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REVIEW ARTICLE

Pannexin 1 as a driver of inflammation and ischemia–reperfusion injury

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Abstract

Pannexin 1 (Panx1) is a ubiquitously expressed protein forming large conductance channels that are central to many distinct inflammation and injury responses. There is accumulating evidence showing ATP released from Panx1 channels, as well as metabolites, provide effective paracrine and autocrine signaling molecules that regulate different elements of the injury response. As channels with a broad range of permselectivity, Panx1 channels mediate the secretion and uptake of multiple solutes, ranging from calcium to bacterial derived molecules. In this review, we describe how Panx1 functions in response to different pro-inflammatory stimuli, focusing mainly on signaling coordinated by the vasculature. How Panx1 mediates ATP release by injured cells is also discussed. The ability of Panx1 to serve as a central component of many diverse physiologic responses has proven to be critically dependent on the context of expression, post-translational modification, interacting partners, and the mode of stimulation.

Keywords Pannexin 1 · Inflammation · Purinergic signaling

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This article is part of the Topical Collection on The contribution of pannexin-1, connexins and CALHM ATP-release channels to purinergic signalling — Guest Editor Charles Kennedy

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Introduction

Stimulated secretion of cytosolic metabolites, including ATP, is an important mechanism for paracrine and autocrine signaling. Among several mechanisms of ATP release, including plasma membrane channels, vesicular exocytosis, and extracellular synthesis [1], pannexin channels have emerged as an important mediator of ATP secretion that regulates multiple processes involved in inflammation and other injury responses.

Pannexins were discovered in 2000 [2], based on a search for mammalian proteins that are homologous to invertebrate gap junction proteins, innexins [3]. Initially, it was thought that pannexins were functionally equivalent to the classical mammalian gap junction proteins, connexins. However, instead of assembling into gap junctions [4], the vast preponderance of evidence supports a role for pannexins as plasma membrane channels (and not hemichannels), forming a high conductance pore that can mediate the release of cytosolic ions and metabolites, including ATP.

Pannexin channels have been linked to pathophysiological processes related to the vasculature, including hypertension [5–8], stroke [9, 10], and inflammation/ischemic injury [11–15], possibly including complications due to COVID-19 [16]. In this review, we summarize current progress in identifying roles for the most ubiquitous pannexin isoform, Panx1, in regulating how the vasculature reacts to injury and inflammation.

Pannexin 1 structure, function, and post-translational modifications

There are three pannexin isoforms (Panx1, Panx2, Panx3) that exhibit a high degree of amino acid sequence conservation [17–19]. It is not common to observe more than one pannexin isoform in a cell type, although Panx1 is fairly ubiquitous. Panx2 is expressed in the central nervous system, and Panx3 can be found in the skin, osteoblasts, or specialized cartilage of the mouse [18, 20]. Elements of the vasculature show differential pannexin expression as well [21]. Although their expression is highly regulated, pannexins share considerable functional redundancy. This is underscored by several studies using pannexin knockout mice demonstrating that global knockout of one pannexin is compensated by upregulation of another isoform [22–25].

Pannexins form large conductance, relatively non-selective channels that can mediate permeability of both anionic and cationic molecules up to 1 kDa in size [26]. Molecules passively diffuse through Panx1 channels, following concentration gradients, and as solute size increases, the permselectivity of Panx1 favors anions over cations [27]. Pannexin 1 forms gated channels, with multiple subconductance states which can also regulate solute permselectivity [28]. Because of the relatively broad selectivity of Panx1 and the confounding effects of other channels in situ, it has proven challenging to directly attribute permeability of specific substrates to Panx1; however, recently, proteoliposomes containing purified Panx1 have been used to directly demonstrate and measure channel permeability and ATP release [26].

The vast majority of work has focused on Panx1 as an ATP channel, with multiple stimuli inducing ATP secretion as a paracrine signaling pathway. However, physiologic roles for Panx1 are not limited to secretion, as more recent evidence has shown that Panx1 can also act as a plasma membrane calcium channel, increasing cytosolic calcium in response to stimuli, such as TNFα [29, 30]. Several other solutes have been shown to be transmitted through Panx1 including fluorescent tracers, anandamide, lactate, glutamate, spermidine, and bacterial products, consistent with roles for Panx1 in multiple different signaling pathways [26, 27, 31–33].

