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Molecular crosstalk in the lung-kidney axis; inflammatory cascades and exosomal signaling pathways mediating renal dysfunction in COVID-19-induced pulmonary injury

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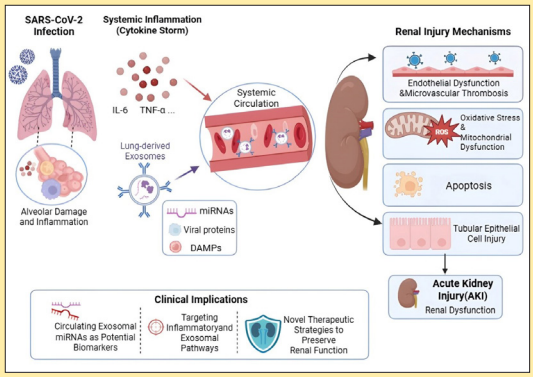
ABSTRACT



COVID-19 primarily manifests as severe pulmonary injury, nevertheless acute kidney injury (AKI) represents a frequent and devastating extrapulmonary complication. The precise mechanisms linking SARS-CoV-2-induced lung damage to renal dysfunction remain incompletely understood, emphasizing the critical importance of the lung-kidney axis. This inter-organ crosstalk is predominantly driven by dysregulated systemic inflammatory cascades and intricate exosomal signaling pathways. Upon severe pulmonary infection, the localized immune response escalates into a systemic cytokine storm, releasing massive quantities of pro-inflammatory mediators such as interleukin-6 and tumor necrosis factor-alpha. This hyperinflammatory state induces widespread endothelial dysfunction, microvascular thrombosis, and direct ischemic damage to renal tubular epithelial cells. Concurrently, recent studies highlight the critical role of exosomes in mediating this distant organ injury. Damaged alveolar epithelial and endothelial cells release lung-derived exosomes packed with damage-associated molecular patterns, viral proteins, and specific microRNAs into the systemic circulation. Upon reaching the kidneys, these extracellular vesicles are internalized by renal cells, where their bioactive payloads dysregulate local transcriptomic profiles, exacerbating oxidative stress, mitochondrial dysfunction, and apoptotic cascades. The synergistic interplay between systemic inflammation and exosomal cargo transfer fundamentally disrupts renal homeostasis, accelerating the progression of AKI. Elucidating the molecular crosstalk within the lung-kidney axis not only clarifies the pathophysiology of multi-organ failure in severe COVID-19 but also identifies circulating exosomal microRNAs as potential diagnostic biomarkers. Furthermore, targeting these specific inflammatory and exosomal signaling pathways offers promising novel therapeutic strategies to preserve renal function and improve overall survival in critically ill patients.

Review

Introduction

The emergence of SARS-CoV-2 has unequivocally demonstrated that viral pathogenesis extends far beyond the primary site of infection, revealing a complex, multi-organ interplay that profoundly challenges traditional paradigms of organ-specific injury (1). Though the respiratory system bears the initial and most visible effect of the infection, the kidneys are frequently and severely affected, with acute kidney injury (AKI) representing a major determinant of mortality in critically ill patients (2). Historically, this pulmonary-renal connection was attributed primarily to hemodynamic alterations, such as hypovolemia, systemic hypotension, and the subsequent renal hypoperfusion (3,4). However, contemporary molecular and cellular research has necessitated a paradigm shift, revealing that the lung-kidney axis in the context of COVID-19 is conducted by a highly regulated, continuous molecular crosstalk (5). This

