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REVIEW

Dual Regulatory Roles of Pannexin 1 in the Pathogenesis and Recovery of Sepsis-Induced Acute Lung Injury

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Abstract: Sepsis-associated acute lung injury (ALI) is a leading cause of death in sepsis patients, characterized by complex pathogenesis involving inflammatory responses, immune dysregulation, cell death, and coagulation system activation. Despite advancements in critical care, specific drugs or therapies for ALI remain unavailable. Pannexin 1 (Panx1), a widely expressed membrane channel protein, has emerged as a pivotal regulator in the onset and progression of sepsis-induced ALI. During the early stages, Panx1 amplifies inflammatory responses by promoting immune cell activation, chemotaxis, cytokine release, and coagulation. Simultaneously, it contributes to epithelial and endothelial cell damage through apoptosis, pyroptosis, and ferroptosis. Conversely, in the recovery phase, Panx1 plays a reparative role, facilitating inflammation resolution, epithelial cell proliferation, and tissue regeneration. This review highlights Panx1's dual role, presenting it as a promising therapeutic target. Preclinical models have demonstrated a key therapeutic advantage: the potential for stage-specific interventions. This strategy involves pharmacological inhibition to mitigate early-stage damage and potential activation to promote later-stage repair. However, a critical knowledge gap remains in defining the precise therapeutic window for such interventions and translating these findings into clinical practice. By elucidating Panx1's complex mechanisms, we aim to provide a theoretical basis for novel therapeutic strategies, addressing a critical unmet need in sepsis-induced ALI management and improving patient outcomes.

Keywords: pannexin 1, ATP, sepsis, acute lung injury, inflammation, cell death

Introduction

Sepsis, a long-recognized and complex syndrome, has historically drawn significant attention in medicine. It is now generally defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.[1] Each year, an estimated 49 million people worldwide develop sepsis, resulting in approximately 11 million deaths. This accounts for 20% of global mortality and surpasses the combined deaths from prostate cancer, breast cancer, and HIV infection.[2] Among the various organs impacted by sepsis, the lungs are particularly vulnerable.[3] Sepsis-associated acute lung injury (ALI), which can progress to acute respiratory distress syndrome (ARDS), remains a leading cause of mortality in sepsis patients, with reported rates ranging from 47.6–70%.[4–6] Despite advances in supportive care, mortality rates for sepsis-induced ARDS remain alarmingly high at 40–50%. A large 2024 multicenter cohort study that included 1,574 patients with sepsis-associated ARDS reported an overall 30-day mortality rate of 33.1%, a figure that rose to 45.5% in those with severe ARDS, underscoring the grave prognosis.[7]

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The core of sepsis pathogenesis is an exaggerated immune response triggered by pathogenic microbes and/or damage-associated molecular patterns. This response leads to excessive production of pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6) and activation of the complement and coagulation systems.[1] Concurrently, anti-inflammatory pathways are also upregulated, with the potential to induce immune cell dysfunction and increased susceptibility to secondary infections. Endothelial injury and dysfunction, microvascular thrombosis, and mitochondrial metabolic failure further contribute to impaired tissue oxygenation and multi-organ dysfunction.[1,8] The pathophysiological mechanisms of sepsis-induced ALI/ARDS involve a complex interplay between disseminated inflammatory signals, innate and adaptive immune cells, and extensive crosstalk with coagulation pathways.[1,8] In the early stages, pro-inflammatory mediators increase alveolar-capillary membrane permeability, resulting in protein-rich edema fluid entering the alveolar spaces and impairing gas exchange. Neutrophils and monocytes are recruited to the lungs, releasing proteases, reactive oxygen species, and additional cytokines that perpetuate epithelial and endothelial damage. This process disrupts both alveolar type I cells, critical for gas exchange, and alveolar type II cells, responsible for surfactant production and alveolar repair, leading to the characteristic diffuse alveolar damage observed in ARDS. As the syndrome progresses, alveolar flooding and hyaline membrane formation compound the respiratory insufficiency. Despite supportive measures, including protective mechanical ventilation, prone positioning, and extracorporeal membrane oxygenation, specific pharmacological therapies to prevent or reverse these events are still lacking.[9] Recent trials targeting IL-6 receptors showed limited benefits. The COVINTOC trial found no significant reduction in disease progression with tocilizumab versus standard care (9% vs 13%, p=0.42).[10] The SARICOR trial showed a non-significant trend toward less ARDS with sarilumab (13% vs 28%, p=0.09).[11] These results underscore the urgent need for new therapeutic targets.

Given the complexity of sepsis-induced ALI/ARDS, numerous biological pathways are implicated in disease progression. Among these, ongoing inflammatory responses, injury to alveolar epithelial and endothelial cells, and coagulation abnormalities are considered pivotal drivers of the pathobiology. Emerging evidence suggests that targeting pannexin (Panx) 1, a "universal" player in many of these processes,[12–14] could offer a new therapeutic avenue. Therefore, this review aims to explore the dual regulatory functions of Panx1 in sepsis-induced acute lung injury, and to discuss its stage-specific roles, underlying molecular mechanisms, and therapeutic implications.

The Structure and Function of Pannexin (Panx)

Discovery of Panx

The Panx family was first identified in the central nervous system of the leech by Panchin et al in 2000. Its sequence resembled that of the innexins family of gap junction proteins, initially leading researchers to classify Panx as a second innexins family in the human genome. However, subsequent studies showed that Panx primarily functions outside gap junctions, distinguishing it functionally from innexins.[15] Given Panx's widespread expression in mammalian cells,[16] Panchin et al proposed renaming it "Pannexin" (from the Greek "pan", meaning "universal") to differentiate it from innexins.[17] The three members of the Panx family—Panx1 (47.6 kDa), Panx2 (74.4 kDa), and Panx3 (44.7 kDa)—are located on human chromosomes 11q14.3, 22q13.31–13.33, and 11q24.2, respectively, sharing 50–60% sequence similarity.[15,17,18]