Endogenous pannexins typically oligomerize into homomeric channels, although it is possible to generate heteromeric channels in vitro using transfected cells expressing two or three different pannexins [34]. Initially, it was thought that Panx1 forms hexamers [17], comparable to connexin hemichannels [35]; however, several labs, remarkably all at once in 2020, provided cryo-EM evidence that Panx1 forms heptameric channels [36–41]. There is evidence suggesting that Panx2 may form octomers [17] and the oligomerization state of Panx3 has not been determined. In general, little is known about how pannexin oligomerization is regulated and this is an area in need of additional research that may provide more insight into structure/function relationships of Panx1, as well as the other pannexin channels.

Evidence suggests Panx1 preferentially occupies caveolin-based cholesterol-enriched membrane microdomains (lipid rafts) [42]. In terms of other purinergic signaling components, this is a logical location for Panx1 channels since localization to rafts has the potential to facilitate complex formation with other components involved in Panx1 signaling that are also localized to caveolin-based lipid domains, e.g., CD73 and CD39 [43, 44], creating a localized signaling microdomain for purinergic-based signaling.

Panx1 is an exceptionally long lived protein, in contrast with connexins, that have a rapid rate of turnover (reviewed in [45, 46]). Although Panx1 turnover has not been measured using traditional pulse-chase assays, transient stimulation of endothelial cells with TNFα causes a spike in Panx1 protein content that takes 6–7 days to return to baseline levels [29]. In addition, the presence of Panx1 in red blood cells, which lack mRNA, also suggests that Panx1 can remain active for an extended amount of time in the plasma membrane [47]. Delivery to the plasma membrane is an exquisitely

regulated process for Panx1, mediated by motifs and/or post-translational modifications (see below) [48, 49]. Once at the plasma membrane, strong evidence has demonstrated that extracellular ATP itself can induce internalization of the channel, providing an important negative feedback loop for Panx1 channel regulation [50, 51].

There are several post-translational modifications of Panx1 that can regulate trafficking and function including glycosylation, S-nitrosylation, caspase cleavage, and Src activation (Fig. 1). N-glycosylation is a critical post-translational modification facilitating trafficking, quality control, and protein folding of Panx1. N-glycosylation consensus sites are present in all three pannexins and have been shown to control the intracellular localization of pannexins and how they interact with other members of the pannexin family [34]. The importance of N-glycosylation for Panx1 processing and function is underscored by recent discoveries that mutations affecting Panx1 glycosylation are associated with cancer, infertility, and neonatal lethality [52, 53].

Caspase cleavage of Panx1 was first described as a mechanism to permanently activate channel opening [54] and increase channel permeability [26]. Caspase 3 and 7 cleaves the human Panx1 isoform [55] at residues 376–379, resulting in a constitutively open and active channel. Because of this constitutive opening, the cells are apoptosing, and cell death is imminent. In this state, ATP is released as a "find-me" signal from apoptotic immune cells in order to recruit macrophages, which is critical for a proper immune response [54].

S-nitrosylation is an important post-translational modification observed extensively in the vasculature and acts by adding a nitrosyl group to cysteine (C) residues to reversibly alter protein function [56]. Lohman et al. showed that nitrosylation of either C40 (N-terminus) or C346 (carboxyl tail) residues [57] potently inhibited Panx1 function, with other cysteines (e.g., C426) having no observable change. They showed the ATP and channel current inhibited by NO donors GSNO and DEA NONOate. This post-translational modification may be especially an important regulator in the nitrosothiol-rich circulation.

