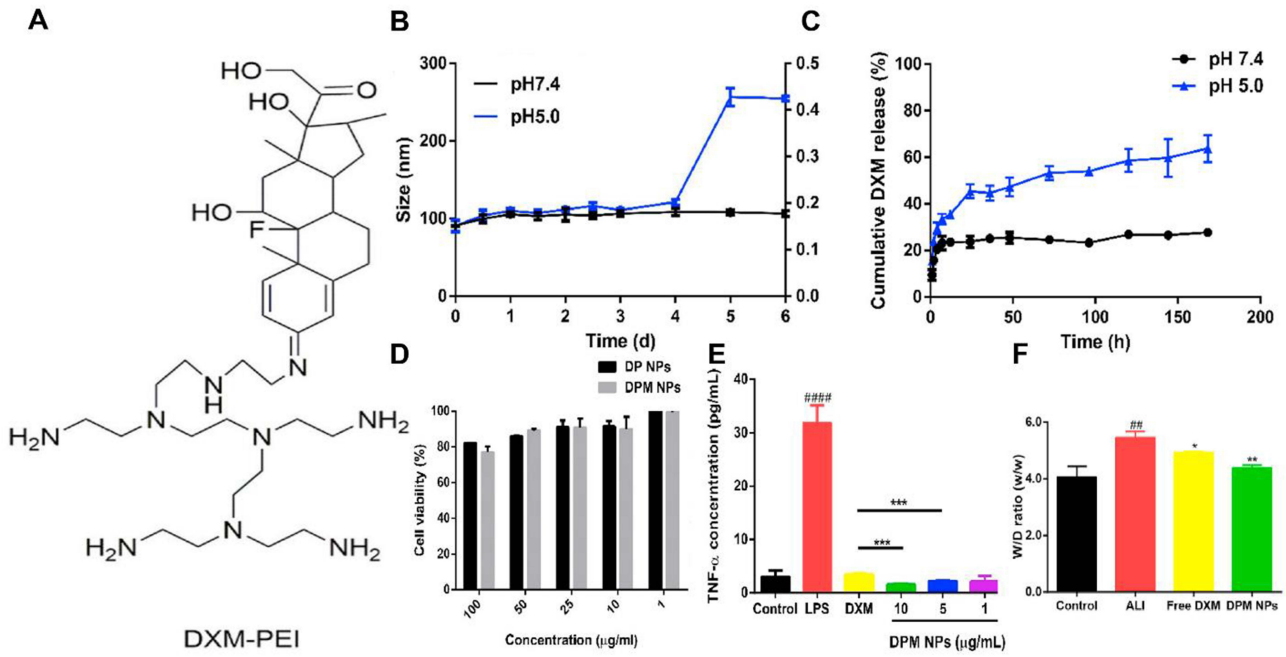

Figure 10 (**A**) Structural representation of DXM-PEI (**B**) Particle size under different pH conditions, DPM was changed, and (**C**) the in vitro release (**D**) Cytotoxicity of DP NPs and DPM NPs on the RAW264.7 cells. (**E**) The anti-inflammatory study of DPM NPs in vitro. (**F**) Results of lung wet/dry weight ratio (W/D). ##p<0.01 vs control, #### p < 0.0001, *p<0.05, **p<0.01, ***p<0.001. Reprinted from Journal of Drug Delivery Science and Technology, 66, Meiling Su, Bowen Yang, Mingrong Xi, ChengQiang, Zongning Yin, Therapeutic effect of pH-Responsivedexamethasone prodrug nanoparticles on acutelung injury, 102738, Copyright 2021, with permission from Elsevier.[346]

and remarkably subdued the release of macrophage-related inflammatory factors (Figure 10E). This was phenomenal in the in vivo study where the wet/dry weight ratio of the lung tissue significantly diminished (Figure 10F).[346] Dexamethasone in general can trigger the expression of mannose receptor (MR) which is remarkably expressed in a macrophage following ALI/ARDS. Dexamethasone can also modulate MR activity when expressed at the mRNA level. The MR in turn plays a crucial role in the pulmonary inflammatory cascade.[296,346–349]

Biomimetic Nanoparticles

Biomimetic nanoparticles are nanoparticles that exhibit a synergistic role from the incorporated biological functionality and normal function of the attached synthetic material for efficient delivery and high accumulation at the target site, employing the biomimetic approach has recently gained attention with those of white blood cells, platelets or red blood cells membrane due to the low immunogenicity associated to it usage.[350–353] These biomimetic materials can either be classified as cell membrane coated, natural protein-based, or targeting ligands. Some limitations they faced with, involving recognition and removal, are, for example, overcomed by the use of PEG attached to nanoparticles to prevent phagocyte recognition after opsonization. Aside, other nanoparticles have their surface decorated with CD47 to facilitate the idea of the use of cell membrane. Where the cell membrane is used to coat the nanoparticle, with the notion that cell membranes have all the required proteins embedded in them enough to withstand the immune invasion,[354–358] a typical example is the exosome membrane coated cancer cell membrane coated, platelet membrane nanoparticles, RBC membrane coated, immune cells membrane coated, etc.[359–364] The nanoparticles with targeting ligands have the surface of the nanoparticles decorated with moieties for active targeting and accumulation, a typical example is targeting ligands as aptamers, folic acids, monoclonal antibodies (mABs), and peptides with tumor penetrating ability. Under this, the penetrating peptide has seen an extensive rise over a period of time now as a therapeutic platform. One factor associated with conventional drugs is their inability to target disease locations rather than normal cells.

Further, other polymers such as PEG-PLGA have been employed, and synthetic polymers under nanotechnology possess functions similar to biological membranes when combined with natural cell membranes, with extensive application even in the field of cancer and tumor therapeutics. PLGA, for example, due to their minimal systematic degradability and high degradability allows the gradual release of drugs.[365–368] PLGA has the potency to reach the

central nervous system via movement across blood-brain barrier.[369–372] Yunlong Chen et al reported on the use of PEG-PLGA in combination with Ulinastatin (U), together in an encapsulated macrophage membrane to form a biomimetic platform (Figure 11A), as the macrophages lean towards chemotactic factors while the adhesion molecules mediated binding and promoted the release of drug.[373–378] The release kinetics was monitored in PBS pH (7.4), 77.75% of U was released by macrophage biomimetic nanoparticle (MU) which peaked at 30 h, demonstrating the stable and efficient release of U (Figure 11B). Also, the protein expression of IL-6, and TNF-α were significantly downregulated. Further Western blotting results showed the inhibition of p-I*k*Bα/I*k*Bα and p-p65/p65 contents associated with the activation of NF-*k*B and prevention of I*k*Bα degradation (Figure 11C–G). Unsurprisingly, the inflammation targeting ability of the MU showed the accumulation of MU within the pancreas as a result of the high targeting of the established pancreatic edema and inflammatory cell infiltration (Figure 11H and I). Interestingly, all indicators for AP (serum amylase, lipase, IL-6, TNF-α) were suppressed to levels comparable to those of the healthy group (Figure 11J–L).[379] The unique inflammatory chemotactic effect of white blood cell biomimetic nanocarriers crucially makes them perfect for inflammatory disease. However, those of macrophage origin have been reported to possess maximum target delivery efficacy and for that reason, they have been employed in targeting atherosclerosis, cancer, rheumatoid, arthritis, and sepsis.[379–383]

