Piezo1 in acute and critical illnesses: From mechanosensing to organ dysfunction (Review)

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Abstract. Acute and critical illnesses are typically accompanied by hemodynamic instability, tissue edema, mechanical ventilation and extracellular matrix remodeling. Abnormal shear stress, mechanical stretch, pressure loading and tissue deformation continuously reshape the local mechanical microenvironment. Piezo1 is a mechanosensitive cation channel that converts mechanical stimuli into intracellular signals dominated by Ca^{2+} influx and contributes to vascular homeostasis, immune regulation and tissue repair. In sepsis-associated intestinal epithelial injury, pulmonary endothelial mechanical loading and infection-related immune responses, Piezo1-associated Ca^{2+} signaling has been implicated in intestinal barrier injury, mitochondrial stress and apoptosis, endothelial barrier disruption or protection, and enhanced host defense. The direction of its effects depends on the cell and experimental context and cannot be determined solely by the intensity or duration of activation. The present review summarizes the fundamental mechanisms of Piezo1-mediated mechanosensing and mechanotransduction in sepsis, acute respiratory distress syndrome, acute kidney injury and trauma/hemorrhagic shock. It also discusses the therapeutic potential and translational challenges of targeting Piezo1. Mechanical alterations in acute and critical illnesses may influence cellular processes, including inflammatory regulation, endothelial barrier function, mitochondrial stress and cell injury, through Piezo1-associated signaling. However, direct evidence and the direction of effects vary between diseases, and shared mechanisms across organs remain to be validated. Defining the cell-specific and stimulus- and disease stage-dependent effects of Piezo1 may deepen understanding of organ dysfunction in acute and critical illness and provide a basis for research into interventions targeting mechanical signaling.

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1. Introduction

Acute and critical illness, including sepsis, acute respiratory distress syndrome (ARDS), severe trauma, shock and acute kidney injury (AKI), impose a substantial global burden of morbidity and mortality (1,2). For example, an estimated 48.9 million cases of sepsis and 11.0 million sepsis-related deaths occurred worldwide in 2017, accounting for approximately 19.7% of all global deaths (1). Despite advances in infection control, organ support and intensive care, organ dysfunction is a principal determinant of disease severity and clinical outcome and a common pathway to multiple organ dysfunction syndrome (MODS) and death (3,4). Although these conditions differ in etiology and the organs primarily affected, they share pathophysiological features, including inflammation, immune dysregulation, microcirculatory

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dysfunction and tissue hypoxia, and may lead to similar patterns of organ dysfunction, suggesting potentially convergent regulatory mechanisms. Elucidating these mechanisms is key for understanding disease pathogenesis and identifying novel therapeutic targets.

Research on acute and critical illnesses has traditionally focused on inflammation, immune dysregulation, oxidative stress, coagulation abnormality and metabolic reprogramming (5,6). Alterations in the mechanical microenvironment, including changes in vascular shear stress, tissue tension and extracellular matrix mechanics, have received increasing attention (7,8). Hemodynamic disturbance alters fluid shear stress and vascular wall tension, whereas tissue edema and cell swelling modify the mechanical properties of tissue and the extracellular matrix (ECM) (7,9). Mechanical ventilation repeatedly stretches the alveoli and microcirculatory dysfunction further redistributes local tissue stress (7,9). These changes are not epiphenomena but can directly influence cell behavior and tissue homeostasis. Determining how cells sense abnormal mechanical stimuli and convert them into biochemical signals is central to understanding organ injury in critical illness.

The discovery of Piezo1 provided a molecular basis for the cellular sensing and transduction of mechanical stimuli. Piezo1 is a well-characterized mechanosensitive cation channel that detects shear stress, stretch and compression and initiates mechanotransduction through cation influx, including Ca^{2+} (10,11). It is widely expressed in endothelial, immune and epithelial cells that are highly relevant to critical illness, and dysregulated Piezo1 signaling has been implicated in tissue injury (10,12). Piezo1 may serve as a molecular interface between mechanical stimuli and pathological responses. Previous studies have investigated the roles of Piezo1 in specific organs, diseases and cell types (13-16). Although previous studies have implicated Piezo1 in organ injury under specific pathological conditions, how Piezo1-mediated mechanotransduction contributes to organ dysfunction across different acute and critical illnesses remains incompletely understood (15-17). The present review aimed to summarize how changes in the mechanical microenvironment activate Piezo1 and the contribution of Piezo1-dependent Ca^{2+} signaling to inflammation, barrier dysfunction, microcirculatory disturbance, metabolic stress and regulated cell death in sepsis, ARDS, AKI and trauma/hemorrhagic shock.

2. Piezo1 as a cell mechanosensor

In addition to inflammation, metabolic derangement and immune dysregulation, acute and critical illnesses are characterized by dynamic changes in tissue mechanics (8,12). For mechanical stimuli to elicit biological effects, cells detect them and convert them into intracellular signals. This process of mechanosensing initiates mechanotransduction (8,9). Understanding the molecular basis of Piezo1-mediated mechanosensing is essential for explaining how abnormal mechanical environments alter cell function and contribute to organ injury.

Piezo1 is a key mechanosensitive, non-selective cation channel (9,18). Unlike classical membrane receptors activated by ligand binding, Piezo1 responds directly to changes in membrane tension or deformation. Channel opening permits the influx of cations, including Ca^{2+}, thereby converting a mechanical input into an intracellular signal (9,18).

Piezo1 is a homotrimeric transmembrane complex with three curved, blade-like structures that enable it to sense changes in membrane tension (9,19). Shear stress, tissue stretch, compression and changes in ECM stiffness alter channel conformation and promote opening, generating intracellular signals dominated by Ca^{2+} influx (9,19,20). These structural and gating properties provide the molecular basis for Piezo1-mediated mechanosensing.

Piezo1 is expressed in endothelial, immune and epithelial cells, erythrocytes and other mechanically responsive cell types. It contributes to flow adaptation, vascular homeostasis, cytoskeletal remodeling, cell adhesion, erythrocyte volume regulation and tissue repair (9,10,21). Piezo1-dependent Ca^{2+} influx activates downstream Ca^{2+}-responsive networks that shape cell adaptation to a changing mechanical environment (9,10). Thus, Piezo1 not only detects mechanical stimuli but also translates them into sustained changes in cellular behavior.

Under physiological conditions, Piezo1 supports adaptive mechanotransduction and tissue homeostasis (9,21). During critical illness, however, hemodynamic abnormality, edema, mechanical ventilation and inflammation-associated tissue remodeling continuously alter local mechanics (8,9,22). These changes may alter the mechanical inputs to Piezo1 and its downstream responses, but an abnormal mechanical environment does not necessarily shift its effects toward injury. For example, endothelial Piezo1 protects the vascular barrier during high-volume mechanical ventilation (13), whereas it contributes to barrier disruption in models of elevated pulmonary microvascular pressure or mechanical stretch in an inflammatory context (17,23).

3. Mechanisms linking Piezo1 activation with organ dysfunction

Physiological Piezo1 signaling helps cells adapt to mechanical changes and maintain tissue homeostasis. Hemodynamic abnormality and tissue edema provide an important context for changes in the mechanical microenvironment in acute and critical illness. The vascular endothelium senses flow-associated mechanical forces, while vascular leakage in sepsis can be accompanied by microcirculatory dysfunction and tissue edema (8,12). Alveolar stretch induced by mechanical ventilation influences pulmonary endothelial Piezo1 signaling and barrier function (13,23). The direction of Piezo1 effects differs between experimental models: It contributes to barrier injury in models of elevated pulmonary microvascular pressure and ARDS-associated stretch (17,23), whereas endothelial Piezo1 protects the pulmonary endothelial barrier in a high-volume mechanical ventilation model studied by Zhong *et al* (13). These findings suggest that the intensity or duration of mechanical stimulation alone is insufficient to determine the net effects of Piezo1; cell type, loading mode, inflammatory context and downstream signaling must also be considered.

The source, mode and principal cellular targets of mechanical stimulation differ across acute and critical illness. Studies involving genetic or pharmacological manipulation of Piezo1 in specific models support its involvement in immune

responses (24,25), barrier regulation (13,17,23) and cell stress, but the strength of evidence varies between processes and diseases. These findings provide a basis for comparison across diseases but do not establish a common Piezo1-driven pathological mechanism across all acute and critical illnesses.

Inflammation, vascular barrier dysfunction, microcirculatory disturbance, metabolic stress and cell injury are interconnected: Persistent inflammation impairs vascular barriers; barrier failure and microcirculatory disturbance promote edema, hypoperfusion and metabolic stress; and injured or dying cells amplify inflammation (4,12). Piezo1 may participate in these interconnected pathophysiological processes by coupling abnormal mechanical inputs with Ca^{2+}-dependent signaling, although the strength of evidence varies between pathways and diseases (4,9,14,26,27).

Piezo1 modulates inflammatory responses. Inflammation is a notable driver of organ injury in critical illness and promotes barrier disruption, microcirculatory impairment and metabolic dysfunction (5,28). Piezo1 regulates inflammatory responses in endothelial cells, macrophages and neutrophils and couples mechanical cues to immune signaling (9,14,21).

In vascular endothelial cells, Piezo1 participates in force-sensing and the regulation of vascular function (21). For example, flow-induced Piezo1 activation promotes ATP release and initiates downstream vasodilatory signaling (29). The aforementioned studies support a role for Piezo1 in converting flow-associated mechanical stimuli into endothelial signals, but do not directly establish its involvement in downstream inflammatory signaling pathways.

In macrophages, Piezo1 modulates mechanosensitive Ca^{2+} signaling, cytokine production and polarization (14,30). In neutrophils, Piezo1 senses mechanical signals during transendothelial migration and enhances bactericidal function (24) and participates in shear-induced neutrophil extracellular trap formation (31). Piezo1-mediated immune regulation involves defined molecular mechanisms and is not merely an accompanying phenomenon under abnormal mechanical stimulation. Geng *et al* (25) found that bacterial infection or lipopolysaccharide stimulation can induce the formation of a complex between toll-like receptor 4 (TLR4) and Piezo1 in macrophages, coupling pathogen recognition signals with Piezo1-mediated Ca^{2+} influx. Ca^{2+} signaling activates the Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII)-mammalian sterile 20-like kinase 1/2 (Mst1/2)-Ras-related C3 botulinum toxin substrate 1 (Rac1) axis, promoting actin cytoskeletal reorganization, pathogen phagocytosis and mitochondria- and phagosome-associated reactive oxygen species production, thereby enhancing bacterial clearance (25). Piezo1 deficiency, CaMKII inhibition and loss of Mst1/2 or Rac1 attenuate the associated bactericidal response, providing causal evidence for this pathway (25).