Multiple lines of evidence demonstrate an important role for sarcoma (Src) family kinases (SFKs) in Panx1 channel

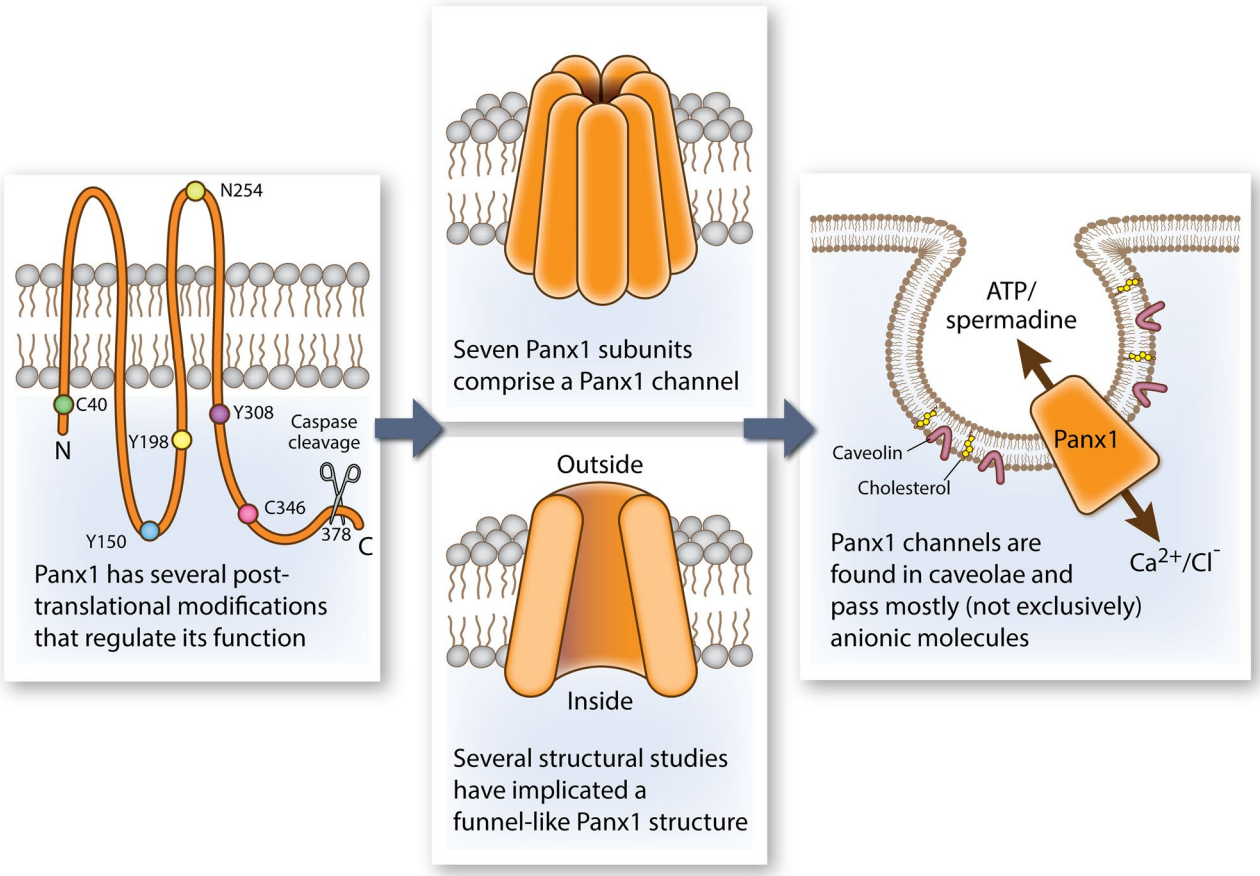

Fig. 1 The Pannexin 1 channel in the plasma membrane, including identified post-translational modification sites, heptameric structure, caveolin-enriched location, and permeability

regulation [58] at tyrosine (Y) sites Y150 [52], Y198 [6], and Y308 [10]. Dynamic regulation of the Y150 site was shown to be required for complex N-glycosylation and overall trafficking of Panx1 to the plasma membrane. This is in comparison to constitutive phosphorylation of Y198 on the intracellular loop of Panx1 which was found to be important for Panx1 channel opening. A mimetic peptide against this region ("PxIL2P") was able to inhibit Panx1 current, ATP release, and alpha-adrenergic vasoconstriction; more general Panx1 inhibition was also noted in endothelium and renin-secreting cells [5–7, 30, 49, 59]. Although the Y308 site has not been found to be as important in terms of plasma membrane localization or trafficking, it is similar to Y198, in that it was important for gating properties, including ATP release and current [10, 60]. Peptides against this region ("TAT-$Panx_{308}$") were also found to be potent inhibitors and were associated with decreased plaque size after stroke [60].