Also, Wei Gao developed a peptide gold nanoparticle consisting of a GNP encapsulated in hexapeptide, giving a stabilized physiological condition and effective modulation of cellular uptake and anti-inflammatory activity (Figure 12A).[384–388] The surface modification aside from the enhancement of cellular uptake promoted endosomal pH modulatory activity as a result of the peptide sequence hydrophobic phenylalanine (FF) and negative charge aspartic acid residue at the end. This was accomplished through the increasing of peptide coat density on the GNP at the end promoting anti-inflammatory activity.[384–388] The estimation of the release of some key cytokine (CCL2 & CCL4) in

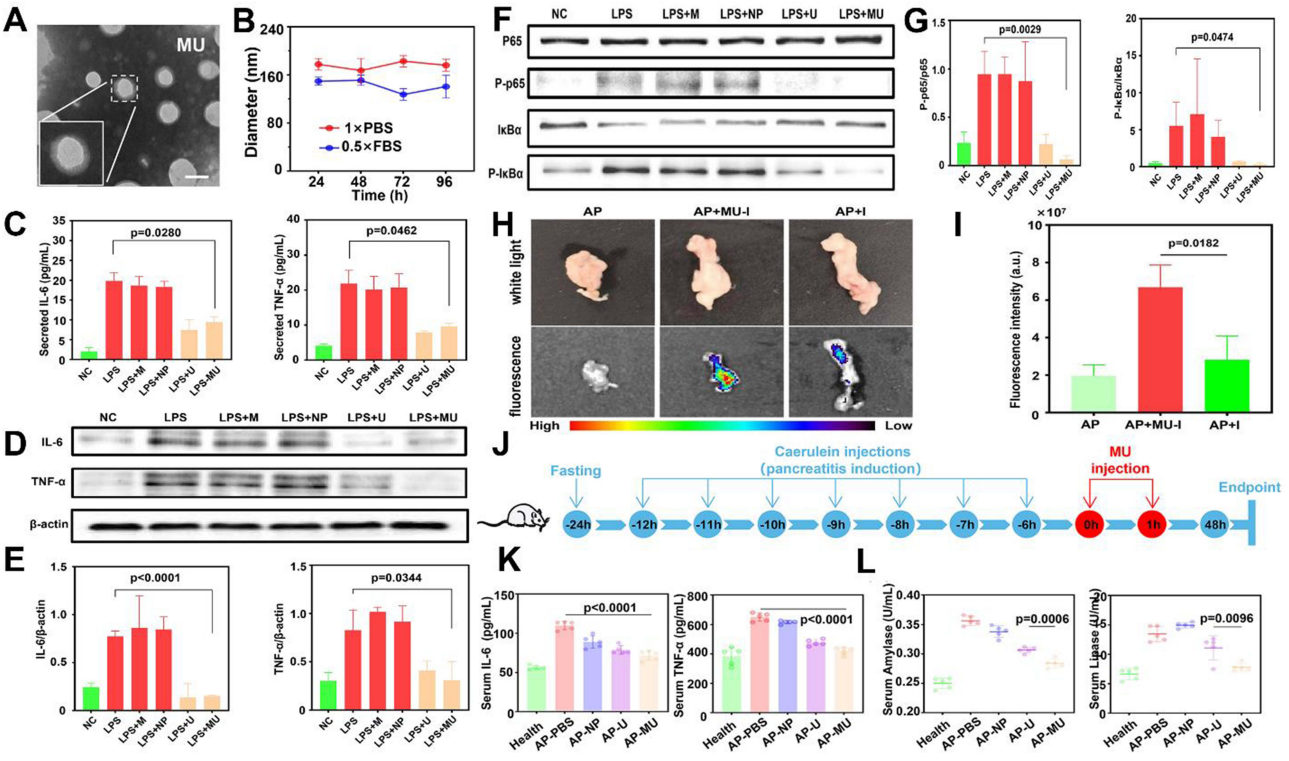

Figure 11 (**A**) TEM image of MU. (**B**) Stability of MU in PBS or FBS, assessed by monitoring nanoparticle size (**C**) ELISA test of MU effects on IL-6 and TNF-α secretion from LPS-induced RAW264.7 cells. (**D** and **E**) Western blot results and quantitative analysis of IL-6 and TNF-α in LPS-induced RAW264.7 cells (**F** and **G**) Western blot results and quantitative analysis of phosphorylated p65 and phosphorylated I*k*Bα in LPS-induced RAW264.7 cells. (**H**) Bright-light image of pancreas and in vivo fluorescence of the different nanoparticles (**I**) Fluorescence semiquantitative statistical map of the pancreas. (**J**) Study protocol of pancreatitis induction and treatment. (**K**) Concentration profiles of typical pro-inflammatory cytokines, IL-6 and TNF-α, in the serum of AP mice. (**L**) Concentration profiles of biochemical markers, amylase and lipase, in the serum of AP mice. $p<0.0001$, $p=0.0006$, $p=0.0029$, $p=0.0096$, $p=0.0182$, $p=0.0280$, $p=0.0344$, $p=0.0462$, $p=0.0474$. Reprinted with permission from Chen Y, Tao H, Chen R, et al. Biomimetic Nanoparticles Loaded with Ulinastatin for the Targeted Treatment of Acute Pancreatitis. Mol Pharm. 2023;20:4108–4119. Copyright 2023, American Chemical Society.[379]