Panx1 is the most widely expressed member, found in mammalian solid organs, blood, and immune cells.[16] Panx2 is primarily expressed in the central nervous systems of humans and rodents,[19] while Panx3 is predominantly found in adult bone, cartilage, and skin.[20] While Panx proteins are mainly expressed on cell membranes, Panx1 and Panx3 can also be found in the ER.[21] Additionally, Panx2 has been identified on intracellular vesicle membranes (Figure 1).[22] Panx1 exists in multiple splice variants, with exon 5 producing subtypes Panx1a and Panx1b, and new splice variants, Panx1c and Panx1d, lacking portions of their sequence.[18,23]

Structure of Panx

Panx proteins are composed of four transmembrane domains, two extracellular loops, one intracellular loop, and intracellular N-terminal and C-terminal regions. Although Panx shares structural similarities with connexins (Cx), it has no sequence homology and distinct functional properties.[24] Within the Panx family, the N-terminal domain is highly

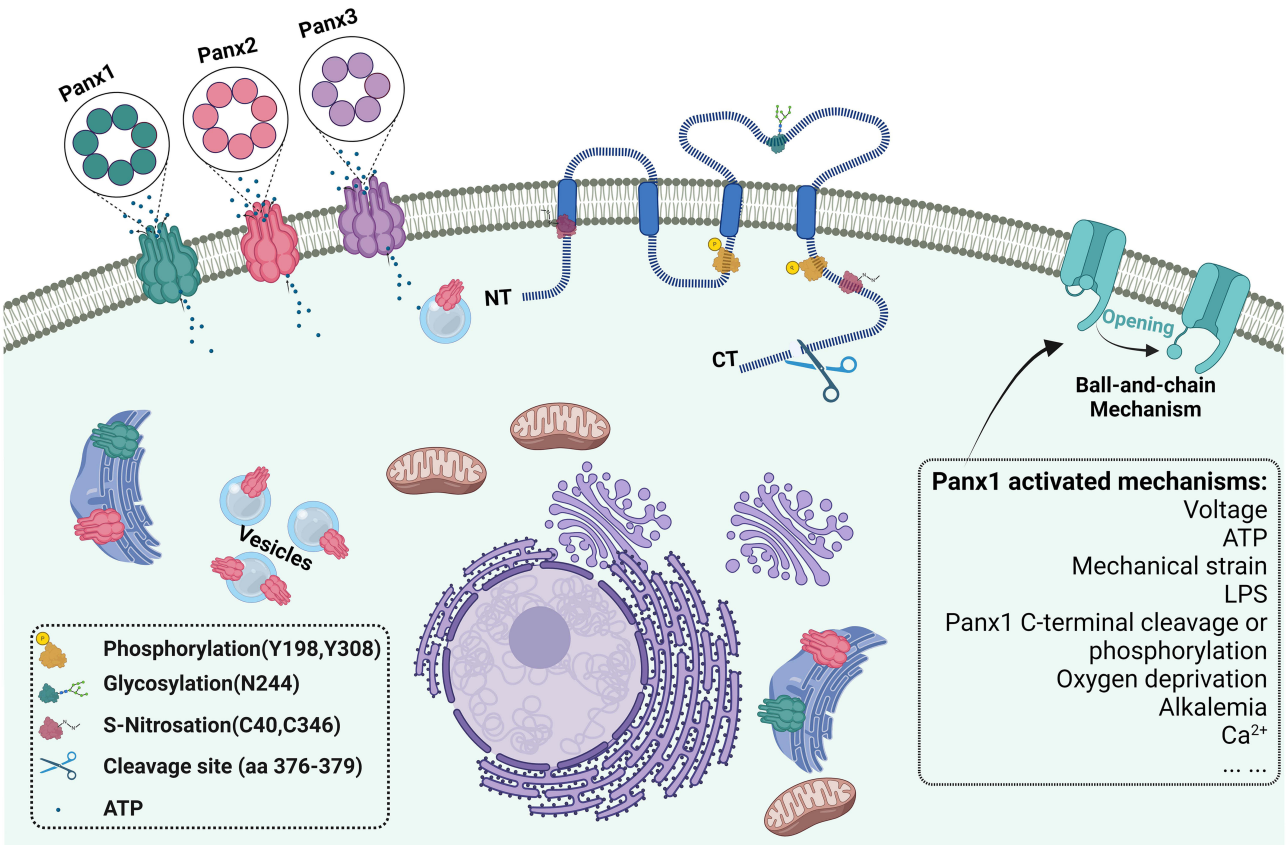

Figure 1 Distribution, structure, modifications, and activation mechanisms of the pannexin family. The pannexin (Panx) family consists of four transmembrane domains, two extracellular loops, one intracellular loop, a cytoplasmic N-terminal domain, and a C-terminal domain. Pannexins exhibit oligomeric diversity: Panx1 demonstrates structural plasticity with predominant heptameric assemblies under physiological activation, Panx2 functions canonically as ATP-permeable heptamers, while Panx3 adopts context-dependent hexameric configurations. While Panx proteins are predominantly expressed on the plasma membrane, Panx1 and Panx3 are also enriched in the ER, and Panx2 is highly expressed on intracellular vesicle membranes. Key modifications of Panx1 include phosphorylation, glycosylation, nitrosylation, and C-terminal cleavage. Conditions that activate Panx1 and promote channel opening include ATP stimulation, voltage changes, mechanical stress, C-terminal modifications (phosphorylation, cleavage, and nitrosylation), hypoxia, alkalosis, and intracellular Ca^{2+} overload.

conserved. In contrast, the C-terminal region exhibits significant sequence variability. This variability provides sites for post-translational modifications and regulatory mechanisms that are crucial for Panx activity, particularly in disease contexts.[16,18,24,25] Initial studies suggested Panx1 and Panx3 assemble as hexamers.[17] Emerging cryo-EM structural evidence now establishes that Panx1 predominantly forms heptamers,[26,27] with functional studies demonstrating both hexameric and heptameric conformations exhibit channel activity depending on activation states.[28] While Panx2 was previously proposed to assemble as octamers,[29] recent high-resolution structures reveal its canonical assembly as a heptamer with ATP-permeable characteristics.[30] Notably, multiple pannexin isoforms demonstrate structural plasticity, with hexameric configurations observed under specific experimental conditions.[28,31] Functional studies using concatenated constructs reveal several critical stoichiometric implications. First, both hexameric and heptameric Panx1 channels can be activated by C-terminal truncation and GPCR stimulation, although heptamers show higher conductance and ATP permeability.[28] Second, Panx2 heptamers maintain a constitutively open state, with extracellular arginine filters governing substrate selectivity.[30] Third, Panx3 exhibits context-dependent oligomerization, acting either as a hexameric channel or as a non-canonical Golgi scaffold to mitigate vascular oxidative stress.[32] These findings collectively suggest pannexin oligomerization is dynamically regulated, with heptamers representing the predominant functional state under physiological conditions (Figure 1).