With respect to peptide inhibition of Panx1, ^{10}Panx1 was the first "specific" pannexin blocker that had demonstrated some specificity in an in vitro based system [61]. Unlike the physiological effects observed with PxIL2P or TAT-$Panx_{308}$, inhibition of Panx1 channel conductance by ^{10}Panx1 in vivo has not been demonstrated. Interestingly, the connexin hemichannel peptide mimetics have also been shown to block Panx1 channels, indicating these inhibitors may be helpful in blocking all large-pore channels rather than just connexin hemichannels alone [62]. Pharmacologically, several inhibitors that are currently utilized show varying degrees of specificity towards pannexins, including mefloquine [63], probenecid [8, 64], trovafloxacin [65], and carbenoxolone [66]. Surprisingly, one of the most potent and specific inhibitors in terms of blocking Panx1 specifically, and not other large-pore channels (e.g., Cx43 or Panx2), is the anti-hypertensive spironolactone [7]. Both spironolactone and trovafloxacin were identified using unbiased screens for Panx1 inhibitors and both blocked Panx1 as demonstrated by single-channel recordings and inhibition of ATP release.

It is now clear genetic deletion of pannexins should preferentially utilize cell type-specific, inducible animals whenever possible. Evidence from multiple laboratories has demonstrated that other pannexins (e.g., Panx3) are upregulated to compensate for loss of Panx1 in global knockout mice (e.g., [22–25]). This is not necessarily an usual finding, considering that global knockouts must compensate during development for the loss of essential proteins (e.g., similar findings are observed with connexins [67]). In addition, sex dimorphism is another potential explanation for apparently discordant results observed for global Panx1 knockout mice [68].

Inflammation and sepsis

ATP release from Panx1 channels has been implicated in several aspects of inflammation. For instance, ATP release via Panx1 channels is necessary for appropriate clearance of apoptotic cells [54], where it acts as a "find-me" signal to instruct the chemotaxis of local immune cells to locate apoptotic cells. ATP release is also stimulated by TNFα, a key mediator of inflammation, where it promotes immune cell transmigration [11]. Panx1 has also been shown to amplify the effects of chronic TNFα exposure on endothelial cells by promoting the secretion of IL-1β through a Ca^{+2} and NFκB-dependent pathway [59]. This result highlights a dual role for Panx1 in regulating the acute phase of inflammation (via ATP release) and chronic phase (via Ca^{+2} uptake) (Fig. 2). This differential role of Panx1 is most likely due to differences in conformation or post-translational modifications leading to different subconductance states. Further work is needed to determine mechanisms that underlie the differential regulation of Panx1 during acute versus chronic inflammation.

In addition to releasing ATP, TNFα stimulated ATP secreted by venous endothelial cells can be metabolized by the CD39/CD73 complex to generate adenosine, which stimulates TRPV4 channels to increase vessel permeability [12]. The Panx1 inhibitor spironolactone was shown to be an effective inhibitor of vascular leak [12]. This suggests a potential Panx-specific pharmacological approach to treat edema associated with inflammation (e.g., pulmonary edema due to sepsis demonstrated using the cecal ligation and puncture model), since venous endothelial cells can distinguish ATP as a homing signal from adenosine as a permeability signal. This enables venules to coordinate an orderly transmigration response to inflammation. In this model, ATP release is an early event that attracts cells to sites of damage. Once recruited, hydrolysis of ATP to adenosine increases vessel permeability, making them more amenable to transmigration of inflammatory cells. Note also that ATP hydrolysis releases immune cells from strong attachment to the endothelium which also stimulates migration across the vascular barrier [69, 70].

In addition to preventing pulmonary edema in response to sepsis, Panx1 deficient mice and mice treated with spironolactone had an increased lifespan following cecal ligation and puncture [12]. This is consistent with reports showing that targeting Panx1 can have a beneficial effect in endotoxemia and models of sepsis [71–73]. Considering that sepsis is a significant public health concern, the ability to target Panx1 to control the severity of sepsis is an appealing pharmacologic approach.