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Implication for health policy/practice/research/medical education:
The molecular crosstalk within the lung-kidney axis profoundly illustrates how severe COVID-19-induced pulmonary injury precipitates remote renal dysfunction through complex inflammatory cascades and exosomal signaling pathways. When SARS-CoV-2 damages the alveolar-capillary barrier, it triggers a systemic cytokine storm, releasing pro-inflammatory mediators such as interleukin-6 and tumor necrosis factor-alpha (TNF-α) into the circulation, which directly induce renal endothelial dysfunction and tubular apoptosis. Concurrently, injured pulmonary cells secrete exosomes packed with pathogenic microRNAs and damage-associated molecular patterns. These circulating extracellular vesicles travel to the kidneys, where they are internalized by renal tubular cells, dysregulating local gene expression, exacerbating oxidative stress, and activating the NLRP3 inflammasome. Finally, this dual mechanism of soluble inflammatory mediators and targeted exosomal crosstalk underscores the systemic nature of COVID-19, emphasizing the critical necessity for therapeutic strategies that target and block these specific inter-organ communication pathways to prevent acute kidney injury in patients suffering from severe respiratory compromise.
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intricate communication network is driven by massive inflammatory cascades and the systemic dissemination of nanoscale extracellular vesicles, particularly exosomes, which collectively mediate profound renal structural and functional decline independent of, and often preceding, overt hemodynamic collapse (6). Identification of this axis requires a deep look into the specific molecular pathways that transform a localized pulmonary infection into a systemic renal catastrophe (6). This overview aimed to consider molecular crosstalk in the lung-kidney axis in COVID-19-induced pulmonary injury through evaluating inflammatory cascades and exosomal signaling pathways mediating renal dysfunction.

Method of the search

To identify relevant literature for this narrative review, we queried multiple databases—including PubMed, Scopus, Embase, Web of Science, EBSCO, DOAJ, and Google Scholar—using keywords related to: reactive oxygen species, renal injury, membrane attack complex, endothelial cells, podocytes, endothelial dysfunction, oxidative stress, neutrophil extracellular traps, tubular epithelial cells, cytokine storm, endothelin-1, antioxidant defense, acute kidney injury and chronic kidney disease.

A fresh look at the lung-kidney axis

The initiation of this detrimental molecular crosstalk begins within the pulmonary microenvironment, where the virus exploits angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 receptors (TMPRSS2) to gain entry into alveolar epithelial cells, particularly type II pneumocytes (7). The resulting cytopathic effect and subsequent cellular necrosis release a massive array of damage-associated molecular patterns and pathogen-associated molecular patterns into the alveolar space (8). This localized danger signal triggers the robust recruitment and activation of alveolar macrophages, neutrophils, and dendritic cells (8). In an attempt to contain the viral replication, these immune cells undergo a hyper-inflammatory polarization, shifting toward a pro-inflammatory M1 macrophage phenotype and releasing a torrent of reactive oxygen species, proteases, and pro-inflammatory cytokines (9). While this localized immune response is intended to be protective, the overwhelming magnitude of the viral load and the resulting cellular damage cause the inflammatory milieu to breach the alveolar-capillary barrier (10). This breach marks the critical transition from localized pulmonary pathology to systemic molecular dissemination, effectively transforming the injured lung into a massive endocrine-like organ that continuously secretes toxic molecular mediators into the systemic circulation (6). Furthermore, the viral down-regulation of angiotensin-converting enzyme 2 in the lungs disrupts the local renin-angiotensin system, leading to an accumulation of angiotensin II, which exerts potent pro-inflammatory and pro-fibrotic effects that further amplify the pulmonary injury and contribute to the systemic toxic load (11). The hallmark of this systemic dissemination is the so-called cytokine storm, a hyper-acute systemic inflammatory response that serves as the primary soluble conduit for lung-to-kidney molecular crosstalk (11). The injured pulmonary tissue and activated resident immune cells release massive quantities of interleukin-6, interleukin-1 beta, tumor necrosis factor-alpha, and various chemokines into the bloodstream (6). Upon reaching the renal circulation, these circulating cytokines actively bind to their cognate receptors expressed on the surface of diverse renal cell populations, including podocytes, mesangial cells, and proximal tubular epithelial cells (12). The binding of interleukin-6 to its receptor complex, particularly through the process of trans-signaling involving the soluble interleukin-6 receptor, triggers the classical Janus kinase and signal transducer and activator of transcription pathway (13). Specifically, Janus kinases phosphorylate signal transducer and activator of transcription 3, which