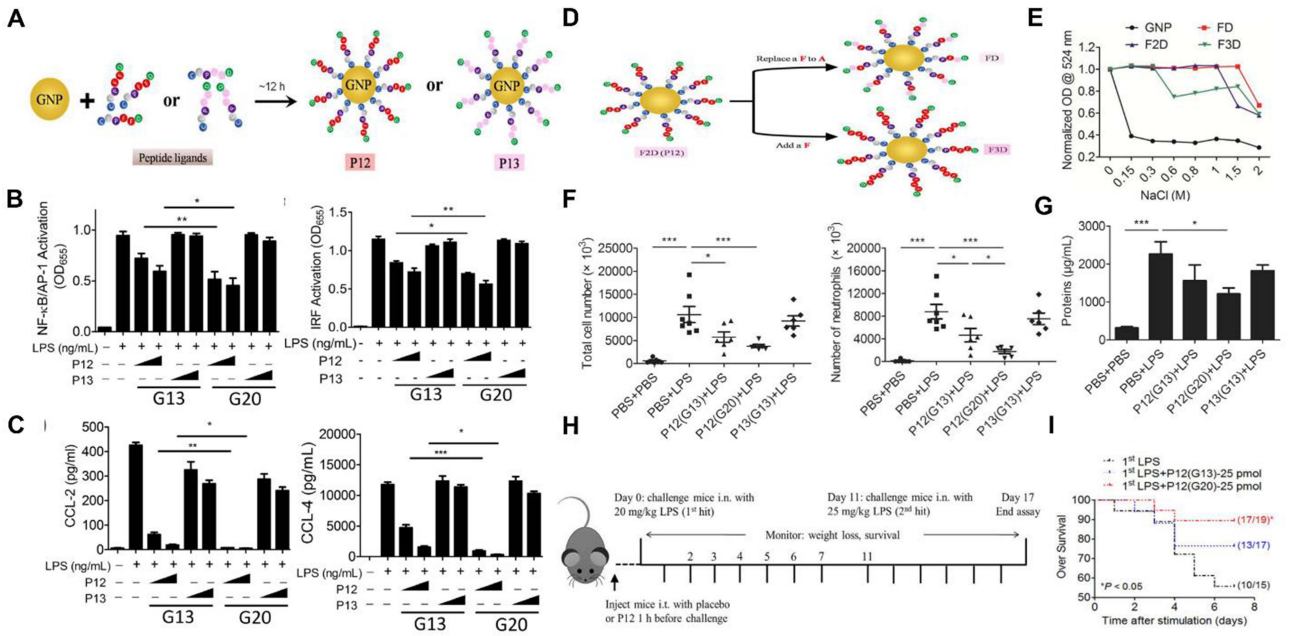

Figure 12 (**A**) schematic diagram of the fabrication of peptide-GNP hybrid (P12 and P13). (**B**) Inhibition of NF-*k*B/AP-1 and IRF activation by P12(G20) upon LPS stimulation in comparison with P12(G13) and the inactive P13. (**C**) Inhibition of the LPS-induced cytokines CCL2 and CCL4 production in THP-1 cell-derived macrophages by the hybrids P12(G20) and P12(G13). (**D**) A scheme illustrating the hybrids formed with different numbers of F in the peptide sequence. (**E**) Stability of FD, F2D (P12) and F3D in NaCl solutions with different concentrations. (**F**) The analysis of the total cell counts and neutrophil counts. (**G**). Nanoparticle concentration, (**H**) A scheme of the prophylactic treatments of P12(G20) or P12(G13) in an LPS-induced ALI model. (**I**) The nanoparticle size effects of P12(G20) comparing to P12(G13) on the short term. **p* < 0.05, ***p* < 0.01, ****p* < 0.001. Reprinted from Acta Biomaterialia, 85, Gao W, Wang Y, Xiong Y, et al, Size-dependent anti-inflammatory activity of a peptide-gold nanoparticle hybrid in vitro and in a mouse model of acute lung injury, 203–217, Copyright 2019, with permission from Elsevier.[388]

THP-1 cell derived macrophage demonstrated the significant inhibition of CCL2 and CCL4 and aside from that showed negligible cellular toxicity as they inhibit NF-*k*B and IRF with reduction of p65 phosphorylated and degradation of I*k*Bα (Figure 12B and C). The P12 with one F was more stabilized in the NaCl solutions. However, the P12 with F2D and F3D demonstrated significant inhibition of NF-*k*B /AP-1 and also decreased the LPS-induced production of CCL2 (Figure 12D and E). Further, the mimicking of mice ALI/ARDS with LPS and observation after 24hrs showed a reduction in the overall inflammatory cells, neutrophil, and macrophage chemotactic cytokine KC & CCL2, respectively (Figure 12F). Also, the W/D ratio remarkably decreased (Figure 12G). Examination of the long-term protective effect of the P12 (G20) showed a high survival rate despite the lethal dosage of LPS (Figure 12H and I).[388] Also, Liu Yu et al targeted inflammatory vascular endothelial cells employing E-selectin binding peptides (Esbp) as a high affinity legend, developing a dexamethasone loaded Esbp modified bovine serum albumin nanoparticle (BSANPs) (Figure 13A). The drug at different concentrations demonstrated good blood biocompatibility (Figure 13B) showing a prolonged drug release and action rate (Figure 13C). The drug also demonstrated high target accumulation (lung) (Figure 13D–I).[210] The use of a suitable targeting carrier such as a biomimetic not only improves the therapeutic efficacy but also reduces the chances of drug resistance as a result of the high accumulation of drugs at the targeted area.[389–391] Aside from the aforementioned advantages, they may be equipped with good penetrability, potent targeting, and prolonged time of action within the target organism.[392–396]

Macrophage Role under AP Developed ALI and the Modulating Effect of Bioactive Nanoparticles

Reports indicate that at the initial phase of ALI/ARDS, toll-like receptors (TLRS) or pattern recognition receptors (PRRS) engage in the shifting of resident alveolar macrophage to the M1 phenotype. This triggers the release of an enormous amount of pro-inflammatory cytokines, further activating inflammatory response and the recruitment of neutrophils into the immediate microenvironment.[397–402] Wang Lu et al bonded the thiol group of a peptide to a gold nanoparticle to create a bioactive platform for the promotion of macrophage polarization toward anti-inflammatory M2 phenotype (Figure 14A and B). Regarding cytokine production, the peptide coated GNP (P12) decreased the level of