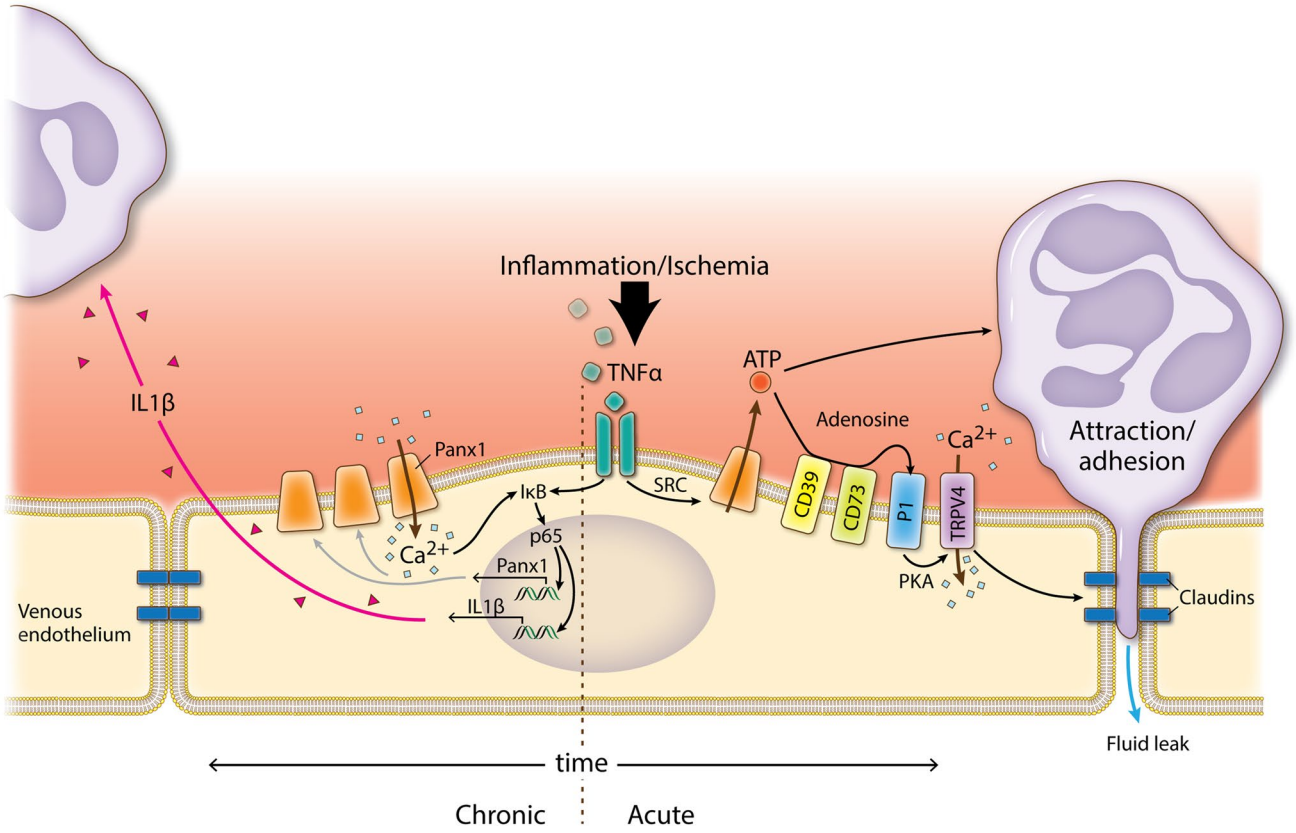

Fig. 2 Possible inflammatory pathways utilized during ischemia reperfusion injury that involve Pannexin 1

Ischemia–reperfusion injury

The interruption of blood flow (ischemia) is catastrophic in that it prevents tissue oxygenation leading to an imbalance between metabolic demand and supply, resulting in tissue hypoxia [74]. Ischemia can be due to multiple insults including thrombosis, atherosclerotic plaques, embolism, and surgically clamped vessels. However, the subsequent restoration of blood flow (reperfusion) and resultant reoxygenation creates a significant injury response called ischemia–reperfusion injury (IRI) [14]. IRI is often accompanied by significant tissue damage and a severe inflammatory response [74, 75]. It also involves a complex cascade of processes involving the interplay between innate immune cells and endothelial cells [76].