dimerizes and translocates to the nucleus to drive the transcription of pro-inflammatory and pro-apoptotic genes within the renal tissue (14). Simultaneously, tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) engage their respective receptors to activate the nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase signaling cascades (15). The activation of NF-κB involves the phosphorylation of the IKK (I kappa B kinase; IκB) complex, which subsequently phosphorylates the inhibitor protein I kappa B alpha, leading to its ubiquitination and proteasomal degradation (15). This condition allows the transcription factor to enter the nucleus and upregulate a vast array of secondary inflammatory mediators, adhesion molecules, and chemokines directly within the kidney (16). This secondary local inflammation amplifies the initial systemic signal, creating a self-sustaining loop of renal injury that exacerbates tubular damage and disrupts the delicate structural integrity of the glomerular filtration barrier (17). Parallel to the direct cytokine-receptor interactions, the systemic inflammatory cascade triggers the widespread activation of the complement system and the coagulation cascade, leading to a state of thromboinflammation that severely compromises renal microvascular perfusion (18). The pulmonary-derived inflammatory mediators, along with exposed subendothelial matrices from damaged pulmonary and systemic vasculature, activate the alternative and lectin pathways of the complement system (19). Then, the complement activation results in the generation of potent anaphylatoxins, specifically C3a and C5a, which further recruit and activate neutrophils and macrophages within the renal interstitium (19). More critically, the terminal complement complex, C5b-9 or the membrane attack complex, is deposited directly on the surfaces of renal endothelial cells and podocytes (20). This deposition induces sub-lytic signaling that promotes cellular activation, oxidative stress, and the release of additional pro-inflammatory mediators, directly contributing to podocyte effacement and proteinuria (21). Concurrently, the systemic inflammatory state induces a profound pro-coagulant shift (21). Circulating cytokines upregulate tissue factor expression on monocytes and endothelial cells, while simultaneously down-regulating natural anticoagulant pathways such as the protein C system (22). In the renal microvasculature, this condition culminates in the formation of widespread microthrombi (23). Furthermore, the activation of neutrophils leads to the release of neutrophil extracellular traps, which provide a scaffold for platelet aggregation and red blood cell trapping, further occluding the peritubular capillaries (24). This thromboinflammatory occlusion creates localized areas of severe ischemia and hypoxia within the renal cortex and medulla, synergizing with the direct molecular toxicity of the cytokine storm to precipitate acute tubular necrosis (18).

Systemic transfer of exosomes

Though the soluble mediators of the cytokine storm and thromboinflammation have traditionally dominated the understanding of multi-organ failure, recent advancements in vesicle biology have illuminated a parallel, equally critical pathway of molecular crosstalk, known as the systemic transfer of exosomes (25). Exosomes are a specialized subset of extracellular vesicles, typically ranging from thirty to one hundred and fifty nanometers in diameter, which are formed through the inward budding of the limiting membrane of multivesicular bodies and subsequent fusion with the plasma membrane, a process regulated by the endosomal sorting complexes required for transport machinery and the ceramide-dependent pathway (26). Under the extreme cellular stress, hypoxia, and inflammatory stimulation characteristic of severe COVID-19 pulmonary injury, lung-derived cells, including alveolar epithelial cells, endothelial cells, and activated macrophages, drastically upregulate the biogenesis and secretion of exosomes (27). Previous authors found that, hypoxia-inducible factor 1 alpha (HIF-1α), stabilized under the low oxygen conditions of the injured lung, directly transcriptionally upregulates genes involved in exosome biogenesis and release (28,29). The molecular cargo of these lung-derived exosomes is profoundly altered by the pathological state of the parent cell. They become heavily enriched with specific microRNAs, messenger RNAs, mitochondrial DNA fragments, damage-associated molecular patterns, and even viral components such as the spike protein or viral RNA (30,31). This specialized cargo transforms the exosomes into highly potent nanoscale messengers capable of reprogramming the gene expression and metabolic state of distant recipient cells, effectively bypassing the need for direct cell-to-cell contact or the binding of soluble ligands to surface receptors (32). Upon entering the systemic circulation, these lung-derived exosomes navigate the vascular tree and are systematically taken up by cells in various organs, with the kidneys being a primary target due to their high blood flow and the fenestrated nature of the glomerular and peritubular capillaries (33,34). The uptake of these exosomes by renal proximal tubular epithelial cells and podocytes occurs through multiple mechanisms, including clathrin-mediated endocytosis, macropinocytosis, lipid raft-dependent internalization, and direct fusion of the exosomal lipid bilayer with the plasma membrane of the recipient cell (33). Once internalized, the exosomal cargo is released into the cytoplasm, often facilitated by the acidic environment of the endolysosomal system which promotes membrane