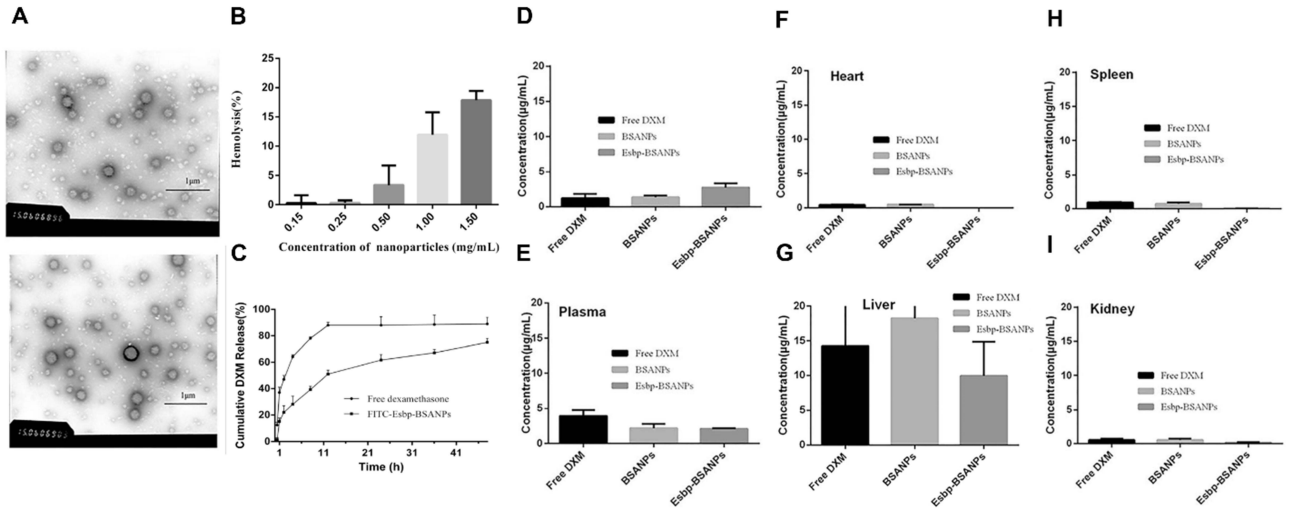

Figure 13 (**A**) TEM imaging of DXM-loaded Fitc-Esbp-BSANPs and DXM-loaded BSANPs. (**B**) Hemolytic rate of DXM-loaded Fitc-Esbp-BSANPs at concentration from 0.15 to 1.5 mg/mL (**C**) Release behaviors of free DXM and DXM-loaded Fitc-Esbp- BSANPs at 37°C in pH 7.4 PBS. (**D**–**I**) Distribution of drugs in different organs. Reprinted from Liu Y, Yang B, Zhao X, Xi M, Yin Z. E-Selectin-Binding Peptide-Modified Bovine Serum Albumin Nanoparticles for the Treatment of Acute Lung Injury. AAPS Pharm Sci Tech. 2019;20:270. https://creativecommons.org/licenses/by/4.0/.[210]

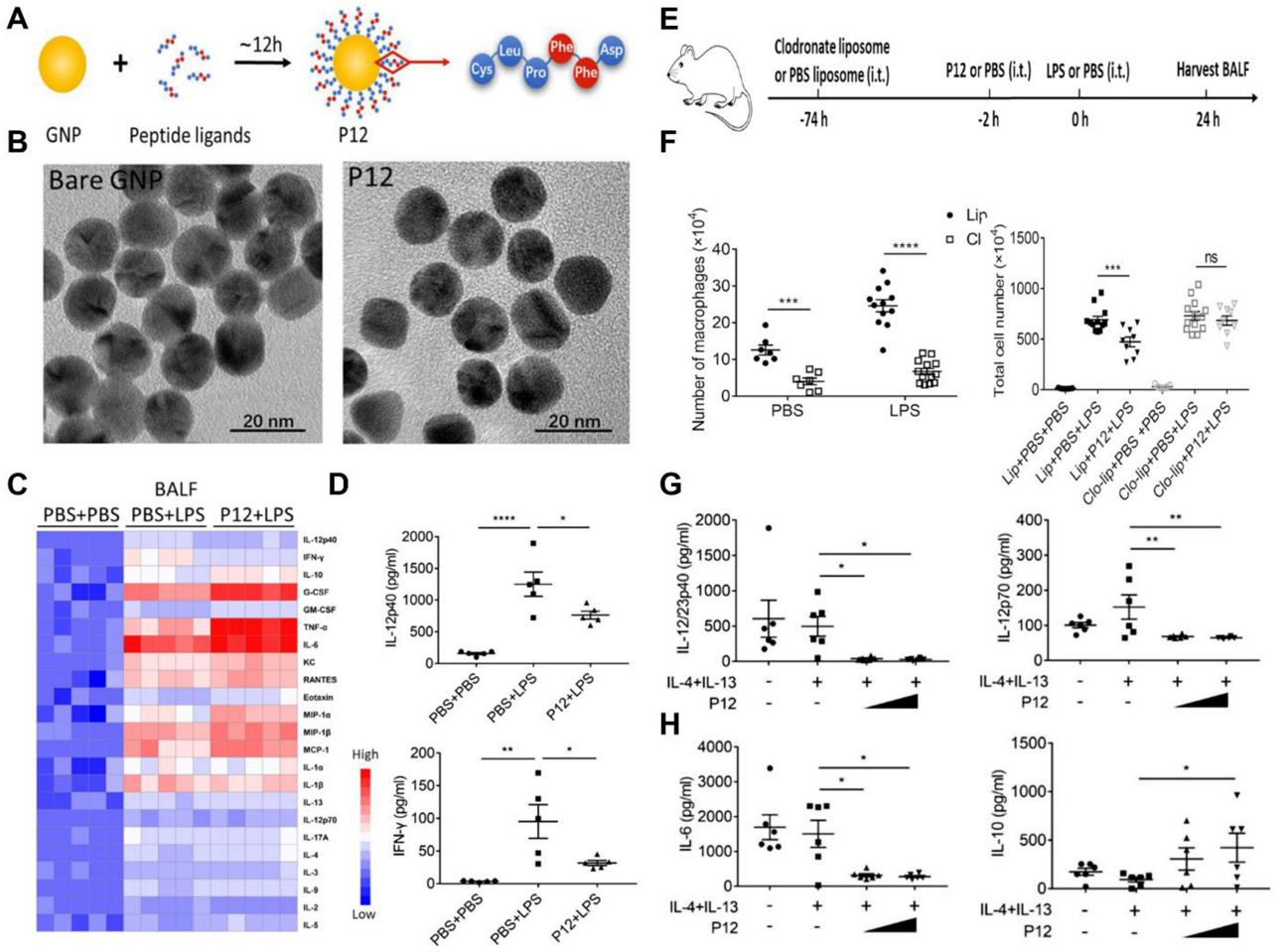

Figure 14 (A) Schematic diagram of peptide-coated GNP P12 synthesis. **(B)** TEM images of bare GNPs and P12. mice. (**C**) The heat map showing cytokine profiles of the BALF under LPS challenge with/without P12 pre-treatment. (**D**) The levels of selected cytokines of IL-12p40 IFN-γ. (**E**) The experimental procedure of macrophage depletion prior to P12 pre-treatment and LPS challenge. (**F**) At 24 h after LPS stimulation, the BALF was harvested to assess the efficiency of macrophage depletion and to analyze the number of total cells neutrophils. The effects of P12 on the polarization of BMDMs to M2 phenotype. Under IL-4 and IL-13 co-stimulation for M2 polarization, cytokine levels of IL-12/23p40 (**G**), IL-12p70, IL-6 and (**H**) IL-10. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$. Reprinted from Wang L, Zhang H, Sun L, et al. Manipulation of macrophage polarization by peptide-coated gold nanoparticles and its protective effects on acute lung injury. J Nanobiotechnol. 2020;18:38.http://creativecommons.org/licenses/by/4.0/.[403]