IRI is implicated in morbidity and mortality in a broad spectrum of pathologies, such as cardiac arrest, acute kidney injury, myocardial infarction, ischemic stroke, trauma, sickle cell disease, and sleep apnea. IRI is also an important comorbidity associated with organ transplant, cardiac, and vascular surgeries [74]. In transplant, IRI has been linked to higher morbidity and mortality by increasing chances of graft rejection and may lead to graft damage [77]. Interestingly, multiorgan failure after inflammatory activation may be a consequence of IRI in a single organ, consistent with a systemic response to local disruption of blood flow [78]. Increased microvascular permeability is another consequence of IRI that is especially dangerous in lung transplant patients as it may lead to respiratory failure due to dysfunction of the alveolar-capillary barrier [15, 79].

During ischemia, anaerobic metabolism in cells predominates, which lowers ATP production and cellular pH. This is due in part to mitochondrial damage, where subsequent impairment of ATP production is caused by the dissipation of membrane potential after the opening of the mitochondrial permeability transition pore (MPT) [76]. Consequently, the Na^+/H^+ exchanger releases excess hydrogen ions from the cytosol, causing an influx in sodium [80, 81]. In addition, there is an increase in intracellular calcium in response to ischemia because decreased ATP levels are unable to support efficient Ca^{2+} efflux and sequestration. Reperfusion restores oxygen supply, and aerobic ATP production is again possible, which restores normal pH. However, there are several deleterious consequences of reperfusion, including endothelial dysfunction, inflammatory responses, and generation of reactive oxygen species (ROS) [75].

Purinergic signaling has a pivotal role during IRI, since ATP is released from apoptotic cells, activated endothelium,

inflammatory cells, and necrotic cells [33]. ATP accumulation acts as a "find me" signal, which recruits phagocytes to sites of injury promoting the chemotaxis of inflammatory cells or activating the Nlrp3 inflammasome [74]. This promotes the release of the key cytokines that primarily regulate the vascular cell phenotype during acute systemic inflammation, including IL-1β and TNFα, intensifying IRI by creating an over-exuberant inflammatory response [82]. Because IRI is so closely related to circulating levels of ATP, the role for pannexins has been an active area of research.

Brain

Panx1 expression has been found through the brain, including in neurons [83–85], astrocytes [86], microglia [87], and cerebral endothelial and smooth muscle cells [9, 88]. Early studies demonstrated the opening of a large conductance plasma membrane channel in hippocampal pyramidal neurons due to oxygen–glucose deprivation (OGD) [89]. This channel was found to be Panx1, and it was postulated that opening of Panx1 channels by OGD was responsible for increased membrane permeability seen in necrotic cell death of neurons and that release of molecules such as ATP and glucose through Panx1 channels might compromise neuronal recovery [89].

Later work established that Panx1 channels are physiologically opened by N-methyl-D-aspartate receptor (NMDAR) stimulation [90]. This finding drove work to define roles of the NMDAR-Panx1 pathway under ischemic conditions, since NMDARs drive ischemic neuronal death through excitotoxicity that dysregulates intracellular Ca^{2+} homeostasis [91]. It should be noted that it was initially reported that Panx1 opening in OGD was NMDAR-independent [89] and that Panx1 was activated by other components of ischemia, including increased extracellular K^+ [92].