Coupling between mechanosensing and immune function is observed in neutrophils. Mukhopadhyay *et al* (24) reported that increased membrane tension as neutrophils pass through narrow endothelial junctions activates Piezo1 and induces Ca^{2+} signaling, which subsequently stabilizes hypoxia-inducible factor-1α (HIF-1α) and promotes NADPH oxidase 4 (NOX4) expression, enhancing bactericidal activity. These findings suggest that Piezo1 participates in sensing mechanical constraints during neutrophil migration and links mechanical signals with the regulation of antibacterial function. However, NOX4 expression in neutrophils and its specific contribution to bacterial killing are disputed. Knaus *et al* (32) questioned the evidence for NOX4 expression, the specificity of the antibodies and inhibitors used in the aforementioned study and the mechanistic interpretation of NOX4-mediated bacterial killing. The original authors cite transcriptomic analyses and genetic interventions, while acknowledging that contributions from other NOX isoforms cannot be excluded (33). The specific role of NOX4 in mechanosensitive signaling, reactive oxygen species production and antibacterial activity in neutrophils, as well as its relationship with NOX2 and other NADPH oxidase isoforms, therefore requires further independent validation. Thus, in the aforementioned models, Piezo1 serves as a regulatory node linking pathogen recognition, mechanosensing and immune responses rather than an independent initiator of inflammation. Its amplifying effects may involve enhanced inflammatory responses or increased phagocytosis and bacterial killing and should not be equated with tissue injury. Extending these mechanisms to persistent inflammation and organ dysfunction in acute and critical illness requires direct, disease-specific evidence.

Piezo1 regulates barrier integrity and microcirculatory homeostasis. Barrier dysfunction is a consequence and an amplifier of persistent inflammation; vascular leakage, edema, impaired microvascular perfusion and local hypoxia can further aggravate inflammation and tissue injury (17,23,34). Piezo1 has bidirectional effects on barrier function that must be interpreted in association with the mode of mechanical loading, inflammatory context and downstream signaling. It contributes to endothelial junction disruption and increased permeability in models of elevated pulmonary microvascular pressure and mechanical stretch in an inflammatory context (17,23), whereas endothelial Piezo1 maintains adherens junctions and protects the vascular barrier during high-volume mechanical ventilation (13).

In injury models, Piezo1-mediated Ca^{2+} signaling activates calpain, promoting adherens junction protein degradation or junction disruption and thereby increasing endothelial permeability and vascular leakage (17,23). Conversely, in a protective stretch model, calpain cleaves and inactivates Src, limiting vascular endothelial cadherin (VE-cadherin) phosphorylation and maintaining junctional stability (13). These findings suggest the targets of Ca^{2+}-dependent downstream signaling and the cellular context provide clues to understanding the divergent effects on barrier function.

Piezo1 contributes to vascular tone and microcirculatory regulation (29,35). In endothelial cells, flow-induced activation promotes ATP release and downstream vasodilatory signaling (29). In erythrocytes, Piezo1 links mechanical stimulation with Ca^{2+} influx and cell volume regulation (36).

During critical illness, inflammation, hemodynamic instability and altered tissue mechanics may destabilize these regulatory mechanisms and affect vascular reactivity, erythrocyte rheology and microvascular perfusion, thereby worsening tissue hypoxia and organ injury (37). Hypoperfusion and edema alter local mechanics, creating reciprocal interactions among mechanical stress, inflammation and barrier

injury. How Piezo1 signaling is coordinated among different barrier-associated cell types and how this coordination varies by organ are insufficiently defined.

Piezo1-associated metabolic changes and mitochondrial stress. Metabolic dysfunction in acute and critical illness is linked to inflammation and tissue hypoperfusion, with mitochondrial dysfunction, reactive oxygen species accumulation and inadequate energy supply representing important components (5,38). General studies of Ca^{2+} biology show that disrupted Ca^{2+} homeostasis affects mitochondrial function and contributes to cellular stress and apoptosis (39,40). These findings provide a biological basis for the metabolic effects of mechanosensitive Ca^{2+} signaling, but do not establish that these changes are mediated by Piezo1. Piezo1-associated metabolic effects should be discussed in the context of specific models. For example, in macrophage infection models, Geng *et al* demonstrated that TLR4/Piezo1 signaling promotes mitochondria- and phagosome-associated reactive oxygen species production via the CaMKII-Mst1/2-Rac axis and enhances bacterial clearance (25). Independently, West *et al* showed that TLR signaling promotes mitochondrial recruitment to phagosomes and enhances mitochondrial reactive oxygen species production and bacterial killing through a TRAF6-ECSIT-dependent mechanism (41). In the aforementioned macrophage infection models, reactive oxygen species contribute to host defense and cannot directly be equated with mitochondrial injury or bioenergetic failure.

Accordingly, when changes in Piezo1-associated Ca^{2+} signaling and reactive oxygen species are observed, their cellular functions and direction of effect require further clarification. In sepsis-related intestinal epithelial injury, GsMTx4, a peptide inhibitor of mechanosensitive ion channels, attenuates the increase in Ca^{2+}, mitochondrial reactive oxygen species accumulation and loss of membrane potential in TNF-α-treated cells (15). Mitochondria-targeted antioxidant intervention also improves tight junction protein expression (15). These findings provide disease-associated mechanistic support for a link between Piezo1-related Ca^{2+} signaling and mitochondrial stress, although the *in vitro* results are limited by inhibitor specificity and the cell model.

Despite the mechanistic evidence from the aforementioned models, evidence remains insufficient to establish whether Piezo1-associated mitochondrial stress represents a shared mechanism across organs, impairs ATP production or influences metabolism through AMPK or mTOR. General studies of mitochondrial Ca^{2+} signaling and AMPK-dependent energy sensing provide biological context but do not establish Piezo1-related metabolic pathways (39,42). Establishing causality requires genetic manipulation of Piezo1, assessments of metabolic function and downstream rescue experiments in disease-relevant models.

Piezo1 regulates cell fate and tissue injury. The effects of Piezo1 on cell survival should be assessed on the basis of intervention results in specific models. In sepsis-related intestinal barrier injury, intestinal epithelial-specific Piezo1 deletion attenuates epithelial apoptosis and barrier injury, providing direct evidence for Piezo1 involvement in cell injury in that model (15). However, apoptosis findings from a single model cannot be generalized to a universal role for Piezo1 in driving different forms of regulated cell death, nor do changes in Ca^{2+} or oxidative stress alone establish a specific cell death mechanism.

Damage-associated molecular patterns released by injured or dying cells can activate innate immunity and influence inflammation and tissue injury (43,44). These studies provide context for understanding the interactions between cell injury and inflammation but do not directly establish Piezo1 involvement. Whether Piezo1-associated cellular injury forms feedback relationships with inflammation, barrier function and microcirculatory dysfunction remains to be validated in disease models.

These processes constitute a mechanistic network in which Piezo1 may participate, but the strength of evidence varies between its components. Some links are supported by genetic or pharmacological manipulation of Piezo1, whereas others are inferred mainly from general Ca^{2+} signaling and cell stress mechanisms and require direct validation (13,15,16,25) (Fig. 1).

Molecular determinants of the Piezo1 functional switch. Piezo1 activation does not necessarily cause injury. Pulmonary endothelial studies show Piezo1 activation maintains adherens junctions or contributes to junction disruption in experimental models, indicating that the direction of its effects cannot be determined solely by whether the channel is activated or by the intensity of mechanical stimulation (13,17,23). Understanding these differences requires further examination of the Ca^{2+} signals generated by mechanical input and the downstream responses they engage in specific cells. A functional switch provides a framework for analyzing these differences but is not an established unified mechanism. How signaling changes within the same cell, opposing effects between different cell populations and stress adaptation each influence the final outcome requires validation in specific disease models.

Membrane tension is a key determinant of Piezo1 mechanosensitivity, suggesting that the same external load may not elicit the same channel response in different cell environments (45). When discussing a functional switch, the threshold for channel opening should be distinguished from the threshold for cell injury. Channel opening reflects the detection of mechanical signals, whereas injury should be assessed in relation to Ca^{2+} signaling, downstream stress response and cell functional outcomes. Comparisons between models should therefore examine stimulation amplitude, duration and frequency separately rather than classify stimuli simply as physiological or excessive. The ability of pulmonary endothelial Piezo1 to protect the barrier during high-volume mechanical ventilation indicates that greater mechanical loading does not necessarily shift its effects toward injury (13).

The intracellular signaling environment influences the functional output of Piezo1 activation. Pulmonary endothelial studies show that Ca^{2+}-dependent calpain signaling produces opposing effects on barrier function (13,17,23). Calpain cleaves and inactivates Src, thereby decreasing Src-dependent VE-cadherin phosphorylation and maintaining adherens junctions (13), whereas Piezo1/Ca^{2+}/calpain signaling contributes to junctional protein degradation and barrier disruption in other experimental models (17,23). These findings suggest downstream substrates and their modes of action may explain differences between models, but whether regulated changes