cytokine linked with IL-12p40 and IFN-γ (Figure 14C and D), while the M2 phenotype (IL-10) increased. This phenomenon of M2 phenotype elevation was evident in the serum. Also, the P12 accumulated in the macrophage and equally targeted pulmonary macrophage to ameliorate the lung inflammation (Figure 14E and F). Additional P12 on M2 polarization showed the suppression of the baseline of pro-inflammatory cytokine increasing IL-10 level in correlation to their concentration and negligible impact on iNOS gene expression (Figure 14G and H).[403] The effect of co-stimulation of IL-4 and IL-3 did not impact the level of IL-12/23p40, IL-12p70, and IL-6, hence the P12 suppressed and elevated the M1 specific gene expression and M2 specific gene expression, respectively. It is important to note that, the macrophage of the lung is seen as key in the pathogenesis of ALI/ARDS and most drugs can be fabricated to target them as they have the superior phagocytic capability as mentioned earlier. Usually, macrophage (Mo) becomes polarized into varying phenotypes (proinflammatory (M1) and anti-inflammatory, (M2)) when activated.

Studies show that alveolar macrophages, like pulmonary macrophages, are involved in the pathogenesis of ALI/ARDS, considering the varying phases of pathogenesis ranging from the exudative phase, and proliferative phase to the fibrotic phase with their initial activation at the exudative phase characterizing tissue injury, which drives M1 phenotype to initiate the acute inflammatory response, and enhancement of this response which eventually leads to further injury and pulmonary edema.[404–407] Interestingly a switch to the M2 phenotypes can also be observed at a point in the progression of the ALI/ARDS, where the macrophage attempts the tissue repair and the fixing of the inflammation. In addition, this macrophage polarization has intrinsic modulation such as the NF-*k*B, STAT, peroxisome proliferator-activated receptor gamma (PPAR-γ), and interferon regulator,[408–411] and can internalize into the macrophage endosomal compartment to impede endosomal acidification. Additional modulation of toll-like receptors has been one of the approaches used to control excessive inflammation under ALI/ARDs. The TLR4, for example, plays a crucial role in infections and non-infections, lung-related inflammation or injury. Most times pathogens that get involved in the process can also make treatment and the efficacy of a drug decline or remain redundant.[412–418] Researchers have therefore concluded on the fact that having bioactive molecules, eg, high-density lipoprotein, non-anticoagulant heparin (NAH) holds the possibility of sequestering these TLR agonists or any inflammatory indicators. The whole concept is premised on modifying or functionalizing the surface property of the nanoparticle, which in turn step up the antigen-specific immune response or suppression of the immune response following an autoimmune disease.[419–425]

Mitochondrial Role in Inflammatory and the Modulating Effect of Bioactive Nanoparticles

Mitochondria as a double-bounded membrane organelle is known for supplying cells with ATP and are engaged in calcium influx redox signaling and programmed cell death. The malfunction or dysfunction of such organelle is associated with varying disorders which include neurodegenerative disease, hypertension, diabetes, obesity, etc.[426–430] Interestingly, AP, ALI, ARDS, and other inflammatory diseases have been associated with it. Researchers have tried to use the resolution of the mitochondria dysfunction to impede or block the injury, by improving the cellular glycolytic activity which acts as a means to shield the airway epithelium during acute injury, a clear pattern observed normally under ALI/ARDS.[198,431–433] Although inflammation can just be a normal biological response to a pathogen or a change in an organism, reverting to damage and tissue injury, improper management within an organism can result in diverse organ dysfunction and deteriorating effects. Most diseases in general, although have peculiar pathogenesis pathways, may one way or the other have inflammation.[434–439] One key condition that clearly points out the link between inflammation and the mitochondria is the aging process which under inflammation happens via a redox means and inflammatory response induced by oxidative stress. The mitochondria play a key role in the aging process, the ATP generation under the mitochondrial respiratory chain (MRC), and the involvement in the oxidative stress process. Generally, the incomplete reduction of MRC in a redox reaction yield (O^{2-}) a ROS which influences the trigger of redox transcriptase factors and further activation and expression of other chemokine cytokines, adhesion molecules, oxidation of mitochondria DNA, protein, and lipids.[440–445] Under this situation, the mitochondrial integrity can be compromised where there is an increased chance of mutagenesis occurring in the mtDNA from the increasing amount of oxidative damage.[446–449] Reports indicate that the mitochondrial distinct related inflammatory and matrix degradation responses, although may not be intrinsic, may most occur via mitochondrial Ca^{2+} exchange aside from the ROS generation and the trigger of NF-*k*B. Moreover, the enormous accumulation of mitochondrial Ca^{2+} can also be a major step in disease pathogenesis. Mostly, excessive accumulation can trigger the tricarboxylic acid

cycle, allowing the flow of electrons into the respiratory chain. Also, this triggers an elevation of NO synthase, promoting the generation of ROS, impeding respiration and the Ca^{2+} binding to cardiolipin.[450–455]

Interestingly, pro-inflammatory mediators (chemokine, cytokine, reactive nitrogen intermediate NO) may in turn induce mitochondria membrane potential. Normally, activities such as mitochondrial membrane potential, ATP production, and AMRC complex 1 are impeded by these mediators, while the overgeneration of ROS continues to occur the NO, for example, becomes involved in the suppression of mitochondrial energy production and is able to merge with superoxide anion to produce peroxynitrite an inhibiting oxidant for potent enzymes which affect the mitochondrial integrity and respiratory complex.[456–460] Muying Wang fabricated $Se@SiO_2$ nanoparticles for the gradual release of Se to attenuate oxidative stress (Figure 15A and B).[461–465] As mentioned earlier porous Silica aside from good biocompatibility has a number of biological functionalities and can moderately be released in response to pH, and is endowed with the capabilities of target drugs, highly accumulating at the target site.[466–470] The $Se@SiO_2$ significantly suppressed the ROS production following treatment with 10ng/mL LPS which was linked to the decrease in the NF-*k*B subunit phosphorylation (Figure 15C and D) and was phenomenal in the mitochondrial ROS suppression (Figure 15E and F). Also, the NP remarkably suppressed the level of inflammatory cells, with neutrophils and macrophages (Figure 15G–J). Further, the total protein and the W/D ratio of the lungs declined a demonstration of injury ameliorating of alveolar-capillary membrane, with a decreased injury score, decreased phosphorylation of ERK1/2 and P38 (Figure 15K and L).[471] In addition, Gene Ontology (GO) annotation and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway demonstrated with the functionality that the NP was largely linked to the cellular response to damaged DNA, modulating the cellular metabolic process, organization of organelle and finally ameliorating the mitochondrial dynamics, protecting and increasing the resistance of the airway epithelium.