Anoxic neurons can aberrantly depolarize, which was observed in hippocampal pyramidal neurons driven by NMDAR activation and subsequent opening of Panx1 channels. Panx1 opening in this context was mediated through activation of sarcoma (Src) family kinase leading to phosphorylation at Y308 on the C-terminal domain of Panx1 [10]. Further work delineated that although NMDAR activation was necessary for ischemia-induced excitotoxicity, neuronal blebbing and cell death occurred as a result of Panx1 channel activity and was not dependent on NMDAR pore function [60]. Blockade of the NMDAR pore with MK-801 or physiological Mg^{2+} did not block excitotoxic blebbing or Panx1 secondary currents in hippocampal pyramidal neurons. Instead, this suggested that NMDAR signaling drives Src kinase-mediated opening of Panx1 channels, resulting in neuronal excitotoxicity [60]. Critically, blockade of this Panx1 using TAT-$Panx_{308}$ reduced infarct volumes and improved sensorimotor deficits after Middle Cerebral Artery Occlusion (MCAO) in rats [60], a finding that has been replicated with probenecid in mice [93].

ATP release through Panx1 channels might also activate ionotropic, Ca^{2+} permeable P2X7 receptors, leading to further Ca^{2+} influx and activation of apoptosis. This P2X7-Panx1 complex has been implicated in ischemic cell death, spreading cortical depression and associated neuroinflammation [94–96]. Specifically, ATP release from Panx1, resulting in autocrine P2X7R stimulation, is important for inflammasome assembly in neurons and astrocytes, and ultimately release of mature IL1β [94], especially in combination with endothelial stimulation with TNFα [59].

Recent studies have also found the importance of Panx1 in cerebral stroke outside of neurons. Genetic deletion of Panx1 from endothelial cells, but not smooth muscles, reduced ischemic stroke infarct size [9]. In these experiments, both arterial vasoconstriction in response to pressure changes, and infiltration of circulating leukocytes, were reduced in mice lacking endothelial Panx1 suggesting a dual role for endothelial Panx1 in the cerebral vasculature [9]. In addition to endothelial Panx1-dependent regulation of inflammation, Panx1 expression in myeloid cells, both microglia and circulating myeloid cells, was found to be important following a traumatic brain injury, which induces an ischemic injury secondary to the primary impact injury. Genetic deletion of Panx1 in myeloid cells using the Cx3Cr1 driven Cre recombinase reduced the presence of pro-inflammatory macrophages and neutrophils and improved functional motor skills [97]. Additional studies will need to be conducted to explore microglia cell activation versus infiltrated activated macrophages; however, together, these studies strongly suggest an important role for Panx1, both in endothelial and myeloid cells, in regulating neuroinflammation following a cerebral ischemic injury.

Kidney

In addition to the brain, the kidney is highly vulnerable to hypoxic injury [98]. ATP release is strongly associated with acute kidney injury (AKI) due to cell damage that takes place during disease progression, which is accompanied by worsening inflammation [99]. Panx1 is present throughout the kidney, especially in the vasculature, apical membranes of proximal tubules, collecting ducts, and thick descending limbs [100]. Regulation of ATP levels by Panx1 mediated release in the kidney is essential under physiological conditions, since it regulates renal hemodynamics and tubular transport in addition to pathological conditions [101]. Pharmacological and genetic screening methods of assessing the effects of Panx1 on renal IRI [14], a mouse model of AKI, revealed that global, endothelial, and epithelial

tissue-specific deletion of Panx1 had a protective effect, as did pharmacological inhibition of Panx1 channels during AKI [14, 102]. Clearly, Panx1 is having a major physiological role in the physiology and pathology of the kidney; however, there has not been extensive investigation.

Heart

Panx1 has also been shown to play a role in IRI in the heart. Multiple studies have now demonstrated an increase in Panx1 expression following coronary IRI [103, 104]. In addition, murine atrial myocytes in vitro exposed to hypoxia induced ATP release in a Panx1-dependent manner [104]. It was hypothesized that the cardiomyocyte-dependent increase in extracellular ATP could activate surrounding fibroblasts and initiate the transformation into a myofibroblast phenotype [104]. Additionally, Panx1 has been demonstrated to play a role in pre-conditioning, short periods of ischemia followed by reperfusion that can protect the heart against longer periods of ischemic injuries [105]. Indeed, both Panx1 and P2X7 channel inhibitors prevented the pre-conditioning protective effect and resulted in larger infarcts following pre-conditioning and a subsequent IRI [105]. The release of cardioprotectants during pre-conditioning, which may include ATP, appears to be Panx1-P2X7-channel dependent [105]; however, it remains unknown which cell types expressing Panx1 are important for this protective role during pre-conditioning of the heart.