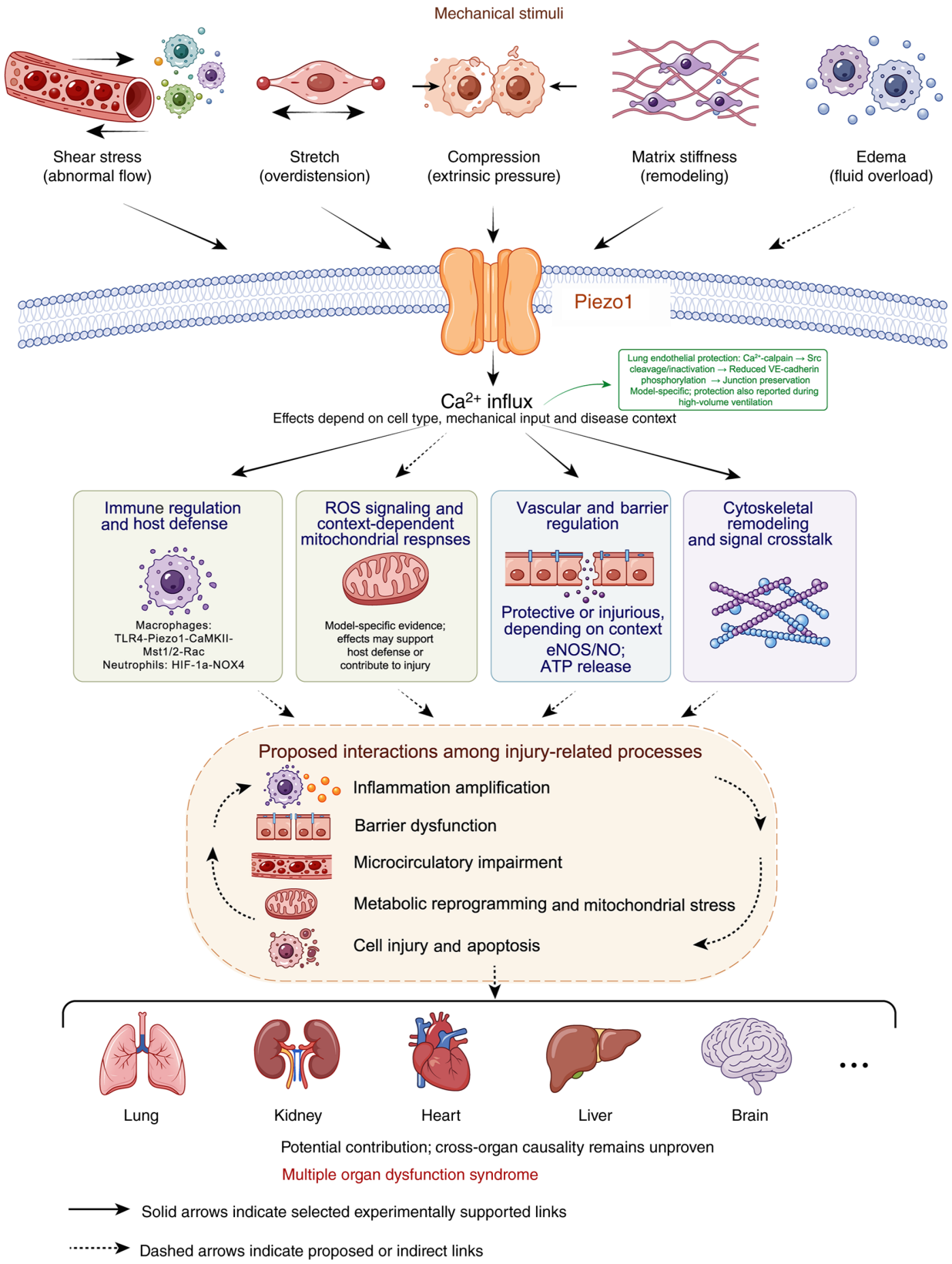


Figure 1. Piezo1-associated signaling and proposed interactions contributing to organ dysfunction. Mechanical stimuli, including shear stress, stretch, compression and changes in matrix stiffness, influence Piezo1 activation and Ca^{2+} signaling. Edema may also alter the local mechanical environment. Downstream responses include immune regulation and host defense, ROS signaling and context-dependent mitochondrial responses, vascular and barrier regulation and cytoskeletal remodeling. In macrophages, TLR4-Piezo1 coupling enhances antibacterial responses through CaMKII/Mst1/2/Rac signaling. A HIF-1α/NOX4 pathway has been reported in neutrophils, although NOX4 expression and its specific contribution to bacterial killing are disputed. In a high-volume mechanical ventilation model, endothelial Piezo1 activates Ca^{2+}-dependent calpain, which cleaves and inactivates Src, limits VE-cadherin phosphorylation and preserves adherens junctions. Effects depend on cell type, mechanical input and disease context, and cross-organ causality remains unproven. CaMKII, calcium/calmodulin-dependent protein kinase II; eNOS, endothelial nitric oxide synthase; HIF-1α, hypoxia-inducible factor-1α; NOX4, NADPH oxidase 4; ROS, reactive oxygen species; TLR4, toll-like receptor 4; VE, vascular endothelial; Mst1/2, mammalian sterile 20-like kinases 1 and 2; Rac, Ras-related C3 botulinum toxin substrate.

in substrate selection occur requires direct validation. Inflammatory receptors alter the signaling networks involving Piezo1. For example, bacterial infection or lipopolysaccharide stimulation induces a TLR4-Piezo1 complex in macrophages, enhancing phagocytosis and bacterial killing through Ca^{2+}/CaMKII/Mst1/2/Rac signaling (25). This supports coupling between pathogen recognition signals and Piezo1 but does not establish that an inflammatory context shifts its effects toward tissue injury.

Cell adaptation to mechanical stress also involves nuclear and chromatin changes. In epithelial cells, Nava *et al* (46) found that stretch-induced nuclear deformation triggers Piezo1-dependent endoplasmic reticulum Ca^{2+} release, decreases H3K9me3-marked heterochromatin and reduces nuclear stiffness, thereby increasing nuclear deformability and limiting mechanical stress-induced DNA damage. The study also suggested that early chromatin softening and longer-term cytoskeletal and cell population rearrangements represent distinct levels of adaptation that contribute to genome protection (46). These findings support a role for Piezo1-associated Ca^{2+} signaling in adaptation to mechanical stress but do not establish a universal temporal boundary for a shift from protective to detrimental effects.

A study of lung injury induced by acid aspiration combined with mechanical ventilation found that changes in the nuclear lamina and chromatin, together with DNA damage, are accompanied by activation of the p53/p21 pathway (47). Loss of p21 attenuates senescence but increases apoptosis and worsens lung injury (47). This study provides background evidence on the association between cellular stress, survival and senescence in mechanical lung injury but did not directly investigate Piezo1. Therefore, the aforementioned studies cannot be combined into a causal sequence in which Piezo1 shifts from protective to detrimental effects as stimulation is prolonged. This requires validation within the same cell type and disease model through Piezo1 manipulation and continuous functional assessment.

Evidence involving ataxia telangiectasia and Rad3-related protein (ATR), a kinase involved in DNA damage responses and cellular responses to mechanical stress, also highlights the importance of considering the experimental context when interpreting nuclear responses to mechanical deformation. In a neural regeneration study, Li *et al* (48) found Piezo-dependent mechanosensing can activate the ATR/checkpoint kinase 1 (Chk1) pathway through nitric oxide signaling and inhibit axon regeneration independently of DNA damage. The aforementioned study provides mechanistic evidence linking mechanosensing with checkpoint signaling but does not directly establish the same pathway in pulmonary endothelial or alveolar epithelial cells, nor can ATR activation be regarded as direct evidence of Piezo1-induced DNA damage. Whether nuclear lamina structure, chromatin adaptation and ATR signaling regulate the protective or detrimental effects of Piezo1 in acute and critical illness requires causal validation in cells and disease models.

Overall, mechanical inputs, downstream signaling context and cellular adaptive capacity provide clues to understanding the divergent protective and detrimental effects of Piezo1, but whether these factors jointly determine a transition between protective and detrimental effects within a single experimental model under different conditions remains to be validated. Future studies should examine stimulation amplitude, duration and frequency separately in defined cell types and disease models, combine manipulation of Piezo1 and candidate downstream molecules with continuous monitoring of Ca^{2+} dynamics and assess barrier function, DNA damage and cell fate. Distinguishing differences in effects across models from a functional switch within a single model may identify its molecular determinants and potential intervention windows that preserve protective signaling while limiting injurious responses.

4. Role of Piezo1 across acute and critical illnesses

Sepsis. Sepsis is one of the most extensively studied critical illnesses in the context of Piezo1, although direct disease-specific evidence is limited (15,49). Sepsis-associated organ dysfunction involves infection-induced immune dysregulation, inflammation, endothelial injury and microcirculatory impairment (50,51). Hemodynamic instability, glycocalyx degradation, edema and ECM remodeling alter shear stress, tissue tension and matrix mechanics (52,53). These changes provide a plausible mechanical context in which Piezo1 may influence inflammatory, barrier and microvascular responses.

Yan *et al* (15) found increased Piezo1 expression in intestinal tissue from mice with cecal ligation and puncture-induced sepsis. Intestinal epithelial-specific Piezo1 deletion attenuates the increase in intestinal permeability, preserves expression of the tight junction proteins zonula occludens-1 and occludin and decreases intestinal epithelial TUNEL positivity, suggesting decreased apoptosis. Deletion also improves 7-day survival (15). In TNF-α-treated Caco-2 cells, the mechanosensitive channel inhibitor GsMTx4 attenuates the increase in Ca^{2+}, mitochondrial reactive oxygen species accumulation, loss of membrane potential and junctional protein abnormality (15). The mitochondria-targeted superoxide scavenger MitoTEMPO improves tight junction protein expression (15). These findings support links between intestinal epithelial Piezo1-related Ca^{2+} signaling, mitochondrial stress and barrier injury (15). A strength of the aforementioned study is its combination of intestinal epithelial-specific genetic manipulation and cell mechanistic experiments, although its conclusions are limited in scope. First, Caco-2 cells are tumor-derived, and TNF-α stimulation reproduces only selected aspects of the inflammatory environment in sepsis, particularly TNF-α-mediated inflammatory signaling, epithelial barrier dysfunction and associated cellular stress responses. Second, GsMTx4 is not a Piezo1-specific inhibitor, so the *in vitro* pharmacological findings must be interpreted alongside the genetic evidence. Furthermore, the study did not directly quantify or manipulate local mechanical loading during sepsis, leaving the specific mechanical stimulus that activates intestinal epithelial Piezo1 unresolved. The findings do not establish how its effects vary across disease stages or predict therapeutic benefit in patients. Thus, the study supports Piezo1 involvement in intestinal barrier injury during experimental sepsis but does not demonstrate that systemic Piezo1 inhibition would benefit all organs (15).

In addition to intestinal epithelial cells, endothelial and immune cells are key subjects of Piezo1 research. Studies of

pulmonary microvascular pressure and infection-associated models provide evidence for Piezo1 involvement in endothelial barrier regulation, neutrophil bacterial killing and macrophage antibacterial responses (17,24,25). However, these findings do not constitute direct evidence in sepsis and their relevance to specific stages and organs in sepsis requires validation.

Endothelial Piezo1 participates in flow-related mechanosensing and the regulation of vascular function, but its effects on barrier function are model-dependent. Models of elevated pulmonary microvascular pressure and ARDS-associated stretch show that Piezo1 contributes to endothelial junction disruption and increased permeability (17,23), whereas a high-volume mechanical ventilation model shows that endothelial Piezo1 helps maintain adherens junctions and the vascular barrier (13). These findings provide a basis for investigating endothelial mechanosensing but do not establish the direction of Piezo1 effects in the vascular endothelium during sepsis. Its specific effects across organs and disease stages require validation through endothelial-specific manipulation of Piezo1, measurement of local mechanical loading and assessment of barrier function.