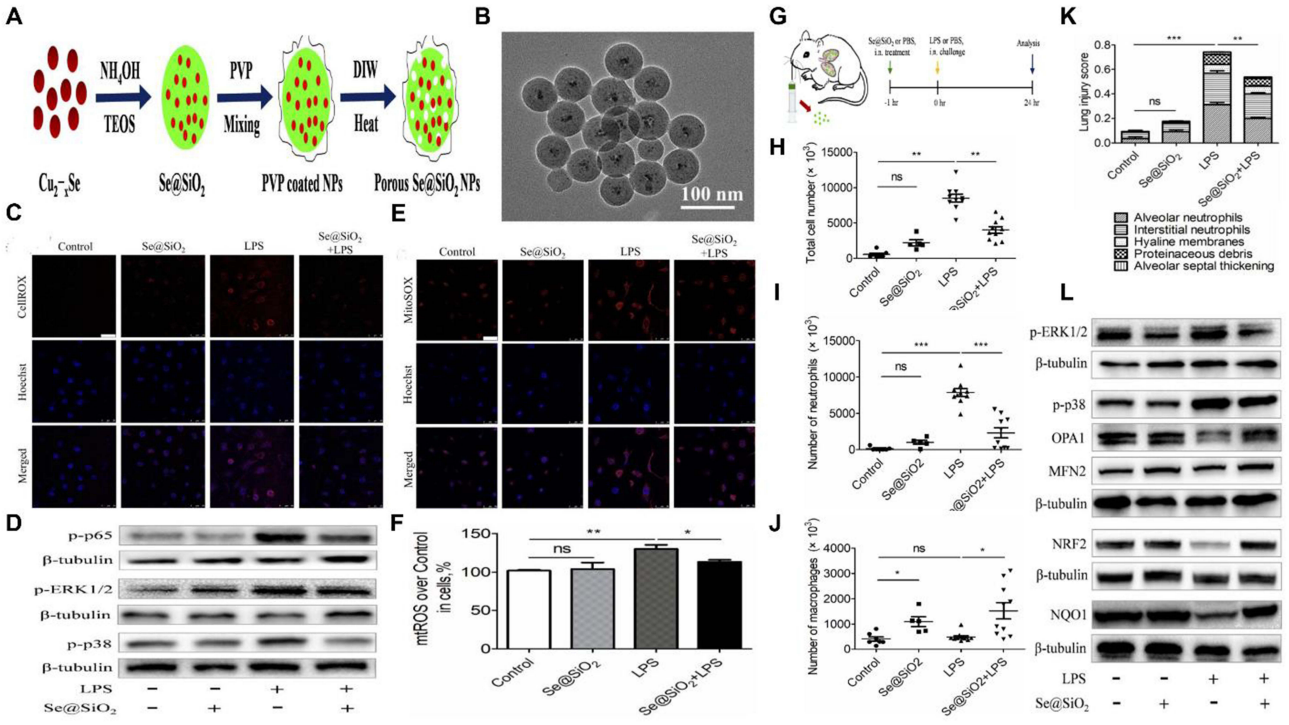

Figure 15 (**A**) Fabrication of porous $Se@SiO_2$ nanoparticles (NPs) and, (**B**) The TEM image (**C**) Representative confocal images showing the effect of $Se@SiO_2$ NPs on LPS-induced oxidative stress in Beas-2B cells. (**D**) WB showing the effect of $Se@SiO_2$ NPs on the increased expression of p-p65, p-ERK1/2 (MAPK), and p-p38 (MAPK) as well as the reduced expression of NRF2, NQO1, ZO-1, and E-Ca. (**E**) Representative confocal images showing the effect of $Se@SiO_2$ NPs on LPS-induced mitochondria-specific ROS in Beas-2B cells. (**F**) Quantification of mitochondrial ROS level by a microplate reader. (**G**) The ALI mouse model with $Se@SiO_2$ pretreatments intranasally 1h before LPS challenge. BALF in each group were collected for the detection of total cell amounts (**H**), neutrophil numbers (**I**), macrophage counts (**J**) as well as cytokines IL-1β. (**K**) Lung damage in each group was evaluated by five pathophysiological features to get the total score. (**L**) The impact of $Se@SiO_2$ NPs on the expression of several proteins in lung tissues of ALI mice. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Reprinted with permission from Wang M, Wang K, Deng G, et al. Mitochondria-Modulating Porous Se@SiO(2) Nanoparticles Provide Resistance to Oxidative Injury in Airway Epithelial Cells: implications for Acute Lung Injury. Int J Nanomed. 2020;15:2287–2302.[471]

Nanocomposites/Hybrid Bioactive Nanoparticles

Nanomaterials in general may exist as polymers, metals, ceramics, or composites. Mostly, the inorganic which has ceramic glass and mineral inclusive is employed for their optical, magnetic, mechanical, and thermal properties. In addition, those consisting of the polymer construct, polymersomes, liposomes, and micelles are employed for drug or gene delivery, release, or imaging.[472–477] Although in the past nanomaterials were singly employed owing to the significance of functionalized biomaterials, the hybrid nanomaterials and nanocomposite have gained widespread attention and usage.[477–482] Hybrid materials consist of an organic and inorganic component, while the nanocomposite consists of two or more different organic or inorganic or both at a nano-size dimension.[477,478] Nanomaterials have size within a range of 1–100nm and consist of quantitative dots, dendrimers, nanotubes, and fullerenes commercially employed in textiles, electronics, cosmetics, dental fillings, paints, etc. per their structuring they can coexist as zero-dimension, one-dimension, two or three-dimension.[479–482] The concept of hybrid composite may have stemmed from the incorporation of nanoparticle additives dated back in the twentieth century where small additives were added to materials to convey magnetization, hardness, or UV absorption and improve their state or value.[483–487]