Unlike Cx proteins, which form gap junction channels between adjacent cells, Panx channels serve both gap junctional and non-gap junctional functions. Early evidence of Panx1 gap junction functionality came from Bruzzone et al, who observed intercellular currents in paired Xenopus oocytes after 24–48 hours of pairing, suggesting low

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efficiency in gap junction formation.[33] Subsequent studies, including Panx1-green fluorescent protein transfection experiments in glioblastoma and prostate cancer epithelial cells, demonstrated dye coupling and Ca^{2+} transfer via Panx1 gap junction channels.[34,35] However, robust evidence for Panx1-mediated gap junction formation in primary cells and other cell types remains elusive.

Increasing evidence supports the non-gap junctional functions of Panx1:

1. Immunohistochemical staining does not reveal the typical punctate pattern seen in gap junctions, as observed in previous studies using mammalian cell lines such as HeLa cells expressing Panx1. Specifically, no gap junction plaques were detected, and no transfer of small fluorescent dyes or neurobiotin occurred in a scrape-loading assay. These observations were consistent in other experimental models, including cultured oligodendrocytes, astrocytes, and hippocampal neurons, where Panx1 immunoreactivity was observed intracellularly but not in gap junction plaques.[36,37]
2. Panx1 is highly expressed in non-junctional single cells like erythrocytes, macrophages, and monocytes.[38,39] In erythrocytes, it acts as a mechanosensitive ATP release channel, triggered by low oxygen or shear stress, independent of vesicles. While erythrocytes lack gap junctions, Panx1-mediated ATP release can be inhibited by carbenoxolone, and fluorescent tracer uptake confirms its role in ATP transport.[38] In neutrophils, Panx1 regulates chemotaxis by mediating ATP release at the front, activating P2Y2 receptors to enhance migration. At the rear, it facilitates A2A receptor activation, increasing cAMP and PKA signaling to inhibit chemoattractant signaling. Panx1 inhibition disrupts neutrophil polarization and migration, underscoring its role in coordinating excitatory and inhibitory chemotactic signals.[39]
3. In polarized human airway epithelia, Panx1 localizes exclusively to the apical membrane, independent of lateral gap junctions. Air-liquid interface (ALI) culture studies revealed that hypotonic stress triggers rapid ATP release, which was suppressed by ~60% using pannexon inhibitors or Panx1-specific knockdown. These conserved responses across human donor-derived models establish Panx1 as a critical apical ATP-release channel, functionally distinct from gap junction activity.[40]
4. In rodent hippocampal and cortical principal neurons, Panx1 exhibits a striking postsynaptic localization, accumulating at postsynaptic densities and co-distributing with the scaffolding protein PSD-95. Light/electron microscopy and co-localization studies in Xenopus oocytes and neuronal models confirmed that Panx1 does not form gap junctions but instead assembles as unopposed hemichannels (pannexons) at postsynaptic sites. This synaptic compartmentalization, conserved across multiple experimental preparations, identifies Panx1 as a novel component of the postsynaptic protein complex, implicating its role in non-junctional signaling.[41]
5. In vertebrate systems, Panx1 undergoes N-glycosylation at Asn-254, a post-translational modification critical for plasma membrane trafficking but incompatible with gap junction assembly. Structural studies (electron microscopy) and site-directed mutagenesis in Xenopus and mammalian models revealed that glycosylation sterically blocks intercellular channel docking, forcing Panx1 to function as unpaired hemichannels distributed across the plasma membrane. This regulatory mechanism, conserved across tissues, positions glycosylation as a key determinant steering Panx1 toward non-junctional roles.[25]

The non-gap junctional functions of Panx1 and their disease relevance have redefined research priorities. Panx1 plays critical roles in non-junctional cells, such as erythrocytes,[38] neutrophils,[39] and neurons.[41] It also has direct associations with epilepsy, ischemic injury, and cancer.[14,21,42] Consequently, the research focus has shifted from historical debates about gap junction competency to the therapeutic targeting of Panx1 hemichannels.[34,35] For instance, glycosylation at Asn-254 enforces Panx1 assembly into functional monomers via steric hindrance,[25] while inhibitors like carbenoxolone alleviate neuroinflammation by blocking these channels.[38,39] These findings establish Panx1's distinct channelopathy mechanisms, terminating functional analogies to classical connexins.[37]

Physiological Functions of Panx1

Unlike Cx hemichannels, Panx1 typically exists as a monomeric channel. Studies indicate that it may be the largest known monomeric channel protein, featuring a pore size sufficient for the dynamic transport of molecules and ions up to

1.5 kDa between intracellular and extracellular compartments, including ATP, glutamate, arachidonic acid, and other nucleotides.[15,43,44] These signaling molecules can exert autocrine, paracrine, or endocrine effects to activate downstream signaling pathways and modulate cell function.[42,45] In standard dye influx assays, Panx1 channels permit passage of both positively and negatively charged fluorescent probes (eg, YO-PRO-1 and fluorescein yellow),[17] and can be blocked by multiple inhibitors, such as probenecid and specific inhibitory peptides.[46–48] Together, these inhibitors, along with dye permeability assays, constitute essential experimental tools for investigating the properties and biological functions of Panx1.