Immune cell studies also provide a basis for investigating the role of Piezo1 in sepsis (14,25). Piezo1 participates in macrophage sensing of matrix stiffness and the regulation of polarization (14). Other studies have implicated Piezo1 in myeloid cell responses to cyclical mechanical force (54) and CD11b-dependent macrophage responses to mechanical cues (55). In neutrophils, mechanical constraints during transendothelial migration activate Ca^{2+} signaling through Piezo1 and enhance bactericidal function (24). The aforementioned studies provide evidence linking mechanosensing with immune function but do not establish the roles of Piezo1 across stages of sepsis. Its effects on pathogen clearance and immune dysregulation require validation in disease models.

Existing studies address macrophage stiffness sensing and polarization (14), myeloid cell response to cyclical mechanical force (54) and neutrophil bactericidal function following transendothelial migration (24). Their experimental conditions and functional endpoints differ, so findings cannot be directly interpreted as evidence of a uniform immune effect (14,24,54).

Reported effects are not uniformly pro- or anti-inflammatory, potentially because they depend on cell type, mechanical stimulus, experimental model, inflammatory stage and the local tissue environment (13,17,25).

Infection-associated studies support a role for Piezo1 in regulating host immune responses but do not establish it as an independent initiator of infection-induced inflammation (14,25). In macrophages, TLR4-Piezo1 coupling can enhance phagocytosis and bacterial killing (25), whereas in neutrophils, mechanical signals generated during transendothelial migration enhance bactericidal activity through Piezo1 (24). These findings indicate that Piezo1 participates in the regulation of antibacterial function by pathogen recognition signals and mechanosensing but enhanced host defense is not equivalent to increased inflammatory injury. The specific effects of these mechanisms on pathogen clearance and tissue injury in sepsis require direct validation in relation to cell type, infection status and disease stage, and cannot be inferred from general infection models.

Evidence on Piezo1 in sepsis is largely based on experimental cell and animal models, while its clinical relevance requires further investigation (15,25). Changes in Piezo1 expression and activity across disease stage and their relationships with severity, organ function and outcome remain unknown. Piezo1 in different organs and cell types may exert divergent effects; sustained activation may be injurious in certain contexts but compensatory in others.

ARDS. ARDS is a key cause of respiratory failure in critically ill patients and a prototypical disorder in which mechanical forces contribute to organ injury (56-58). Repeated alveolar collapse and reopening, decreased lung compliance, inflammation-associated ECM remodeling and mechanical ventilation expose lung tissue to abnormal stretch, compression and shear stress (56,57). Alveolar epithelial and pulmonary microvascular endothelial cells are continuously subjected to altered mechanics that may be sensed through Piezo1 (56,57,59).

Research has focused primarily on Piezo1 in alveolar epithelial and pulmonary microvascular endothelial cells (23,59,60). Experimental studies involving Piezo1 manipulation provide direct evidence for its involvement in pulmonary endothelial barrier injury (17,23). Friedrich *et al* (17) found that endothelial-specific Piezo1 deletion attenuates vascular leakage caused by elevated pulmonary microvascular pressure, while Jiang *et al* (23) found that Piezo1 knockdown decreases endothelial junction disruption in ARDS-associated mechanical stretch. These findings support detrimental effects of Piezo1 in these models but cannot be generalized to all mechanical loading conditions.

In lung epithelial cells, mechanical stimulation activates a disintegrin and metalloproteinase 10 (ADAM10) and ADAM17 through Piezo1, promoting the proteolytic release of the growth factor amphiregulin and junctional adhesion molecule A (JAM-A) (61). JAM-A shedding is accompanied by decreased intercellular contact (61).

Piezo1 knockdown attenuates mechanical stretch-induced apoptosis in A549 lung epithelial cells, an *in vitro* model used to investigate ARDS-associated alveolar epithelial injury (62). These findings concern growth factor release, changes in cell junctions and apoptosis and cannot collectively be described as decreased repair capacity. Pulmonary vascular endothelial Piezo1 exerts detrimental or protective effects on barrier function in different models (13,17,23). Epithelial and endothelial findings should be discussed separately to avoid combining them into a uniform mechanism of pulmonary barrier injury. Comparisons between studies need to account for the mode of mechanical loading, inflammatory context and intervention. Friedrich *et al* (17) increased pulmonary microvascular pressure in mice by elevating left atrial pressure or constricting the aorta and found that endothelial-specific Piezo1 deletion attenuates vascular leakage and pulmonary edema. Mechanistic experiments show that Piezo1-mediated Ca^{2+} signaling activates calpain, promoting VE-cadherin internalization and adherens junction protein degradation (17). Jiang *et al* (23) used short hairpin RNA *in vivo* and small interfering RNA *in vitro* to knock down Piezo1 in ARDS rats and lipopolysaccharide-treated pulmonary endothelial cells subjected to 20% cyclic stretch, respectively. Knockdown attenuates junction disruption and the increase in permeability, supporting a

role for Piezo1/Ca^{2+}/calpain signaling in barrier injury in these models. These studies examined vascular pressure loading and mechanical stretch in an inflammatory context, respectively, and their findings should be interpreted within their experimental conditions.

By contrast, Zhong *et al* (13) found that endothelial-specific Piezo1 deletion in mice undergoing high-volume mechanical ventilation and Piezo1 depletion in human pulmonary endothelial cells exposed to cyclic stretch exacerbate the increase in permeability.

Piezo1-mediated Ca^{2+} influx activates calpain, which cleaved and inactivated Src kinase, decreasing Src-dependent VE-cadherin phosphorylation and thereby maintaining adherens junction stability (13). Increasing intracellular Ca^{2+} and promoting calpain activity using the calcium ionophore A23187 attenuates pulmonary microvascular leakage in Piezo1-deficient mice, further supporting this protective pathway (13). These findings demonstrate that endothelial Piezo1 serves a barrier-protective role in this high-volume mechanical ventilation model. Its protective effects cannot be attributed exclusively to physiological or low-intensity stretch.

Although the aforementioned studies concern endothelial Piezo1, they differ in the mode of mechanical loading, inflammatory context and intervention. Friedrich *et al* (17) examined barrier injury caused by elevated vascular pressure, Jiang *et al* (23) investigated mechanical ventilation and cyclic stretch in an inflammatory context and Zhong *et al* (13) combined endothelial-specific deletion, cell Piezo1 depletion and downstream rescue experiments to identify a stretch-related barrier-protective pathway. Although all involve calpain, their downstream effects differ: Adherens junction protein degradation is associated with barrier disruption, whereas Src cleavage and inactivation maintain junctional stability (13,17,23). These findings suggest that the net effects of Piezo1 cannot be determined solely by stimulation intensity and duration, but should also be interpreted in association with loading mode, cellular state and downstream signaling. Whether differences in calpain substrate selection or other regulatory mechanisms account for these divergent effects remains to be directly tested under comparable experimental conditions. Piezo1 inhibition strategies in ARDS should consider the possibility of weakening endothelial barrier protection, with benefits and risks assessed in defined cell types and disease contexts.

Studies of mechanical ventilation indicate that assessment of Piezo1 effects should consider both ventilatory loading and the response of different cell types, including epithelial and endothelial cells (13,23,62).

Lung-protective mechanical ventilation is a key component of ARDS management (56-58). Larger tidal volume, higher plateau pressure and repeated alveolar opening and closure can increase mechanical stress in lung tissue (56-58). However, these ventilatory parameters are not equivalent to the local loads experienced by specific cells and do not directly reflect the extent of Piezo1 activation (13,17,23). Experimental studies show Piezo1 can contribute to junction disruption or protect the endothelial barrier in ventilation or stretch models (13,23). Ventilation-related lung injury therefore cannot uniformly be attributed to Piezo1, nor can the benefits of lung-protective ventilation be directly interpreted as resulting from Piezo1 inhibition. Its specific effects must be assessed in association with cell type, local mechanical loading and downstream signaling.

Piezo1 participates in ADAM10/17-mediated growth factor and adhesion molecule release (61), as well as mechanical stretch-induced apoptosis in A549 lung epithelial cells (62). These findings concern distinct cell responses and should be interpreted within their experimental conditions. They do not establish a unified causal sequence in which Piezo1 links inflammation, microcirculatory dysfunction and mitochondrial stress.

Most studies remain based on experimental models, and the specific effects of Piezo1 across ARDS etiology, ventilator settings and disease stages are not fully resolved (13,23,62).

AKI. AKI is a frequent form of organ dysfunction in critically ill patients, affecting 57.3% of patients during the first week of ICU admission in a multinational study (63), and involves altered renal hemodynamics, inflammation, microcirculatory impairment, metabolic stress and tubular epithelial injury (64-66). The kidney has a distinctive mechanical environment created by high perfusion, continuous filtration, tubular flow, fluid shear stress, intraluminal pressure and ECM mechanics (67-69). Under physiological conditions, tubular epithelial cells sense urine flow and use mechanical cues to regulate tubular structure and transport (69,70).

Sepsis, ischemia-reperfusion, shock and nephrotoxic injury alter renal blood flow, tubular patency, interstitial pressure and edema, thereby changing local shear stress and tissue tension (64,65). These changes may alter the mechanical environments of renal cells, but whether they influence AKI progression through Piezo1 requires direct validation. Studies of myeloid Piezo1 have demonstrated its involvement in macrophage immune responses (25) and ischemia-reperfusion-induced renal injury (16). However, the principal mechanical inputs responsible for these effects remain unclear, and the available evidence does not establish that changes in renal blood flow or tubular fluid flow directly cause injury through tubular epithelial Piezo1. Assessment of Piezo1 in AKI should distinguish its roles in myeloid cells, tubular epithelial cells and other cell types, and define the mechanical load, downstream signaling and their specific contributions to injury in models.

Direct mechanistic evidence in ischemia-reperfusion-associated AKI demonstrates the involvement of myeloid cell Piezo1 (16). In mice subjected to bilateral renal vascular clamping and bone marrow-derived macrophages exposed to hypoxia, Chen *et al* (16) found that Piezo1 upregulates HIF-1α via Ca^{2+}-dependent calpain signaling and modulates the Notch and CCL2/CCR2 pathways, promoting inflammatory macrophage polarization. Myeloid-specific Piezo1 deletion attenuates renal injury (16). The aforementioned study supports the involvement of myeloid cell and macrophage Piezo1 in ischemia-reperfusion injury but does not establish these pathways as intrinsic Piezo1 mechanisms in tubular epithelial cells.