fusion, where it exerts its biological effects (33). The microRNAs packaged within these lung-derived exosomes are of particular significance in mediating renal dysfunction (35,36). Likewise, hypoxia-induced exosomes from injured lung cells are often enriched with microRNAs that target and silence protective genes within the renal tubular cells (37). The transfer of specific pro-fibrotic and pro-inflammatory microRNAs, such as microRNA-21, microRNA-155, and microRNA-146a, directly into renal cells leads to the post-transcriptional repression of negative regulators of critical signaling pathways (38). MicroRNA-21, for instance, targets and downregulates suppressor of cytokine signaling 1 and phosphatase and tensin homolog, thereby hyperactivating the Janus kinase and signal transducer and activator of transcription pathway and the phosphoinositide 3-kinase and protein kinase B pathway, respectively (39). Similarly, the transfer of microRNAs that target Smad7, an inhibitory Smad, removes the negative feedback loop on the transforming growth factor-beta (TGFβ) signaling cascade (40). This epigenetic reprogramming forces the renal cells into a state of chronic inflammation and initiates the early molecular signatures of epithelial-to-mesenchymal transition, a process that compromises tubular integrity and primes the kidney for subsequent fibrotic remodeling (41). Furthermore, the exosomal transfer of damaged mitochondrial components and viral proteins introduces a direct mechanism of metabolic and structural toxicity to the kidney (42). The delivery of oxidized mitochondrial DNA and misfolded proteins from hypoxic lung cells to renal tubular cells activates intracellular pattern recognition receptors, such as the cyclic GMP-AMP synthase and stimulator of interferon genes pathway, as well as various Toll-like receptors within the endosomes (43). The recognition of cytosolic double-stranded DNA by cyclic GMP-AMP synthase leads to the synthesis of cyclic GMP-AMP, which subsequently binds to and activates stimulator of interferon genes on the endoplasmic reticulum (44,45). This activation triggers the translocation of stimulator of interferon genes to the Golgi apparatus, where it recruits TANK-binding kinase 1, leading to the phosphorylation and dimerization of interferon regulatory factor 3 and the subsequent transcription of type I interferons and additional pro-inflammatory cytokines directly within the renal parenchyma (46). This intracellular recognition amplifies the local inflammatory response independently of the systemic cytokine storm (46). Additionally, the presence of viral spike protein within the exosomes has been shown to interact with ACE2 on the surface of renal cells (47). This interaction not only facilitates localized viral entry but also induces the proteolytic shedding of the angiotensin-converting enzyme 2 ectodomain by the disintegrin and metalloproteinase domain-containing protein 17 (48). This shedding disrupts the protective arm of the renin-angiotensin-aldosterone system (RAAS), leading to an unopposed accumulation of angiotensin II, which exerts potent vasoconstrictive, pro-inflammatory, and pro-fibrotic effects on the renal microvasculature and tubulointerstitium, thereby exacerbating the structural damage initiated by the primary pulmonary injury (49). The molecular fallout from the lung, whether mediated by soluble cytokines or exosomal cargo causes devastating effect on the renal endothelium, which serves as the critical interface between the systemic circulation and the renal parenchyma (49). The continuous exposure to circulating inflammatory mediators and exosomal microRNAs induces profound endothelial dysfunction (4). At the molecular level, this is characterized by the rapid degradation of the endothelial glycocalyx, as a crucial protective layer of glycoproteins and proteoglycans, such as syndecan-1 and heparan sulfate, that lines the luminal surface of the blood vessels (50,51). The shedding of the glycocalyx, mediated by inflammatory cytokines, reactive oxygen species, and matrix metalloproteinases, exposes the underlying endothelial cells to direct shear stress and circulating inflammatory factors, while also abolishing the mechanotransduction signals that normally maintain endothelial quiescence (51). Concurrently, the expression and activity of endothelial nitric oxide synthase are significantly downregulated, while the production of potent vasoconstrictors such as endothelin-1 is upregulated. This imbalance disrupts the delicate regulation of renal microvascular tone, leading to sustained vasoconstriction and reduced cortical blood flow (52). Furthermore, the activated endothelial cells upregulate the surface expression of cellular adhesion molecules, including vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM), which facilitate the firm adhesion and transmigration of circulating leukocytes into the renal interstitium (53). This leukocyte infiltration further damages the tubular structures and perpetuates the cycle of inflammation and oxidative stress, eventually culminating in the breakdown of the endothelial barrier, capillary leak, and interstitial edema, which physically compresses the renal tubules and worsens the decline in glomerular filtration rate (54). In total, the convergence of intense inflammatory signaling, exosomal epigenetic reprogramming, and microvascular dysfunction finally dictates the fate of the renal parenchymal cells, driving them toward various forms of regulated cell death (55). Proximal tubular epithelial cells, which are highly metabolically active and possess a massive demand for adenosine triphosphate to fuel reabsorptive processes, are exquisitely sensitive to the molecular insults originating from the injured lung (56,57). The persistent activation of pro-apoptotic signaling pathways, driven by