Qixiang Mei employed fabricated COS@SiO_2, COSs loaded into a porous silica nanoparticle, based on the biological functionality of chitosan oligosaccharides and the good biocompatibility of porous silica (Figure 16A). Their work was directed towards targeting SAP and ALI/ARDS. Following the successful establishment of the SAP model, higher attenuation of pancreatic injury was demonstrated by the COS@SiO_2 (Figure 16B–D). Also, the pathological injury was minimized in COS@SiO_2 group with reduced specific indices of AP (serum amylase and serum lipase) equally reducing inflammation and oxidative stress (Figure 16E–H). A clear indication of severity, where alveolar walls and alveolar space are characterized by thickness and wideness, respectively, with the interstitium infiltrated with neutrophil-associated inflammatory cells. The influence of COS@SiO_2 on Nrf2 reduced the NLP3 inflammasome and activation of NF-*k*B and a protective effect was

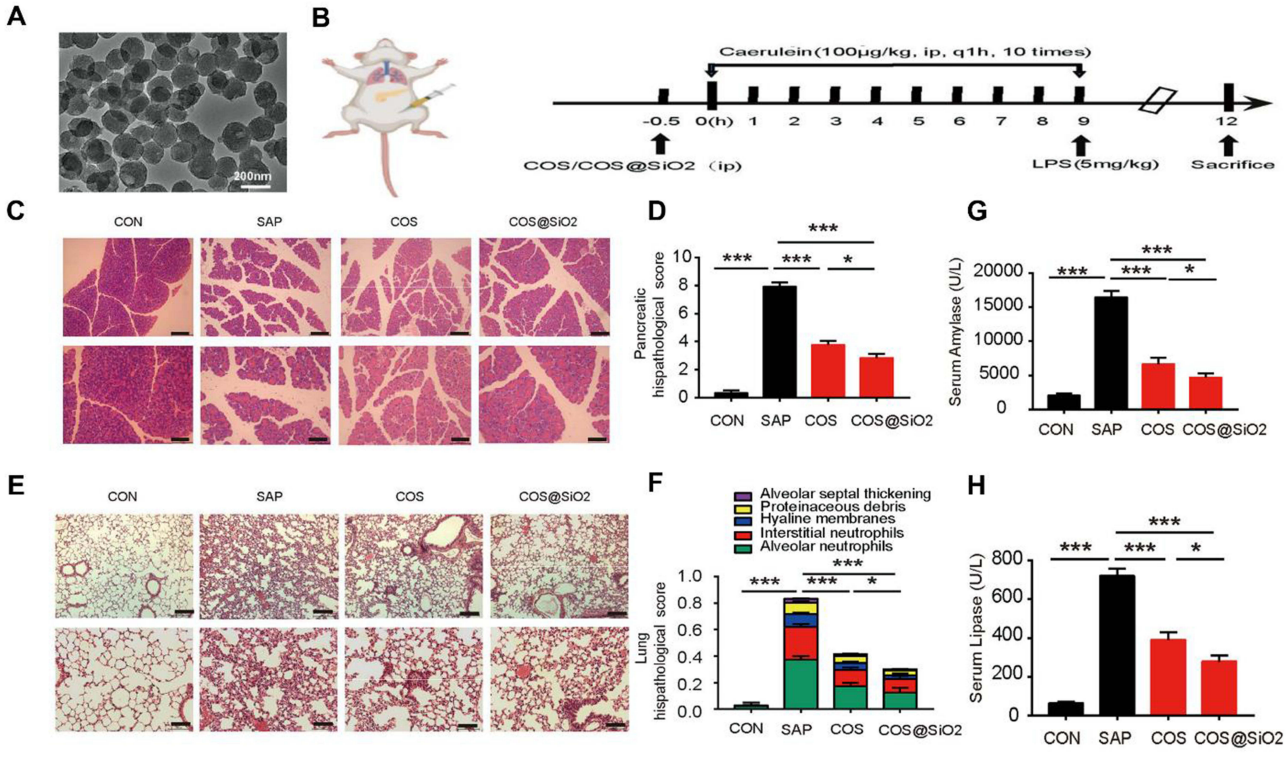

Figure 16 (**A**) Transmission electron microscopy images of COS@SiO_2. (**B**) The time axis of AP model building and drug intervention. (**C** and **D**) Pancreatic samples from the four groups of mice were stained with H&E. Representative images of the pancreas are shown. (**E** and **F**) Lung histopathology scores were evaluated by alveolar neutrophils, interstitial neutrophils, hyaline membranes, proteinaceous debris, and alveolar septal thickening. COS@SiO_2 reduced (**G**) the level of serum amylase and (**H**) the level of serum lipase. Reprinted from Mei Q, Deng G, Huang Z, et al. Porous COS@SiO(2) Nanocomposites Ameliorate Severe Acute Pancreatitis and Associated Lung Injury by Regulating the Nrf2 Signaling Pathway in Mice. Front Chem. 2020;8:720. https://creativecommons.org/licenses/by/4.0/.[488] *$p < 0.05$; ***$p < 0.001$.

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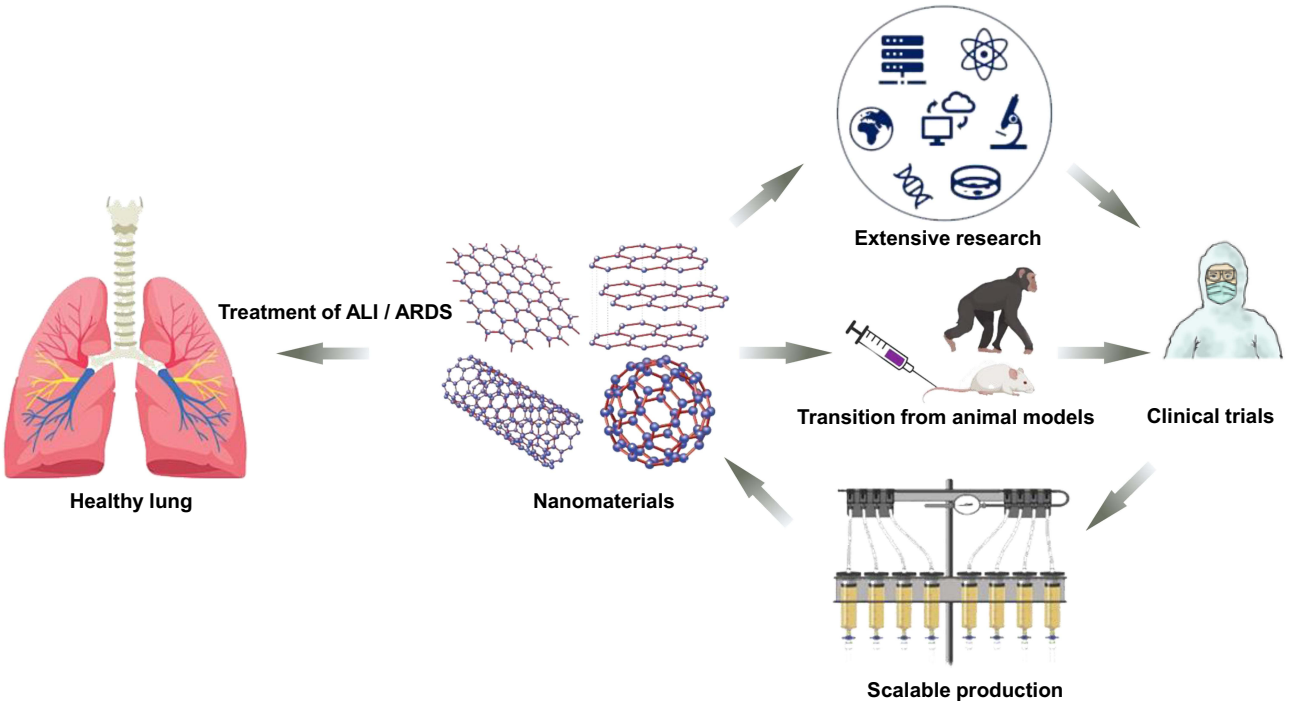