Tubular epithelial cell stress and organelle injury are key pathological processes in AKI, but studies of these processes do not establish that they are directly mediated by Piezo1 (71,72). Whether renal vascular endothelial Piezo1 influences local blood flow and microcirculation in AKI requires validation

through cell-specific manipulation in the corresponding models.

It is not clear whether renal Piezo1 in AKI responds predominantly to vascular shear stress, tubular shear stress, luminal pressure or a combination of forces. Ischemia-reperfusion, sepsis-associated and drug-induced AKI have distinct hemodynamic and tissue injury profiles and may engage Piezo1 differently. Their effects should not be reduced to a single unified mechanism.

Chen *et al* (16) support a role for myeloid cell Piezo1 in inflammatory injury during experimental ischemia-reperfusion-associated AKI, but this mechanism cannot yet be generalized to AKI of other etiologies (16). Because myeloid-specific Piezo1 deletion is not restricted to macrophages, more precise cell-specific interventions are needed to identify the cell sources of the protective effects observed *in vivo*. The relative contributions of Piezo1 in tubular epithelial and vascular endothelial cells, podocytes and different immune cell populations, as well as possible cooperative or opposing effects between these cells, also require validation. Future studies should define the principal responding cells, sources of mechanical stimulation and downstream effects in association with AKI etiology and disease stage.

Trauma and hemorrhagic shock. Severe trauma and hemorrhagic shock are notable causes of MODS and typically coexist, creating a complex mechanical stress environment (73,74). Trauma directly deforms tissue and disrupts the ECM, whereas hemorrhage and resuscitation produce marked hemodynamic fluctuations and ischemia-reperfusion injury. Hemodynamic changes during hemorrhage and resuscitation, together with trauma-associated glycocalyx injury and tissue edema, may alter the local mechanical environment (74,75). The coexistence of mechanical perturbations distinguishes trauma/hemorrhagic shock from other types of critical illness.

Direct experimental evidence for the role of Piezo1 in trauma and hemorrhagic shock remains limited; its potential involvement is inferred primarily from studies of endothelial mechanobiology (8,21,29) and established trauma pathophysiology (73,74). Endothelial Piezo1 senses shear stress and vascular tension and regulates endothelial structure and function through Ca^{2+}-dependent signaling (18,21,29,76,77). Post-traumatic hypoperfusion and hemodynamic changes during resuscitation, together with glycocalyx injury and tissue edema, may alter the mechanical environment of endothelial cells (74,75).

Pulmonary vascular pressure and mechanical stretch models show that endothelial Piezo1 can contribute to adherens junction disruption and vascular leakage through Ca^{2+}-dependent calpain signaling (17,23). However, whether this mechanism operates in trauma or hemorrhagic shock requires direct validation.

Vascular leakage and tissue edema may exacerbate microcirculatory dysfunction and tissue hypoxia, thereby contributing to organ injury (28,52,78).

Piezo1 may participate in post-traumatic immune responses (14). Studies have shown that macrophage Piezo1 participates in matrix stiffness sensing and the regulation of cell polarization (14), whereas neutrophil Piezo1 senses mechanical constraints during transendothelial migration and enhances bactericidal function (24). These findings provide a mechanistic basis for the link between mechanosensing and immune responses but do not directly establish the role of Piezo1 in trauma or hemorrhagic shock. Based on the available evidence, Piezo1 may modulate and amplify inflammatory responses following initiation by tissue injury rather than act as an independent initiator of post-traumatic inflammation (14,25). Its effects may vary with injury type, severity and resuscitation strategy.

Addressing these gaps requires characterization of Piezo1 expression and activity across trauma models, injury stages and resuscitation conditions, together with comparisons between endothelial, immune and parenchymal cells. Single-cell and spatial omics may define cellular sources and spatiotemporal patterns. Establishing causality between Piezo1 signaling and post-traumatic organ injury, however, requires cell-specific intervention.

In summary, Piezo1 operates within distinct mechanical environments across acute and critical illness. Sepsis involves mechanical alterations associated with inflammation and circulatory disturbance (12,15,25); ARDS is characterized by abnormal lung stretch (13,17,23); AKI involves changes in renal blood and tubular flow (64-66,70); and trauma/hemorrhagic shock combines tissue deformation, hemodynamic fluctuation and ischemia-reperfusion (73,74). The principal responding cells and proposed pathological consequences differ among these conditions. The proposed Piezo1-associated signaling mechanisms and their potential contributions to organ dysfunction are summarized in Fig. 2. Table I summarizes representative experimental models, intervention approaches, the direction of Piezo1 effects and the limitations of the available evidence (13,17,23-25).

5. Therapeutic targeting of Piezo1-mediated mechanotransduction

Therapeutic strategies. As the contribution of Piezo1 to organ injury has attracted increasing attention, modulation of Piezo1-mediated mechanotransduction is a potential therapeutic strategy (10,13).

Piezo1-dependent Ca^{2+} signaling intersects with inflammation, barrier function, vascular homeostasis and cellular stress (10,25). Targeting the channel could therefore influence several pathological processes simultaneously. However, Piezo1 is also integral to normal physiology, and therapeutic development remains at a preclinical stage (10,18).

Direct pharmacological modulation is a widely used experimental strategy (79-82). Available tools include the Piezo1 agonist Yoda1, Dooku1, which antagonizes Yoda1-induced effects, and GsMTx4, a non-selective peptide inhibitor of mechanosensitive ion channels (79-82). These compounds are valuable for investigating channel biology, but limitations in selectivity, *in vivo* stability, pharmacokinetics and long-term safety preclude their current use as established therapeutics.

Beyond direct modulation of Piezo1 activity, downstream signaling in specific cell types may offer candidate targets for intervention. Pulmonary endothelial studies show that Piezo1-associated calpain signaling can contribute to adherens junction protein degradation and barrier injury (17,23)

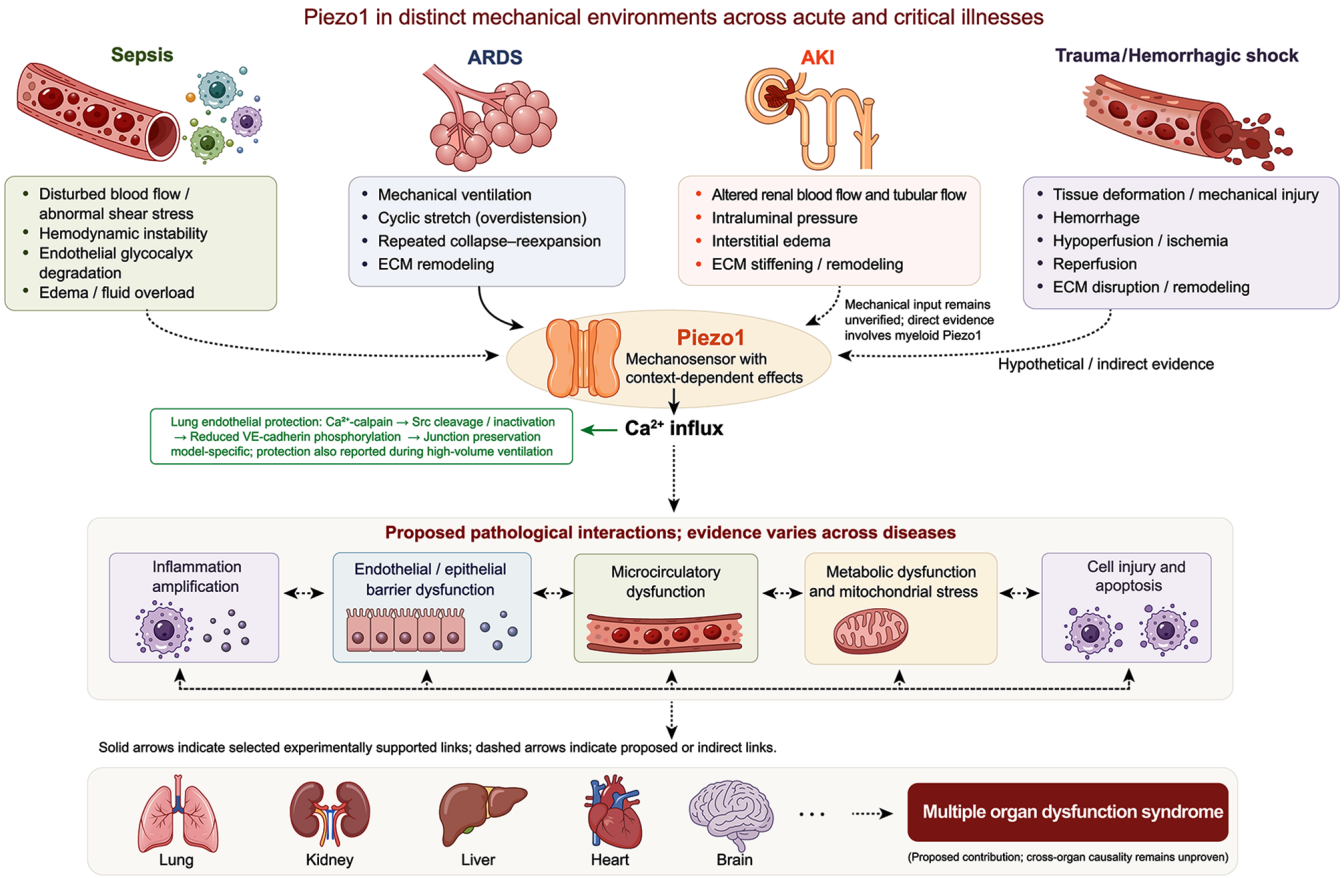


Figure 2. Piezo1 in distinct mechanical environments across acute and critical illnesses. Sepsis, ARDS, AKI and trauma/hemorrhagic shock involve different combinations of altered blood flow, mechanical stretch, pressure loading, tissue deformation, edema and ECM remodeling. These changes provide potential mechanical inputs to Piezo1, but direct evidence and the direction of its effects vary between diseases and cell types. Pulmonary endothelial studies demonstrate both barrier-disruptive and -protective effects. The protective Ca^{2+}/calpain/Src pathway shown here was identified in a high-volume mechanical ventilation model. In ischemia-reperfusion-associated AKI, direct mechanistic evidence involves myeloid Piezo1, while the relevant mechanical input is unverified. Proposed roles in trauma and hemorrhagic shock rely primarily on indirect evidence and inference across models. AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; Ca^{2+}, calcium ion; ECM, extracellular matrix; MODS, multiple organ dysfunction syndrome; VE-cadherin, vascular endothelial cadherin.

or maintain junctional stability by cleaving and inactivating Src (13).