both extrinsic cytokine receptor engagement and intrinsic mitochondrial stress induced by exosomal cargo, leads to the permeabilization of the outer mitochondrial membrane (58). This condition results in the release of cytochrome c into the cytosol, the formation of the apoptosome, and the subsequent activation of the caspase-9 and caspase-3 cascade, culminating in the orderly dismantling of the tubular cells and their sloughing into the tubular lumen (59). This sloughing not only reduces the functional mass of the nephron but also causes the formation of cellular casts that obstruct the tubular flow, increasing intratubular pressure and further compromising the glomerular filtration rate (60). Beyond classical apoptosis, the unique molecular milieu generated by the lung-kidney crosstalk in severe COVID-19 has been increasingly implicated in triggering ferroptosis, as a novel form of regulated cell death characterized by the iron-dependent accumulation of lethal lipid reactive oxygen species (61). The systemic inflammatory state and the transfer of oxidative stress-inducing exosomal cargo from the lungs severely deplete the intracellular antioxidant defenses of renal tubular cells (62). Specifically, the expression and activity of glutathione peroxidase 4, the central enzyme responsible for reducing lipid hydroperoxides to non-toxic lipid alcohols, are significantly suppressed through the action of specific exosomal microRNAs and the depletion of intracellular glutathione (63). Likewise, the intracellular labile iron pool is expanded due to the release of iron from damaged red blood cells within the microthrombi and the dysregulation of iron metabolism proteins (64). The combination of depleted glutathione peroxidase 4 activity and elevated free iron creates a perfect storm for uncontrolled lipid peroxidation of the cellular membranes by the Fenton reaction (64). This ferroptotic cascade leads to the rupture of the plasma membrane and the release of highly immunogenic intracellular contents, which act as secondary damage-associated molecular patterns, further fueling the local and systemic inflammatory response and ensuring the propagation of renal injury (65,66). Additionally, the activation of the NLRP3 inflammasome by exosomal mitochondrial DNA and extracellular ATP leads to the cleavage of caspase-1, which subsequently cleaves gasdermin D to form pores in the cell membrane, driving the highly inflammatory form of cell death known as pyroptosis, further exacerbating tissue damage (67).