Among the molecules that traverse Panx1, ATP not only serves as the classic intracellular energy currency but also as a critical chemotactic and inflammatory mediator, with multifaceted regulatory roles during ALI/ARDS in sepsis.[42,49] On the one hand, ATP and other damage-associated molecular patterns facilitate immune cell recruitment and amplify early inflammatory responses. On the other hand, when inflammation enters the resolution phase, extracellular ATP modulates macrophage activation to enhance clearance of damaged cells and tissue debris, thereby mitigating excessive inflammation and promoting tissue repair.[46] Panx1 is considered one of the principal channels mediating rapid ATP release without depending on vesicular exocytosis, owing to its large pore diameter and specific channel characteristics.[46]

In addition to promoting ATP release, Panx1 also plays a key role in maintaining intracellular Ca^{2+} homeostasis through multiple mechanisms. Excessive Ca^{2+} influx or release often leads to mitochondrial dysfunction and cellular injury, especially in sepsis. First, extracellular ATP released via Panx1 may activate P2X7R, thereby mediating Ca^{2+} influx; meanwhile, the open Panx1 channel itself can also directly allow Ca^{2+} to flow across the membrane.[42,50] Second, ATP and other signals can increase IP_3 levels, which in turn promote Ca^{2+} release from the ER. Cytosolic Ca^{2+} accumulation further enhances Panx1 channel opening, forming a positive feedback loop.[50] Third, Panx1 channels residing on the ER membrane may directly influence ER Ca^{2+} storage and release, as shown by increased ER Ca^{2+} permeability in Panx1-overexpressing cells.[51] Under septic conditions, Panx1-mediated disruption of Ca^{2+} homeostasis can intensify the inflammatory response and exacerbate cellular injury, ultimately aggravating multiple organ dysfunction including lung injury.

Mechanisms of Panx1 Activation

As a channel protein, Panx1's open or closed state is regulated by membrane potential changes. Panx1 channels can also be activated under various physiological and pathological conditions relevant to sepsis-induced ALI/ARDS (Figure 1). These conditions include:

1. **Mechanical Stress**: Mechanical stress is a significant cause of alveolar injury in ALI/ARDS, particularly in patients undergoing mechanical ventilation.[9] Panx1's mechanosensitivity has been demonstrated in electrophysiological experiments, where negative pressure stimuli activated Panx1 in oocytes.[52,53] Similar findings have been reported in red blood cells,[38] vascular endothelial cells,[54] cardiac myocytes and fibroblasts,[55] skeletal muscle cells,[56] and smooth muscle cells.[57]
2. **Ca2+**: As previously mentioned, ATP-induced Ca^{2+} overload promotes Panx1 channel opening and ATP release.[50] Intracellular Ca2+ overload contributes to mitochondrial dysfunction and cell damage in ALI/ARDS.[58]
3. **ATP**: ATP acts in autocrine and paracrine modes to stimulate Panx1 via purinergic receptors, creating a positive feedback loop described as "ATP-induced ATP release".[48,59,60] Elevated ATP levels have been observed in the blood of sepsis-induced ALI/ARDS patients due to Panx1 channel activation and cell injury.[49,61]
4. **Post-Translational Modifications**: Modifications such as phosphorylation, N-glycosylation, S-nitrosylation, and C-terminal cleavage regulate Panx1 channel gating.[62] For example, Src family kinases phosphorylate conserved tyrosine residues (eg, Y308 and Y198), promoting channel opening.[63–65] N-glycosylation facilitates Panx1 trafficking to the membrane, although its role in gating remains unclear.[25,66] Additionally, S-nitrosylation inhibits ATP release through Panx1,[67] while C-terminal cleavage by caspases results in constitutive channel opening, contributing to apoptosis.[44,68]
5. **pH**: Kurtenbach et al demonstrated that Panx1 is a pH-sensitive channel, activated by elevated pH levels. This property has implications for ALI/ARDS, where acidosis and alkalosis are common.[69]

6. **Other Factors**: Ischemia, hypoxia, hyperinsulinemia, nitric oxide, N-methyl-D-aspartate receptor activation, potassium levels, and ubiquitination have been implicated in Panx1 activation. However, their roles in ALI/ARDS remain uncertain and warrant further investigation.[70–74]

Potential Roles and Mechanisms of Panx1 in Sepsis-Induced ALI/ARDS

Panx1 in Inflammasome Formation and Pro-Inflammatory Cytokine Release

Excessive inflammatory responses are hallmarks of sepsis-induced ALI/ARDS and several other diseases.[1,75] In the early stages of sepsis, stimuli such as ATP promote the maturation and release of pro-inflammatory cytokines, primarily TNF-α, IL-1β, and IL-18. Experimental studies employing lipopolysaccharide (LPS)-stimulated murine macrophages, human monocytic leukemia cells, and alveolar macrophages to establish an ex vivo sepsis-induced acute lung injury model have demonstrated that Panx1 channel activation is indispensable for IL-1β and IL-18 maturation and secretion.[47] In myeloid cells, apoptosis-associated metabolic products released via Panx1 channels induce the expression of pro-inflammatory cytokine genes.[14,42] Notably, although this investigation primarily utilized myeloid cells rather than native alveolar macrophages, the identified Panx1-dependent regulatory mechanisms governing cytokine release are mechanistically conserved and likely constitute a central driver of alveolar inflammation and tissue injury in sepsis-induced ALI/ARDS pathophysiology. This concept is supported by recent work in asthma models, a disease with inflammatory pathways similar to ALI/ARDS. In these models, delivering the Panx1 antagonist 10Panx1 via adeno-associated viral vectors reduced extracellular ATP levels in bronchoalveolar lavage fluid. This intervention also attenuated airway hyperresponsiveness and suppressed eosinophilic inflammation and Th2 responses by modulating T cell activation.[76] These findings highlight the translational potential of targeting Panx1-mediated ATP release to mitigate pulmonary inflammation, a mechanism directly relevant to sepsis-induced ALI/ARDS.[77,78] Notably, Panx1's role in inflammatory amplification extends beyond cytokine secretion to encompass NLRP3 inflammasome regulation —a critical pathophysiological axis driving both cytokine maturation (notably IL-1β and IL-18) and alveolar injury progression in sepsis-associated ALI/ARDS. This inflammasome activation cascade operates through two Panx1-coupled phases:

1. Damage- or pathogen-associated molecular patterns bind TLRs, activating the NF-κB signaling pathway and inducing production of IL-1β and IL-18 precursors.[42] NF-κB can also be triggered by TNF family cytokines, CD40 ligands, and other factors.[42]
2. NLRP3 subsequently recruits and activates caspase-1, cleaving the precursors into active IL-1β and IL-18, which are then released into tissues to drive inflammation.[79] Panx1 contributes predominantly to this second step by releasing ATP, thereby activating P2X7R and inducing intracellular Ca^{2+} overload and K^+ efflux.[50,59] Potassium efflux, in turn, activates NLRP3, further promoting inflammation (Figure 2).[47,80] This ATP-P2X7R axis has been further validated in lung-specific injury models. For instance, in lung ischemia-reperfusion injury (IRI)—a condition characterized by ALI-like inflammation and edema—endothelial Panx1 channels mediate ATP efflux to activate the P2Y2R-TRPV4 pathway, exacerbating vascular permeability and inflammation.[81] Genetic disruption of endothelial Panx1 or P2Y2R significantly attenuated lung edema and NLRP3-driven inflammatory responses in this model, providing mechanistic parallels to sepsis-induced ALI/ARDS.[82]

The fundamental role of Panx1 in NLRP3 activation has been observed in various models, including those for neuronal,[83] liver,[84] and kidney injury.[85] This same ATP-dependent, P2X7R-mediated pathway is also highly relevant to lung pathology. Specifically, experiments in alveolar macrophages underscore Panx1's importance in regulating IL-1β and IL-18 secretion.[47] The aforementioned studies in asthma and lung IRI further bridge these mechanisms to pulmonary systems, demonstrating that Panx1-driven ATP release orchestrates both innate (NLRP3 activation) and adaptive (T cell modulation) immune components in diverse lung injury models.[76,82] In the context of sepsis-induced ALI/ARDS, alveolar macrophages are pivotal to local immune responses, and dysregulated Panx1 activity can intensify inflammatory signaling through NLRP3. Thus, while some studies address models of neuronal or kidney injury, their mechanistic findings—along with emerging evidence from pulmonary disease models—strongly suggest that Panx1 exerts

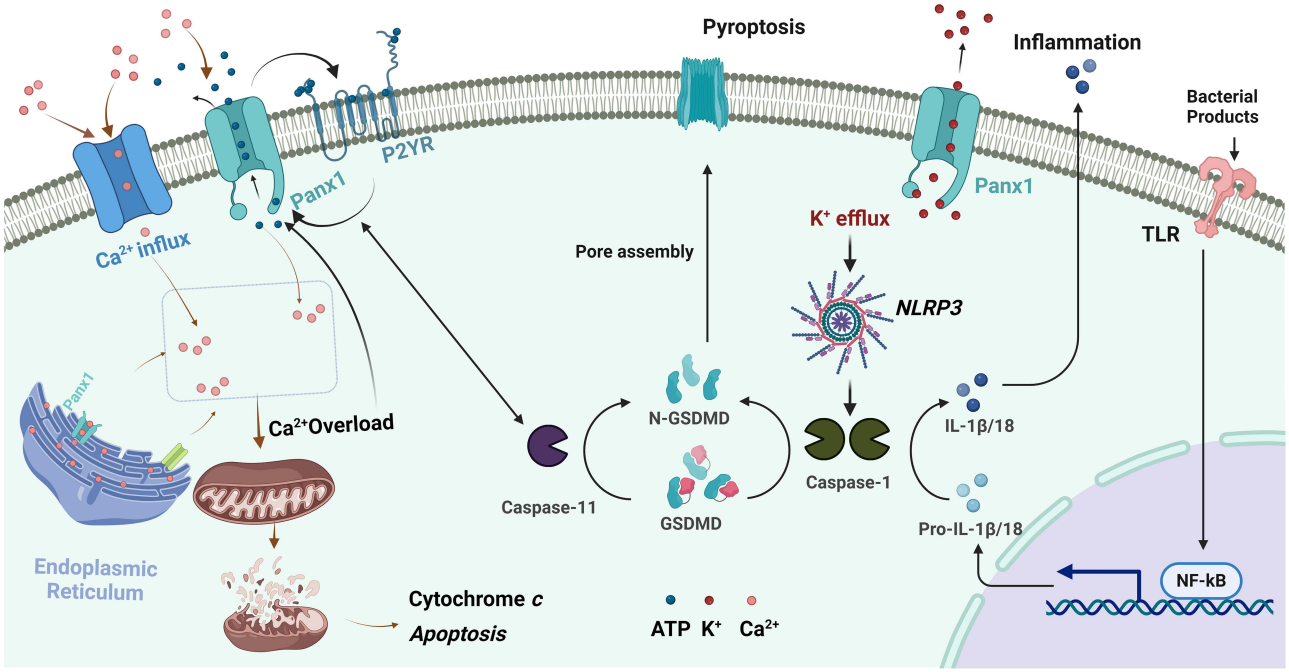

Figure 2 Pannexin 1 activation of inflammasomes, apoptosis, and pyroptosis. Upon activation, pannexin (Panx) 1 channels open to release ATP, which stimulates purinergic receptors, inducing Ca^{2+} influx and ER Ca^{2+} release. Intracellular Ca^{2+} overload establishes a positive feedback loop that further activates Panx1 and triggers the mitochondrial apoptosis pathway. Concurrently, Panx1-mediated K^+ efflux activates inflammasomes, recruiting Caspase-1 to cleave gasdermin D (GSDMD) and pro-inflammatory cytokines IL-1β/18, thereby initiating inflammatory responses and pyroptosis. Additionally, Panx1 enhances Caspase-11-mediated cleavage of GSDMD through purinergic receptor activation, leading to membrane perforation and pyroptosis.

a comparable effect on inflammasome-related processes within the alveolar microenvironment, exacerbating pulmonary inflammation and contributing to ALI/ARDS pathophysiology.

Panx1 in Immune Cell Recruitment, Activation, Chemotaxis, and Adhesion

Leukocytes in ALI/ARDS patients exhibit enhanced chemotaxis, high metabolic activity, delayed apoptosis, and unique transcriptional profiles, making them key therapeutic targets.[9,86] Panx1 regulates leukocyte generation in the bone marrow, activation, migration, and adhesion to sites of inflammation.[39]

Macrophages (Mø) are nearly ubiquitous in tissues and play essential roles in tissue repair, immune responses, and migration. Macrophage fusion into multinucleated giant cells (MGCs) is a feature of various diseases, including lung injury.[81,87,88] Lemaire et al demonstrated that P2X7R is indispensable for macrophage fusion, a process inhibited by P2X7R blockers such as oATP and KN-62. ATP release and its metabolite adenosine mediate this effect. As a component of the P2X7R signaling pathway, Panx1 directly contributes to ATP release.[74] Evidence from Panx1-mimetic peptides and Panx1-knockout mice confirms that Panx1 is crucial for MGC formation, potentially through a mechanism that may deviate from P2X7R's classic pathway.