Sepsis-associated intestinal epithelial injury provides experimental evidence linking Piezo1-mediated Ca^{2+} signaling, mitochondrial stress and barrier injury (15). Selection of downstream targets should be guided by their effects in specific models and interventions should be assessed for their potential to weaken protective signaling. Whether the benefits of modulating Ca^{2+}, reactive oxygen species or cell death depend on Piezo1 requires validation through genetic manipulation of Piezo1 and downstream rescue experiments. These candidate targets should not be regarded as established therapeutic strategies.

Lung-protective ventilation, circulatory support and resuscitation are important components of care for acute and critical illness, but their clinical benefits cannot be directly attributed to Piezo1. Lung-protective ventilation aims to limit ventilation-associated mechanical stress and reduce ventilator-induced lung injury (57), while treatment of sepsis and major traumatic hemorrhage emphasizes circulatory support and resuscitation tailored to the patient condition (83,84). These measures may alter the mechanical environment of cells, but whether they influence Piezo1 activity and the direction of effects requires direct validation. Improved perfusion cannot be assumed to decrease Piezo1 activity. In AKI, the association between improved renal perfusion and changes in Piezo1 signaling is unclear. Combining modulation of the mechanical environment with cell-specific intervention targeting Piezo1 or its downstream pathways requires validation and does not provide a basis for clinical treatment recommendations.

Challenges for clinical translation. Despite its potential therapeutic value, the clinical translation of Piezo1 targeting faces limitations (9,10,18). The foremost challenge is that Piezo1 participates in both physiological mechanical adaptation and pathological mechanotransduction. Piezo1 contributes to flow-associated mechanosensing and vascular regulation (21,29). In a high-volume mechanical ventilation model, endothelial Piezo1 was shown to maintain pulmonary vascular barrier stability (13). In infection-associated models, neutrophil Piezo1 senses mechanical constraints during transendothelial migration and enhances bactericidal function (24), while macrophage Piezo1 enhances phagocytosis and bacterial killing (25).

In models of elevated pulmonary microvascular pressure and mechanical stretch in an inflammatory context, Piezo1 contributes to endothelial junction disruption and increased vascular permeability (17,23), whereas endothelial Piezo1 maintains adherens junctions and barrier stability during high-volume

Table I. Representative evidence and limitations of Piezo1 effects in models related to acute and critical illness.

Disease/model	Experimental model/cells	Intervention	Findings	Limitations and scope of evidence	(Refs.)
Sepsis/intestinal barrier injury	Cecal ligation and puncture in mice; TNF-α-treated Caco-2 cells	Intestinal epithelial-specific Piezo1 deletion; GsMTx4 inhibition	Ca^{2+}-related signaling participates in tight junction disruption and epithelial apoptosis; deletion attenuates increased permeability and inflammation	Findings from a sepsis model may not be generalizable to other critical illness; tumor-derived cells used *in vitro* may not fully reflect the responses of normal epithelial cells or the complex *in vivo* microenvironment; GsMTx4 is not Piezo1-specific	(15)
Infection-associated macrophage defense	Bacterial infection or LPS stimulation; bone marrow-derived macrophages	Myeloid Piezo1 deletion; Piezo1 knockdown or pharmacological inhibition, and inhibition of downstream Ca^{2+}-dependent signaling	Enhanced host defense: TLR4-Piezo1 complex promotes phagocytosis and bacterial clearance via CaMKII/Mst1/2/Rac	Supports immune mechanisms in infection; not equivalent to sepsis-associated organ injury or amplification of injurious inflammation	(25)
Infection-associated neutrophil defense	Transendothelial migration, microfluidic and infection models; neutrophils	Genetic Piezo1 deficiency; mechanosensing and functional experiments	Enhanced host defense: Mechanical constraint during transendothelial migration activates Piezo1/Ca^{2+} signaling and enhances bacterial killing; HIF-1α/NOX4 signaling	No direct evidence for every sepsis stage; enhanced killing does not imply uniformly pathogenic effects; NOX4 expression and its specific contribution are disputed and require independent validation	(24,32,33)
Pulmonary barrier injury/pressure loading	Mice with elevated left atrial pressure or aortic constriction; pulmonary vascular endothelium	Inducible endothelial Piezo1 deletion; GsMTx4 and calpain inhibitor PD150606 treatment	Calpain promotes VE-cadherin and junctional protein degradation; Piezo1 deletion decreases leakage and edema	Pressure-associated pulmonary barrier model; not representative of all ARDS or ventilation contexts	(17)
ARDS-associated ventilation injury	ARDS rats; LPS-treated endothelial cells exposed to 20% cyclic stretch	*In vivo* Piezo1 shRNA; *in vitro* siRNA; Ca^{2+} and calpain pathway intervention	Piezo1/Ca^{2+}/calpain signaling contributes to adherens junction disruption and increased permeability	Combined inflammation and mechanical loading; findings differ from the protective effects of endothelial Piezo1 observed during high-volume ventilation	(23)
Ventilation-associated endothelial protection	High-volume ventilation in mice; cyclic stretch in human pulmonary endothelial cells	Endothelial-specific Piezo1 deletion or cell Piezo1 depletion; rescue experiments using the calcium ionophore	Calpain cleaves Src and limits VE-cadherin phosphorylation; Piezo1 deficiency worsens leakage	Protective effects in a high-volume ventilation model; generalizability to other ventilation conditions and clinical Piezo1 activation remains uncertain	(13)

Table I. Continued.

Disease/model	Experimental model/cells	Intervention	Findings	Limitations and scope of evidence	(Refs.)
		A23187 to increase intracellular Ca^{2+} and promote calpain activity			
Ischemia-reperfusion-associated AKI	Bilateral renal vascular clamping in mice; hypoxia-treated bone marrow-derived macrophages	Myeloid-specific Piezo1 deletion; Yoda1-mediated Piezo1 activation and calpain inhibition using PD150606	Macrophage Ca^{2+}/calpain/HIF-1α signaling involves Notch and CCL2/CCR2 and promotes inflammatory polarization; Piezo1 deletion attenuates AKI	Myeloid-specific deletion cannot isolate macrophage-specific effects; do not establish a tubular epithelial mechanism or generalizability across AKI etiologies	(16)
Trauma/hemorrhagic shock	Models of matrix stiffness sensing and vascular mechanotransduction, with trauma-associated pathophysiological evidence	Not applicable	Barrier, immune and microcirculatory effects are inferred across models	Insufficient direct causal evidence; Piezo1 is not a validated pathogenic or therapeutic target in hemorrhagic shock	(14,73-76,82)

ARDS, acute respiratory distress syndrome; AKI, acute kidney injury; LPS, lipopolysaccharide; TNF-α, tumor necrosis factor-α; VE, vascular endothelial; HIF-1α, hypoxia-inducible factor-1α; NOX4, NADPH oxidase 4; GsMTx4, Grammostola mechanotoxin 4; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; Mst1/2, mammalian sterile 20-like kinases 1 and 2; Rac, Ras-related C3 botulinum toxin substrate; sh, short hairpin; si, small interfering.

mechanical ventilation (13). These opposing findings indicate that inhibition or activation strategies cannot be selected solely on the basis of stimulation intensity or duration. The direction of intervention should be assessed in association with loading mode, inflammatory context and downstream signaling.

Prolonged systemic Piezo1 inhibition may attenuate pathological signaling while interfering with normal mechanosensing and tissue homeostasis (10).

Zhong *et al* (13) suggest that Piezo1 inhibition may weaken barrier-protective responses to mechanical stress in pulmonary endothelial cells. Endothelial-specific Piezo1 deletion exacerbates pulmonary vascular leakage induced by high-volume mechanical ventilation, indicating a protective role for endothelial Piezo1 (13). This suggests that broad Piezo1 inhibition may also weaken protective endothelial signaling, although its net effects on overall lung injury require validation. Piezo1-targeted strategies in ARDS should define the target cells and downstream pathways and assess potential benefits and risks, without assuming that channel inhibition produces consistent therapeutic effects.

The functional output of Piezo1 depends on cell type and experimental context. For example, pulmonary vascular endothelial Piezo1 protects or disrupts the barrier in different mechanical loading models (13,17); macrophage Piezo1 enhances infection-related phagocytosis and bacterial killing (25) and epithelial Piezo1 can participate in mechanical stretch-induced cell proliferation (26). Systemic treatment lacking cell specificity may suppress both harmful and beneficial responses. Achieving organ- or cell-targeted delivery while minimizing interference with mechanosensing in normal tissue is therefore an important challenge in the development of Piezo1-directed therapy.

The timing of Piezo1 intervention should be assessed in relation to disease stage, the inflammatory and metabolic status of the affected cells, the extent of cellular injury, and downstream signaling responses. Existing evidence is insufficient to define a universal intervention window across acute and critical illness (13,23). Early disease cannot be equated with a protective phase, nor can sustained mechanical stimulation be assumed to cause injury (13,17,23). Future studies should apply interventions at defined times in specific disease models, combining measurements of Piezo1 function with serial assessment of protective and injurious outcomes to identify potential intervention windows. Evidence remains insufficient to define the appropriate timing, duration, dose or intensity of intervention.

Mechanical environments in acute and critical illness are highly dynamic and disease-specific. The predominant mechanical stimuli differ among diseases, and a single disease may progress through successive changes involving hypoperfusion, tissue edema, increased pressure or reperfusion. A uniform Piezo1-directed regimen based solely on diagnosis may fail to produce consistent benefit. Clinical translation requires measures that reflect the local mechanical environment and Piezo1 activity to identify patients who may benefit and the appropriate timing of intervention.

Future perspectives. A priority is to map Piezo1 expression and activity across diseases, organs, cell types and disease stages. Cell-specific genetic manipulation, single-cell transcriptomics and spatial transcriptomics may identify Piezo1-expressing populations and their distribution. These descriptive data should be integrated with functional experiments to establish causal relationships between Piezo1 signaling and organ injury.