It is possible that expression of Panx1 in the coronary vasculature could have important roles in regulating vascular tone as well as inflammation. Previous studies have found that P2Y2 receptor-mediated vasoconstriction is reduced in coronary arteries following IRI, possibly due to a compensatory mechanism to combat the increased extracellular ATP during IRI [103]. Deletion of endothelial Panx1 or pharmacological inhibition of Panx1 at time of reperfusion protected cardiac function following IRI, although without a change in infarct volume [13]. This is hypothesized to be due to a reduction in pro-inflammatory macrophage infiltration into the non-injured cardiac tissue [13]. Together, these data suggest an important role for Panx1 in myocardial infarction; however, further studies are needed to understand the cell type-specific roles and potential beneficial versus detrimental roles of Panx1 in determining post-IRI cardiac function and outcome.

Lung

Transplanted lungs are particularly susceptible to IRI. Using a hilar ligation model revealed roles for Panx1 in the IRI response, which includes pulmonary edema, inflammation, neutrophil infiltration, increased microvascular permeability, and lung dysfunction (increased airway resistance, decreased compliance, and increased pulmonary artery pressure) [15]. All of these pathological consequences of lung IRI were ameliorated with the Panx1 inhibitors carbenoxolone or probenecid. Endothelial specific Panx1 deficient mice also were resistant to the effects of IRI on the lung, suggesting that Panx1 is a viable target to prevent the deleterious effects of IRI in lung transplant. Whether this is the case and whether it will translate to a protective effect in other transplant models remains to be determined.

Other organ systems

Although the above is generally focused on inflammation involved with IRI, there are other organ systems where pannexin-mediated inflammation may also play an important role in disease etiology, including: atherosclerosis [106], colitis [107], and multiple sclerosis [108]. The role of Panx1 continues to evolve as an important inflammatory mediator.

Conclusions and future directions

Given that Panx1 channels are relatively non-selective, it is remarkable that Panx1 is central to the regulation of many diverse processes. In many ways, this may be because Panx1 is flexible in its ability to interact with multiple different receptors. Panx1 also is heavily influenced by multiple different classes of post-translational modifications, meaning it can be regulated by multiple signal transduction pathways. As such, understanding the context of Panx1 expression and stimulation are critical to determining how it can regulate inflammation and injury responses, especially when considering Panx1 as a pharmacological target to prevent the debilitating pathology of diseases such as sepsis and tissue damage due to IRI.

Spironolactone has been shown to be a highly effective Panx1 inhibitor that does not affect other pannexins and connexin hemichannels, which makes it an important tool to define roles for Panx1 signaling and it may have therapeutic application [7, 12]. However, like all drugs, spironolactone does have multiple targets (e.g., mineralocorticoid receptor antagonist) and so there is a need for further drug discovery [7]. The ability to target Panx1 by repurposing other drugs, such as probenecid, identifying novel small molecules, and developing peptide-based drugs, such as PxIL2P, is anticipated to expand the scope of Panx1 as an effective pharmacologic target.

Most research on Panx1 has focused on its role in ATP secretion. However, it is clear that a broad range of

molecules can be transmitted through Panx1, as a channel mediating both secretion and uptake (e.g., [26, 33]). The detailed structural models that have recently been developed will help identify key residues that control channel permselectivity that can be validated by expressing mutants in transfected cells or reconstituted in liposomes.

While global Panx1 knockout mice were critical to identifying initial roles for Panx1 in many different physiologic processes, they suffer from significant pitfalls due to compensatory expression of other proteins. Tissue-specific, inducible transgenic Panx1 deficient mice have provided a more specific way to target Panx1, which is especially critical for distinguishing roles for Panx1 in the endothelium versus leukocytes, both of which are involved in inflammation. Future research including mice expressing Panx1 point mutants targeting key regulatory sites will provide a deeper understanding of the cellular mechanisms that regulate Panx1 and enable it to be central to so many diverse physiological and pathophysiologic processes.

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Declarations

Ethical approval No experimental data was generated for this review.

Informed consent No experimental data was generated for this review.

Conflicts of interest The authors declare no competing interests.

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