Panx1 also mediates T-cell activation, likely via ATP release that stimulates P2X7R and sustains MAPK signaling. Blocking Panx1 reduces MAPK activation, suppressing T-cell activity.[89] In inflammatory bowel disease models, Panx1 inhibition limits T-cell responses, curbing cytokine release and attenuating inflammation.[89,90] While the role of Panx1 in B-cell activation remains unclear,[91] its function in T-cell-driven inflammation may hold therapeutic value for sepsis-induced ALI/ARDS.

Neutrophil chemotaxis, which drives neutrophil migration to the lungs in ALI/ARDS, is tightly regulated by Panx1.[39] Migration requires front-based stimulatory signals and rear-based inhibitory signals. Panx1-mediated ATP release activates P2Y receptors at the leading edge, driving forward migration. Concurrently, Panx1 influences inhibitory signals by releasing ATP at the rear, polarizing A2A receptors and initiating cAMP/PKA signaling.[39]

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Panx1 further governs leukocyte-endothelial adhesion and transendothelial migration by releasing ATP in response to TNF-α stimulation. TNF-α binds its receptor, activating Src family kinases that phosphorylate Panx1 and promote ATP release.[14,39,65] The released ATP amplifies NF-κB signaling, upregulating endothelial adhesion molecules such as P-selectin. These effects are diminished in Panx1-knockout mice but can be restored by exogenous ATP, underscoring Panx1's importance in leukocyte adhesion and migration.[65] Notably, TNF-α-induced NF-κB activation also augments Panx1 expression in endothelial cells.[92]

Emerging research indicates that Panx1 may contribute to endothelial permeability and neutrophil transendothelial migration during TNF-α-induced inflammation. ATP released by Panx1 is hydrolyzed by CD39 into adenosine, which activates A2A receptors. In turn, adenosine stimulates transient receptor potential vanilloid 4 channels, downregulating tight junction proteins, increasing endothelial permeability, and facilitating neutrophil passage across the endothelium.[12]

Panx1 in Cell Death

Damage to alveolar epithelial and vascular endothelial cells, disrupting the alveolar-capillary barrier, is central to sepsis-induced ALI/ARDS pathogenesis.[1] Panx1 influences multiple cell death pathways, including apoptosis, pyroptosis, ferroptosis, and autophagy.[93]

1. Apoptosis. Apoptosis involves caspase-mediated cleavage of proteins to drive programmed cell death.[94] Panx1 contributes to apoptosis in various ways:[12,13,21,42,95]

• Early in apoptosis, Panx1 activation increases membrane permeability. Damaged cells release ATP through Panx1 channels, resulting in energy depletion and cell death.[96]

• Panx1 channel opening promotes excessive Ca^{2+} influx and ER Ca^{2+} release, activating mitochondria to secrete cytochrome c, thereby triggering apoptosis.[51,96,97]

• Panx1 is a substrate of caspase-3 and −7, which cleave its C-terminus and lock the channel open. This leads to sustained ATP release and amplifies apoptosis via positive feedback.[44,98–100] Furthermore, Panx1 generates an ATP-derived "find-me" signal[46] that attracts phagocytes to clear cell debris (Figure 2).[42,95]

1. Pyroptosis. Pyroptosis is an inflammatory form of cell death involving caspase-1, −4, −5, and −11, which cleave gasdermin proteins to create membrane pores and cause cell lysis. Similar to caspase-3 and −7, caspase-11 cleaves Panx1's C-terminal domain, causing sustained channel opening and continuous ATP release. Additionally, intracellular LPS plus extracellular ATP sensitize P2X7R, promoting membrane permeabilization and pyroptosis.[99] During pyroptosis, caspase-11 facilitates P2X7R activation, instigating Panx1 channel opening and K^+ efflux to activate NLRP3 and release IL-1β/IL-18.[99] Thus, Panx1 may influence pyroptosis both through direct P2X7R-mediated mechanisms and by NLRP3 recruitment of caspases (Figure 2).
2. Autophagy. Also termed type II programmed cell death, autophagy involves lysosomal degradation of damaged or aging cellular components. Although it generally confers protection, especially under homeostatic conditions, excessive autophagy may lead to cell death.[101] In sepsis-induced ALI/ARDS, autophagy critically shapes inflammation and cell survival.[101] Studies indicate a potential relationship between Panx1 and autophagy. During immunogenic cell death, LAMP1 and Panx1 colocalize on the cell membrane, and knockout of either protein reduces expression of the other. Moreover, caspase inhibition abolishes Panx1-LAMP1 colocalization, implying complex interplay that warrants further study. In a CLP-induced murine sepsis model, Panx1 modulated neuron pyroptosis through autophagy, and Panx1 inhibition was neuroprotective.[102] Likewise, silencing Panx1 promoted autophagy in cisplatin-resistant testicular cancer cells.[103] Despite these insights, Panx1's autophagic role in ALI/ARDS demands further investigation.
3. Ferroptosis. Ferroptosis is a form of iron-dependent cell death involving lipid peroxidation of unsaturated fatty acids in cell membranes.[104] It notably contributes to alveolar epithelial and endothelial cell death in sepsis-induced ALI/ARDS.[104] The link between Panx1 and ferroptosis is an emerging area of research, with accumulating evidence suggesting Panx1 acts as a key regulator. Mechanistically, our laboratory research demonstrated that

Panx1 knockdown in HK-2 cells reduces erastin-induced lipid peroxidation and the expression of ferroptosis-associated proteins, indicating a pro-ferroptotic role for Panx1.[105] Subsequent studies have corroborated this function in other disease models. For example, in preeclampsia, Panx1 was shown to directly advance trophoblast ferroptosis.[106,107] Similarly, in inflammatory bowel disease, Panx1 exacerbates colitis by enhancing ferroptosis in macrophages.[108] Crucially, this connection is also being established within the context of lung pathology. Recent bioinformatic studies on lung adenocarcinoma have identified PANX1 as a key component of a ferroptosis-related gene signature that predicts patient prognosis.[109] Another study proposed PANX1 as a potential antigen for mRNA vaccines designed to induce ferroptosis in lung cancer cells.[110] Taken together, these findings strongly suggest that the Panx1-ferroptosis axis is a critical mechanism in tissue injury and inflammation. Elucidating its precise role in sepsis-induced ALI/ARDS is therefore a promising new research direction.