More selective, tissue-targeted and temporally controllable Piezo1 modulators are also needed. Alternatives to direct channel modulation include targeting downstream signaling in defined cell types and decreasing abnormal mechanical stimulation through optimized ventilation, resuscitation and organ perfusion. Whether these strategies can act synergistically with anti-inflammatory treatment, organ support and other standards of care requires further evaluation in disease models and clinical studies.

Future Piezo1-targeted strategies should account for cell type and disease context, prioritize injury-associated pathways supported by direct mechanistic evidence and assess whether interventions decrease injury while preserving normal mechanosensing, barrier maintenance and host defense. This goal requires defining the conditions under which Piezo1 shifts from adaptive to detrimental effects and identifying biomarkers that reflect the mechanical environment, channel activity and treatment response. Until sufficient human evidence is available, Piezo1 is better regarded as a research target for understanding the mechanobiology of acute and critical illness and its therapeutic value should be assessed.

6. Conclusion

Cell and animal models support a role for Piezo1 in transducing mechanical stimuli into Ca^{2+}-associated signals involved in immune regulation, barrier function and cellular stress (13,15,25). However, evidence in sepsis, ARDS and AKI comes from different models, with differences in the principal responding cells and the direction of effects (15-17,23). Proposed mechanisms in trauma and hemorrhagic shock rely mainly on indirect evidence and inference across models. Existing findings indicate that Piezo1 contributes to injury, protects barriers and enhances host defense, but do not establish a common pathological mechanism across acute and critical illness. Investigating Piezo1 from the perspective of mechanosensing and mechanotransduction complements understanding of the mechanisms underlying organ dysfunction in acute and critical illness.

Piezo1 maintains endothelial junctions or contributes to barrier disruption in different experimental models, and the direction of its effects cannot be determined solely by the intensity and duration of mechanical stimulation. Future targeting strategies should account for cell type and disease context and assess whether injury-associated signaling can be limited while preserving barrier protection and normal mechanosensing.

To the best of our knowledge, there is a lack of direct evidence in trauma, hemorrhagic shock and patients. Future research should define the roles of Piezo1 in different cell types and how these roles change during disease progression and develop tissue-targeted strategies with precise temporal control. Limiting pathological signaling while preserving normal mechanosensing may offer greater clinical value than prolonged systemic Piezo1 inhibition.

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Availability of data and materials

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Authors' contributions

LZ and HG conceived the study. YZ, LT, JA, HJ, JZ and BT revised the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, Colombara DV, Ikuta KS, Kissoon N, Finfer S, *et al*: Global, regional, and national sepsis incidence and mortality, 1990-2017: Analysis for the Global Burden of disease study. Lancet 395: 200-211, 2020.
2. Adhikari NK, Fowler RA, Bhagwanjee S and Rubenfeld GD: Critical care and the global burden of critical illness in adults. Lancet 376: 1339-1346, 2010.
3. Marshall JC: Why have clinical trials in sepsis failed? Trends Mol Med 20: 195-203, 2014.
4. Cecconi M, Evans L, Levy M and Rhodes A: Sepsis and septic shock. Lancet 392: 75-87, 2018.
5. van der Poll T, Shankar-Hari M and Wiersinga WJ: The immunology of sepsis. Immunity 54: 2450-2464, 2021.

6. Rousseau AF and Martindale R: Nutritional and metabolic modulation of inflammation in critically ill patients: A narrative review of rationale, evidence and grey areas. Ann Intensive Care 14: 121, 2024.
7. Fang Y, Wu D and Birukov KG: Mechanosensing and mechanoregulation of endothelial cell functions. Compr Physiol 9: 873-904, 2019.
8. Lim XR and Harraz OF: Mechanosensing by vascular endothelium. Annu Rev Physiol 86: 71-97, 2024.
9. Xiao B: Mechanisms of mechanotransduction and physiological roles of PIEZO channels. Nat Rev Mol Cell Biol 25: 886-903, 2024.
10. Murthy SE, Dubin AE and Patapoutian A: Piezos thrive under pressure: Mechanically activated ion channels in health and disease. Nat Rev Mol Cell Biol 18: 771-783, 2017.
11. Karkempetzaki AI and Ravid K: Piezo1 and its function in different blood cell lineages. Cells 13: 482, 2024.
12. McMullan RR, McAuley DF, O'Kane CM and Silversides JA: Vascular leak in sepsis: Physiological basis and potential therapeutic advances. Crit Care 28: 97, 2024.
13. Zhong M, Wu W, Kang H, Hong Z, Xiong S, Gao X, Rehman J, Komarova YA and Malik AB: Alveolar stretch activation of endothelial piezo1 protects adherens junctions and lung vascular barrier. Am J Respir Cell Mol Biol 62: 168-177, 2020.
14. Atcha H, Jairaman A, Holt JR, Meli VS, Nagalla RR, Veerasubramanian PK, Brumm KT, Lim HE, Othy S, Cahalan MD, *et al*: Mechanically activated ion channel Piezo1 modulates macrophage polarization and stiffness sensing. Nat Commun 12: 3256, 2021.
15. Yan Z, Niu L, Wang S, Gao C and Pan S: Intestinal Piezo1 aggravates intestinal barrier dysfunction during sepsis by mediating Ca(2+) influx. J Transl Med 22: 332, 2024.
16. Chen X, Jiang J, He B, Luo S, Tan Q, Yao Y, Wan R, Xu H, Liu S, Pan X, *et al*: Piezo1 aggravates ischemia/reperfusion-induced acute kidney injury by Ca(2+)-dependent calpain/HIF-1α/Notch signaling. Ren Fail 47: 2447801, 2025.
17. Friedrich EE, Hong Z, Xiong S, Zhong M, Di A, Rehman J, Komarova YA and Malik AB: Endothelial cell Piezo1 mediates pressure-induced lung vascular hyperpermeability via disruption of adherens junctions. Proc Natl Acad Sci USA 116: 12980-12985, 2019.
18. Coste B, Xiao B, Santos JS, Syeda R, Grandl J, Spencer KS, Kim SE, Schmidt M, Mathur J, Dubin AE, *et al*: Piezo proteins are pore-forming subunits of mechanically activated channels. Nature 483: 176-181, 2012.
19. Ge J, Li W, Zhao Q, Li N, Chen M, Zhi P, Li R, Gao N, Xiao B and Yang M: Architecture of the mammalian mechanosensitive Piezo1 channel. Nature 527: 64-69, 2015.
20. Syeda R, Florendo MN, Cox CD, Kefauver JM, Santos JS, Martinac B and Patapoutian A: Piezo1 channels are inherently mechanosensitive. Cell Rep 17: 1739-1746, 2016.
21. Li J, Hou B, Tumova S, Muraki K, Bruns A, Ludlow MJ, Sedo A, Hyman AJ, McKeown L, Young RS, *et al*: Piezo1 integration of vascular architecture with physiological force. Nature 515: 279-282, 2014.
22. Zhang X, Liu J, Deng X and Bo L: Understanding COVID-19-associated endothelial dysfunction: role of PIEZO1 as a potential therapeutic target. Front Immunol 15: 1281263, 2024.
23. Jiang L, Zhang Y, Lu D, Huang T, Yan K, Yang W and Gao J: Mechanosensitive piezo1 channel activation promotes ventilator-induced lung injury via disruption of endothelial junctions in ARDS rats. Biochem Biophys Res Commun 556: 79-86, 2021.
24. Mukhopadhyay A, Tsukasaki Y, Chan WC, Le JP, Kwok ML, Zhou J, Natarajan V, Mostafazadeh N, Maienschein-Cline M, Papautsky I, *et al*: trans-Endothelial neutrophil migration activates bactericidal function via Piezo1 mechanosensing. Immunity 57: 52-67.e10, 2024.
25. Geng J, Shi Y, Zhang J, Yang B, Wang P, Yuan W, Zhao H, Li J, Qin F, Hong L, *et al*: TLR4 signalling via Piezo1 engages and enhances the macrophage mediated host response during bacterial infection. Nat Commun 12: 3519, 2021.
26. Gudipaty SA, Lindblom J, Loftus PD, Redd MJ, Edes K, Davey CF, Krishnegowda V and Rosenblatt J: Mechanical stretch triggers rapid epithelial cell division through Piezo1. Nature 543: 118-121, 2017.
27. Liu H, Hu J, Zheng Q, Feng X, Zhan F, Wang X, Xu G and Hua F: Piezo1 channels as force sensors in mechanical force-related chronic inflammation. Front Immunol 13: 816149, 2022.
28. Joffre J, Hellman J, Ince C and Ait-Oufella H: endothelial responses in sepsis. Am J Respir Crit Care Med 202: 361-370, 2020.
29. Wang S, Chennupati R, Kaur H, Iring A, Wettschureck N and Offermanns S: Endothelial cation channel PIEZO1 controls blood pressure by mediating flow-induced ATP release. J Clin Invest 126: 4527-4536, 2016.
30. Mei F, Guo Y, Wang Y, Zhou Y, Heng BC, Xie M, Huang X, Zhang S, Ding S, Liu F, *et al*: Matrix stiffness regulates macrophage polarisation via the Piezo1-YAP signalling axis. Cell Prolif 57: e13640, 2024.
31. Baratchi S, Danish H, Chheang C, Zhou Y, Huang A, Lai A, Khanmohammadi M, Quinn KM, Khoshmanesh K and Peter K: Piezo1 expression in neutrophils regulates shear-induced NETosis. Nat Commun 15: 7023, 2024.
32. Knaus UG, Clark RA, Nauseef WM, Dinauer MC, Leto TL and Jaquet V: Challenging the role of a NOX4-Piezo1 axis in neutrophil bactericidal function. Immunity 57: 1716-1718, 2024.
33. Mukhopadhyay A, Natarajan V, Komarova Y and Malik AB: Neutrophils meet their fate in endothelial adherens junctions. Immunity 57: 1719-1720, 2024.
34. Dalal PJ, Muller WA and Sullivan DP: Endothelial cell calcium signaling during barrier function and inflammation. Am J Pathol 190: 535-542, 2020.
35. Rode B, Shi J, Endesh N, Drinkhill MJ, Webster PJ, Lotteau SJ, Bailey MA, Yuldasheva NY, Ludlow MJ, Cubbon RM, *et al*: Piezo1 channels sense whole body physical activity to reset cardiovascular homeostasis and enhance performance. Nat Commun 8: 350, 2017.
36. Cahalan SM, Lukacs V, Ranade SS, Chien S, Bandell M and Patapoutian A: Piezo1 links mechanical forces to red blood cell volume. Elife 4: e07370, 2015.
37. De Backer D, Orbegozo Cortes D, Donadello K and Vincent JL: Pathophysiology of microcirculatory dysfunction and the pathogenesis of septic shock. Virulence 5: 73-79, 2014.
38. Singer M: The role of mitochondrial dysfunction in sepsis-induced multi-organ failure. Virulence 5: 66-72, 2014.
39. Giorgi C, Marchi S and Pinton P: The machineries, regulation and cellular functions of mitochondrial calcium. Nat Rev Mol Cell Biol 19: 713-730, 2018.
40. Pinton P, Giorgi C, Siviero R, Zecchini E and Rizzuto R: Calcium and apoptosis: ER-mitochondria Ca2+ transfer in the control of apoptosis. Oncogene 27: 6407-6418, 2008.
41. West AP, Brodsky IE, Rahner C, Woo DK, Erdjument-Bromage H, Tempst P, Walsh MC, Choi Y, Shadel GS and Ghosh S: TLR signalling augments macrophage bactericidal activity through mitochondrial ROS. Nature 472: 476-480, 2011.
42. Hardie DG: AMPK: A key regulator of energy balance in the single cell and the whole organism. Int J Obes (Lond) 32 (Suppl 4): S7-S12, 2008.
43. Kono H and Rock KL: How dying cells alert the immune system to danger. Nat Rev Immunol 8: 279-289, 2008.
44. Gong T, Liu L, Jiang W and Zhou R: DAMP-sensing receptors in sterile inflammation and inflammatory diseases. Nat Rev Immunol 20: 95-112, 2020.
45. Lewis AH and Grandl J: Mechanical sensitivity of Piezo1 ion channels can be tuned by cellular membrane tension. Elife 4: e12088, 2015.
46. Nava MM, Miroshnikova YA, Biggs LC, Whitefield DB, Metge F, Boucas J, Vihinen H, Jokitalo E, Li X, García Arcos JM, *et al*: Heterochromatin-Driven nuclear softening protects the genome against mechanical stress-induced damage. Cell 181: 800-817. e22, 2020.
47. Blázquez-Prieto J, Huidobro C, López-Alonso I, Amado-Rodriguez L, Martín-Vicente P, López-Martínez C, Pantoja C, Fernandez-Marcos PJ, Serrano M, Sznajder JI and Albaiceta GM: Activation of p21 limits acute lung injury and induces early senescence after acid aspiration and mechanical ventilation. Transl Res 233: 104-116, 2021.
48. Li F, Lo TY, Miles L, Wang Q, Noristani HN, Li D, Niu J, Trombley S, Goldshteyn JI, Wang C, *et al*: The Atr-Chek1 pathway inhibits axon regeneration in response to Piezo-dependent mechanosensation. Nat Commun 12: 3845, 2021.
49. Borges A and Bento L: Organ crosstalk and dysfunction in sepsis. Ann Intensive Care 14: 147, 2024.
50. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, *et al*: The Third International consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 315: 801-810, 2016.