Figure 17 Schematic representation of the current usage, challenge and the means to harness its potentials.

projected to occur via the Nrf2 pathways.[488] The keap 1 and Nrf2 in the cytoplasm immediately dissociate under oxidative stress as the Nrf2 translocates to the nucleus and functions with antioxidant responders and other proteins to shield the body from the damaging effect of ROS. Chitosan oligosaccharides, for example, have been employed in antioxidant, antibacterial, anti-inflammatory, and immunomodulatory functions. This has been attributed to minimal molecular weight and high solubility,[489–491] also Selenium can be considered an essential trace element, stable, and used antioxidant. Although could equally pose harm by generating superoxide by catalyzing the oxidation of thiols.[492–494]

Conclusion

The ALI/ARDS associated with severe AP may not have a remarkable difference from those linked to other disorders. However, conventional intervention might have done little to overcome the disorder completely and its rate of mortality. Another challenge faced with the disorder is the immediate evaluation of the specifically involved mechanism and the precise target. The potential of newly emerging drugs has also not seen immediate usage due to the pace of clinical trials or translation to human trials. Despite the trials and development of enormous amounts of conventional drugs, the efforts made are largely empirical which can be associated with the complexity of the drug development process and the mechanism involved under the AP/ALI. However, the thriving advancement of nanotechnology has set to close some inherent loopholes of conventional drugs. Progress is made on a daily basis with regard to the design, fabrication, and biomedical application of nanodrug or nanomedicine, although not without challenges such as the approach involved in the fabrication and biomedical application of nanodrug or nanomedicine, the materials employed, and the concerns of toxicity.

By understanding the function of the factors involved in the mechanism, the conditions for the staging of oxidative stress and inflammation induction can inform the fabrication or synthesis of a drug in order to attain certain therapeutic effects. In the face of nanomedicine, varying number of challenges could have been addressed contrary to the conventional approach, however, one key impediment is the clinical translation and the concerns of toxicity. With that being said, nanoparticles related drugs may not be as harmful or toxic as they can be modified or fabricated in a manner depending on their size and charge, to minimize the level of accumulation within the body. Aside from this, some have a short biodegrading timeline with some even filtered and expelled timely from the body depending on the particle size. Also, others have allowed the incorporation into cell membranes, etc., have the ability to even mimic and present

membrane-like effects.[354–358,495] As nanomaterials have received attention in recent years, the potential of emerging conventional drugs has also been held back mostly due to the duration of clinical approval. Further, the major concern for the use of nanodrugs, which is the impression of toxicity, should gradually be erased through education and the use of synthesis or approaches that may be considered more biological or environmentally friendly. For some time now only, a few have been extensively employed for human use. Interestingly, the potential and efficiency have been limited to small and large animal models, which is also applicable to the centers used for such research been limited to animal models. Hence, a need for much attention and focus to be directed towards research, approval, facilities, and gadgets for human use to harness such potential. Since their inception, nanomaterials have posed a greater advantage over conventional drugs due to the ability to combine multiple nanomaterials or even with conventional drugs for therapeutic purposes making it difficult for such drugs to lose their potency or efficiency with time, as shown in the graphical abstract. Regarding ways of improvement for effective therapeutic purposes and also user-friendly, nanomaterials can be modified easily for inhalation, injection, better carriers, and drug delivery. Further, others can act as specific target carriers for efficient drug delivery. Interestingly, most of the nanodrug/nanomedicine reported are mainly in murine, thus issues of metabolism, immunogenicity, metabolism, toxicity, and biocompatibility when it comes to humans may be genuine and will require systematic investigation. An in-depth understanding of the functionality of the drugs and their limitation could also inform the capability improvement of the nanodrug/nanomedicine or medicine in future (Figure 17).

Abbreviations

AMPK, AMP-activated protein kinase; ALI, Acute lung injury; AP, Acute pancreatitis; ARDS, Acute respiratory distress syndrome; BALF, Bronchoalveolar lavage fluid; CAT,Catalase; Ce, Ceria; CNP, Cerium oxide nanoparticles; DPM, DXM-PEI-mannose; DAMP, Damaged molecular patterns; ERK, Extracellular signal-regulated kinase; GSK3β, Glycogen synthase kinase 3 beta; HPMECS, Human lung microvascular endothelial cells; HMGB1, High-mobility group box protein 1; ICAM-1, Intercellular adhesion molecule; IL-8, Interleukin 8; mABs, Monoclonal antibodies MODS, Multiple organ dysfunction syndrome; JNK, C-Jun N terminal kinase; LAMC2, Laminin gamma 2; Nrf2, Erythroid-2-related factor 2; MPO, Myeloperoxidase; MAPK, P38 mitogen-activated protein kinase; MRC, Mitochondrial respiratory chain; NAH, Non-anticoagulant heparin; NQO1, Quinone oxidoreductase-1; POD, Peroxidase; PRC, Protein kinase C; PPAR-γ, Peroxisome proliferator-activated receptor gamma; PMN, Polymorphonucleocyte; PEEP, Positive expiratory-end pressure; RIP, Receptor interacting protein; RNS, Reactive nitrogen species; RT, Resatorvid; TMDCs, Transitional metal dichalcogenides; TLRS, Toll-like receptors; TRADD, TNF-R1 related death domain; SSeCKS, Src-inhibited C kinase substrate; SOD, Oxide dismutase; SIR, Systematic inflammatory response; STAT3, Signal transducer and activator of transcription 3.

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Disclosure

The authors report no conflicts of interest in this work.

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