Panx1 and Coagulation System Activation

Coagulation system activation is a defining feature of sepsis-induced ALI/ARDS, often contributing to pathological thrombus formation and multi-organ failure.[111] Extensive research has assessed anti-platelet and anticoagulant therapies in sepsis. As early as the 1990s, glycoprotein IIb/IIIa inhibitors decreased mortality in endotoxemic rabbits.[112] In animal models of ARDS, anticoagulants reduced pulmonary edema and improved survival.[113] A recent randomized controlled trial demonstrated that aerosolized heparin prevented ARDS,[114] while a meta-analysis of 34 studies found aspirin lowered all-cause mortality in COVID-19.[115] Anticoagulant or anti-platelet strategies improve oxygenation, shorten ventilation times, and reduce mortality.[116,117]

Platelet activation underlies thrombus formation, and Panx1 is a key platelet regulator. Human platelets express only glycosylated Panx1 on their plasma membranes. Phosphorylation of Panx1 at Y198 and Y308 triggers channel opening, enabling ATP release and subsequent P2X1 receptor activation, driving Ca^{2+} influx, platelet aggregation, and thrombosis.[118] The Src family kinase-platelet receptor axis serves as Panx1's primary activation pathway (Figure 3), while PKC and Akt play secondary roles.[119] Panx1 inhibitors such as probenecid, mefloquine, and 10Panx1 peptides reduce collagen-induced platelet aggregation.[43] Panx1-knockout mice display prolonged bleeding times and decreased thrombus formation following collagen/epinephrine injection or $FeCl_3$-induced vascular injury.[120] These observations

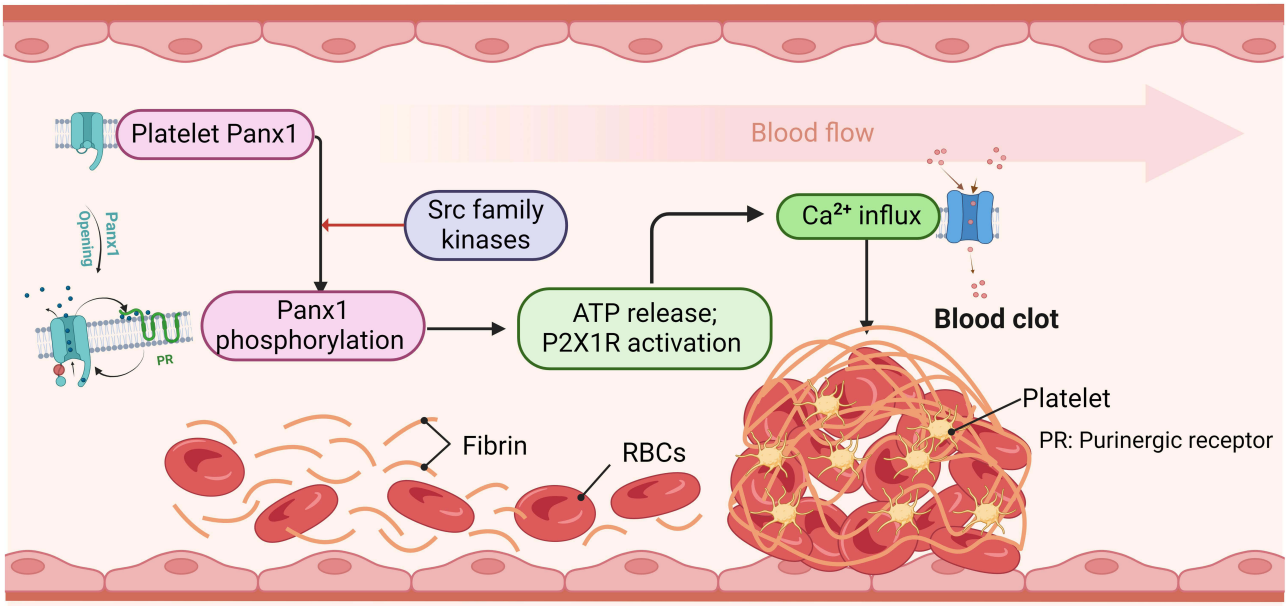

Figure 3 Schematic representation of pannexin 1 in platelet activation and thrombosis. Phosphorylation and activation of pannexin (Panx) 1 channels on the platelet membrane facilitate ATP release, which activates purinergic receptors and triggers intracellular Ca^{2+} influx. This cascade promotes platelet activation and aggregation, driving thrombus formation.

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pinpoint Panx1 as a central player in hemostasis and thrombosis, making it a promising target for intervention in sepsis-induced ALI/ARDS.

Panx1 in Inflammation Resolution and Epithelial Cell Regeneration

During the recovery phase of sepsis-induced ALI/ARDS, resolving inflammation and repairing damaged tissues are crucial for restoring organ function.[121] In severe ARDS patients, epithelial cell damage, inadequate repair, and persistent inflammation sustain acute respiratory failure and elevated mortality.[122] Understanding mechanisms that foster tissue repair and inflammation resolution is vitally important. Emerging evidence suggests that Panx1, via ATP release, can facilitate airway epithelial repair and immune homeostasis after tissue injury.[123,124]

Although Panx1-mediated ATP release is often considered a danger signal, it plays an essential role in clearing dead cells and debris, a key step in resolving inflammation. Downregulation of pro-inflammatory cytokines and upregulation of anti-inflammatory or growth factors further drive resolution. P2X7R activation supports monocyte secretion of pro-angiogenic factors,[123,124] whereas pyrophosphate (a product of ATP hydrolysis) attenuates TLR-mediated inflammatory signaling.[125] The ATP breakdown product adenosine also suppresses inflammation via A2B receptors to promote IL-10 release, as shown in murine colitis models.[126] In rodent ALI models, adenosine receptor activation decreases apoptosis and improves lung function.[127,128]

Alveolar epithelial cell proliferation is key for functional recovery. Lucas et al found that Panx1-mediated ATP release stimulates macrophage-driven epithelial repair after lung injury.[124] Damaged epithelial cells release ATP via Panx1, activating macrophages that produce pro-reparative signals to enhance epithelial proliferation. In zebrafish caudal fin injury models, Panx1 likewise promotes tissue regeneration.[124] These findings collectively suggest that Panx1 exerts a context-dependent influence—amplifying inflammation in early injury phases, then aiding in recovery during later stages.