51. Hotchkiss RS, Moldawer LL, Opal SM, Reinhart K, Turnbull IR and Vincent JL: Sepsis and septic shock. Nat Rev Dis Primers 2: 16045, 2016.
52. Uchimido R, Schmidt EP and Shapiro NI: The glycocalyx: A novel diagnostic and therapeutic target in sepsis. Crit Care 23: 16, 2019.
53. Ince C, Mayeux PR, Nguyen T, Gomez H, Kellum JA, Ospina-Tascón GA, Hernandez G, Murray P and De Backer D; ADQI XIV Workgroup: The endothelium in sepsis. Shock 45: 259-270, 2016.
54. Solis AG, Bielecki P, Steach HR, Sharma L, Harman CCD, Yun S, de Zoete MR, Warnock JN, To SDF, York AG, *et al*: Mechanosensation of cyclical force by PIEZO1 is essential for innate immunity. Nature 573: 69-74, 2019.
55. Atcha H, Meli VS, Davis CT, Brumm KT, Anis S, Chin J, Jiang K, Pathak MM and Liu WF: Crosstalk between CD11b and piezo1 mediates macrophage responses to mechanical cues. Front Immunol 12: 689397, 2021.
56. Matthay MA, Zemans RL, Zimmerman GA, Arabi YM, Beitler JR, Mercat A, Herridge M, Randolph AG and Calfee CS: Acute respiratory distress syndrome. Nat Rev Dis Primers 5: 18, 2019.
57. Slutsky AS and Ranieri VM: Ventilator-induced lung injury. N Engl J Med 369: 2126-2136, 2013.
58. Thompson BT, Chambers RC and Liu KD: Acute respiratory distress syndrome. N Engl J Med 377: 562-572, 2017.
59. Tao M, Xu Y, Bai L, Wang G, Liang W, Chen Q, Qin C and Yu H: Piezo1 in respiratory diseases: Mechanotransduction, cell-specific functions, and translational implications. Front Physiol 17: 1885524, 2026.
60. Jia Q, Yang Y, Chen X, Yao S and Hu Z: Emerging roles of mechanosensitive ion channels in acute lung injury/acute respiratory distress syndrome. Respir Res 23: 366, 2022.
61. Grannemann C, Pabst A, Honert A, Schieren J, Martin C, Hank S, Böll S, Bläsius K, Düsterhöft S, Jahr H, *et al*: Mechanical activation of lung epithelial cells through the ion channel Piezo1 activates the metalloproteinases ADAM10 and ADAM17 and promotes growth factor and adhesion molecule release. Biomater Adv 152: 213516, 2023.
62. Liang GP, Xu J, Cao LL, Zeng YH, Chen BX, Yang J, Zhang ZW and Kang Y: Piezo1 induced apoptosis of type II pneumocytes during ARDS. Respir Res 20: 118, 2019.
63. Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, Edipidis K, Forni LG, Gomersall CD, Govil D, *et al*: Epidemiology of acute kidney injury in critically ill patients: The multinational AKI-EPI study. Intensive Care Med 41: 1411-1423, 2015.
64. Kellum JA, Romagnani P, Ashuntantang G, Ronco C, Zarbock A and Anders HJ: Acute kidney injury. Nat Rev Dis Primers 7: 52, 2021.
65. Zarbock A, Nadim MK, Pickkers P, Gomez H, Bell S, Joannidis M, Kashani K, Koyner JL, Pannu N, Meersch M, *et al*: Sepsis-associated acute kidney injury: Consensus report of the 28th acute disease quality initiative workgroup. Nat Rev Nephrol 19: 401-417, 2023.
66. Ostermann M and Rosner MH: Paths to organ damage and risk factors in AKI. Nat Rev Nephrol 19: 77-78, 2023.
67. Ferenbach DA and Bonventre JV: Mechanisms of maladaptive repair after AKI leading to accelerated kidney ageing and CKD. Nat Rev Nephrol 11: 264-276, 2015.
68. Ingber DE: Mechanobiology and diseases of mechanotransduction. Ann Med 35: 564-577, 2003.
69. Verschuren EHJ, Castenmiller C, Peters DJM, Arjona FJ, Bindels RJM and Hoenderop JGJ: Sensing of tubular flow and renal electrolyte transport. Nat Rev Nephrol 16: 337-351, 2020.
70. Nauli SM and Zhou J: Polycystins and mechanosensation in renal and nodal cilia. Bioessays 26: 844-856, 2004.
71. Li ZL, Li XY, Zhou Y, Wang B, Lv LL and Liu BC: Renal tubular epithelial cells response to injury in acute kidney injury. EBioMedicine 107: 105294, 2024.
72. Li Z, Liu Z, Luo M, Li X, Chen H, Gong S, Zhang M, Zhang Y, Liu H and Li X: The pathological role of damaged organelles in renal tubular epithelial cells in the progression of acute kidney injury. Cell Death Discov 8: 239, 2022.
73. Lord JM, Midwinter MJ, Chen YF, Belli A, Brohi K, Kovacs EJ, Koenderman L, Kubes P and Lilford RJ: The systemic immune response to trauma: an overview of pathophysiology and treatment. Lancet 384: 1455-1465, 2014.
74. Cannon JW: Hemorrhagic shock. N Engl J Med 378: 370-379, 2018.
75. Anand T, Reyes AA, Sjoquist MC, Magnotti L and Joseph B: Resuscitating the endothelial glycocalyx in trauma and hemorrhagic shock. Ann Surg Open 4: e298, 2023.
76. Ranade SS, Qiu Z, Woo SH, Hur SS, Murthy SE, Cahalan SM, Xu J, Mathur J, Bandell M, Coste B, *et al*: Piezo1, a mechanically activated ion channel, is required for vascular development in mice. Proc Natl Acad Sci USA 111: 10347-10352, 2014.
77. Beech DJ and Kalli AC: Force sensing by piezo channels in cardiovascular health and disease. Arterioscler Thromb Vasc Biol 39: 2228-2239, 2019.
78. Aird WC: Endothelium as an organ system. Crit Care Med 32 (5 Suppl): S271-S279, 2004.
79. Evans EL, Cuthbertson K, Endesh N, Rode B, Blythe NM, Hyman AJ, Hall SJ, Gaunt HJ, Ludlow MJ, Foster R and Beech DJ: Yoda1 analogue (Dooku1) which antagonizes Yoda1-evoked activation of Piezo1 and aortic relaxation. Br J Pharmacol 175: 1744-1759, 2018.
80. Gnanasambandam R, Ghatak C, Yasmann A, Nishizawa K, Sachs F, Ladokhin AS, Sukharev SI and Suchyna TM: GsMTx4: Mechanism of inhibiting mechanosensitive ion channels. Biophys J 112: 31-45, 2017.
81. Syeda R, Xu J, Dubin AE, Coste B, Mathur J, Huynh T, Matzen J, Lao J, Tully DC, Engels IH, *et al*: Chemical activation of the mechanotransduction channel Piezo1. Elife 4: e07369, 2015.
82. Coste B and Delmas P: PIEZO ion channels in cardiovascular functions and diseases. Circ Res 134: 572-591, 2024.
83. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, Machado FR, Mcintyre L, Ostermann M, Prescott HC, *et al*: Surviving sepsis campaign: International guidelines for management of sepsis and septic shock 2021. Crit Care Med 49: e1063-e1143, 2021.
84. Rossaint R, Afshari A, Bouillon B, Cerny V, Cimpoesu D, Curry N, Duranteau J, Filipescu D, Grottke O, Grønlykke L, *et al*: The European guideline on management of major bleeding and coagulopathy following trauma: sixth edition. Crit Care 27: 80, 2023.

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