The concept of maladaptive repair

As the acute injury phase progresses, the persistent molecular crosstalk between the injured lung and the kidney shifts the renal microenvironment from one of acute inflammation to one of maladaptive repair and fibrogenesis (68). The continuous supply of pro-fibrotic cytokines, such as transforming growth factor-beta, and the sustained epigenetic reprogramming by lung-derived exosomes prevent the normal restitution of the tubular epithelium (69,70). Instead of undergoing healthy proliferation and differentiation to restore the tubular lining, the surviving epithelial cells remain arrested in the G2/M phase of the cell cycle. This cell cycle arrest promotes a pro-fibrotic, senescent-like state (71). These arrested cells secrete a complex mixture of pro-fibrotic mediators, a phenomenon known as the senescence-associated secretory phenotype (72,73). This local secretion, combined with the systemic influx of lung-derived fibrotic signals, hyperactivates the resident renal fibroblasts and pericytes, driving their differentiation into alpha-smooth muscle actin-positive myofibroblasts (74,75). The activation of canonical profibrotic pathways, such as the Smad and Wnt/beta-catenin signaling cascades, locks the kidney into this fibrotic trend. These myofibroblasts excessively deposit extracellular matrix proteins, including collagen types I and III, and fibronectin, into the tubulointerstitium (76). If the patient survives the acute phase of the pulmonary infection and the initial AKI resolves, the molecular crosstalk initiated by the lung injury can leave a lasting structural legacy, manifesting as chronic kidney disease, persistent proteinuria, and a permanently reduced nephron mass (68,77,78).

Conclusion

In summary, the renal dysfunction observed in the context of COVID-19-induced pulmonary injury is not a mere passive consequence of systemic hypoperfusion or hemodynamic instability. Rather, it is the result of a highly active, continuous, and devastating molecular crosstalk along the lung-kidney axis. The injured lung acts as a pathological endocrine organ, continuously discharging a toxic payload of pro-inflammatory cytokines, complement activators, pro-coagulant factors, and, crucially, nanoscale exosomes into the systemic circulation. These soluble and vesicular mediators systematically target the renal microvasculature and parenchymal cells, inducing profound endothelial dysfunction, triggering lethal apoptotic, ferroptotic, and pyroptotic cell death pathways, and driving the epigenetic reprogramming that leads to maladaptive repair and fibrosis. Identification of intricate molecular mechanisms of this lung-kidney crosstalk, particularly the underappreciated role of exosomal signaling and specific intracellular inflammatory cascades, is necessary; since, it not only elucidates the complex pathophysiology of multi-organ failure in severe viral infections but also highlights novel, highly specific therapeutic targets. Future interventions aimed at intercepting these molecular messengers, inhibiting the biogenesis or uptake of pathogenic exosomes, or

selectively blocking the downstream intracellular signaling cascades and preserving renal function in the face of severe pulmonary injury.

Authors' contribution

Conceptualization: Sousan Mohammadi Kebar.
Data curation: Saeed Hosseininia.
Investigation: Sousan Mohammadi Kebar.
Resources: Saeed Hosseininia.
Supervision: Sousan Mohammadi Kebar.
Validation: Sousan Mohammadi Kebar.
Visualization: Sousan Mohammadi Kebar.
Writing–original draft: Both authors.
Writing–review and editing: Both authors.

Conflicts of interest

The authors declare that they have no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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