Additional Roles

In sepsis-induced ALI/ARDS, hypoxic pulmonary vasoconstriction and right ventricular dysfunction contribute to disease severity. Panx1 regulates pulmonary vascular tone and has been identified as a novel mediator of hypoxic pulmonary vasoconstriction.[129] Panx1 also participates in ischemia-reperfusion injury (IRI)[130] and vascular elasticity regulation,[131,132] highlighting its involvement in various pathological processes related to sepsis-induced ALI/ARDS.

Panx1 Inhibitors: Potential Therapeutics for Sepsis-Induced ALI/ARDS

Since Panx1's discovery over two decades ago, numerous inhibitors have been identified, including antimalarial agents, chloride channel blockers, and purinergic receptor antagonists.[133,134] However, most lack specificity for Panx1. Below, we discuss several clinically available Panx1 inhibitors and their potential applications.

Carbenoxolone (Cbx)

Carbenoxolone, a drug originally used to treat gastric ulcers, inhibits both connexin 43 (Cx43) and Panx1,[135] albeit with low selectivity. Recent cryo-electron microscopy analyses revealed that Cbx binds to a groove between the EL1 and EL2 domains of Panx1, locking the channel in a closed conformation.[136] In experimental models, Cbx reduced melanoma metastasis in mice,[137] inhibited platelet aggregation,[120] and suppressed NLRP3 inflammasome activation.[138] Additionally, Cbx exhibited protective effects in various ischemia-reperfusion injuries (IRI), including acute kidney IRI,[85] lung IRI,[13] and stroke.[139]

Probenecid (Pbn)

Probenecid, a commonly prescribed gout medication, demonstrates stronger Panx1 inhibition than Cbx while lacking significant effects on connexin channels.[100,140] Compared to Cbx, Pbn shows a slower inhibition mechanism, suggesting different modes of action.[141] Pbn effectively reduces caspase-1 activation and inflammasome assembly in diverse cell types,[142] highlighting its potential in inflammation control.

Spironolactone

Spironolactone, a widely used antihypertensive agent, also inhibits Panx1 channel opening.[143] It reduces vascular resistance by suppressing Panx1-mediated α-adrenergic vasoconstriction and relaxing vascular smooth muscle cells, providing therapeutic benefits for resistant hypertension.[143] In COVID-19-associated ARDS, spironolactone alleviated lung inflammation, oxidative stress, and fibrosis, although its specific effects on ALI/ARDS through Panx1 inhibition remain unclear.[144]

Emerging Specific Panx1 Inhibitors

Newer Panx1 inhibitors with higher specificity are under development. These include ATP analogs,[133] small peptide inhibitors like 10Panx1 and TAT-Panx308,[143] monoclonal antibodies,[145] and nanobodies.[146] These targeted inhibitors exhibit greater efficacy and stability in preclinical studies, providing promising therapeutic tools for managing sepsis-induced ALI/ARDS.

Conclusions and Future Perspectives

Panx1 has emerged as a pivotal, stage-dependent regulator in the complex pathophysiology of sepsis-induced ALI/ARDS. This review highlights Panx1's dual role. In the acute injury phase, it acts as a potent amplifier of inflammation, cell death, and coagulation. Conversely, during recovery, it paradoxically facilitates inflammation resolution and epithelial regeneration. The clinical significance of this duality is profound. It positions Panx1 as a sophisticated molecular switch for dynamic, stage-specific therapy, rather than just a target for simple inhibition. The approach of suppressing Panx1 early to preserve lung integrity and later activating it to accelerate repair represents a novel therapeutic paradigm. Such a strategy could address the current lack of specific treatments for ALI/ARDS.

However, translating this promising concept from preclinical models to clinical reality is fraught with challenges. The primary obstacle is the "therapeutic paradox" of Panx1 itself: mistimed intervention could either exacerbate injury or impede natural recovery. To bridge this critical gap, future investigations must pursue an integrated strategy. First, future work must deconvolute the molecular switch governing Panx1's functional transition. This can be achieved by using single-cell and spatial multi-omics to map cell-specific signals and post-translational modifications in the injured lung. This fundamental knowledge will enable the development of precision pharmacological tools. The goal is to move beyond non-specific agents and engineer highly selective inhibitors for the acute phase and novel agonists for the recovery phase. These tools should ideally be coupled with lung-targeted delivery systems to maximize safety and efficacy. Finally, forging a robust translational bridge is paramount. This requires using human-relevant platforms, such as lung organoids, to validate new modulators. Critically, these platforms should also be used to identify clinical biomarkers that can accurately define a patient's disease stage. This synergistic approach is essential for defining the therapeutic window. By linking mechanistic discovery with targeted pharmacology and translational validation, we can ultimately unlock the potential of personalized, stage-specific Panx1 modulation for sepsis-induced ALI/ARDS.

Abbreviations

ALI, Acute Lung Injury; ARDS, Acute Respiratory Distress Syndrome; ATP, Adenosine Triphosphate; Cbx, Carbenoxolone; CLP, Cecal Ligation and Puncture; Cx, Connexin; ER, Endoplasmic Reticulum; IL, Interleukin; IRI, Ischemia-Reperfusion Injury; LAMP1, Lysosome-Associated Membrane Protein 1; LPS, Lipopolysaccharide; MAPK, Mitogen-Activated Protein Kinase; MGC, Multinucleated Giant Cells; NF-κB, Nuclear Factor-Kappa B; NLRP3, NOD-Like Receptor Protein 3; Panx, Pannexin; Pbn, Probenecid; P2X7R, Purinergic P2X7 Receptor; TLR, Toll-Like Receptor; TNF-α, Tumor Necrosis Factor-Alpha.

Data Sharing Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflict of interest.

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